# MeiraGTx Announces the Presentation of Nine Posters at the American Society of Gene and Cell Therapy (ASGCT) 2023 Annual Meeting

May 16, 2023

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

LONDON and NEW YORK, May 16, 2023 (GLOBE NEWSWIRE) -- MeiraGTx Holdings plc (Nasdaq: MGTX), a vertically integrated, clinical stage gene therapy company, today announced the Company will exhibit nine poster presentations at the American Society of Gene and Cell Therapy (ASGCT) 2023 Annual Meeting, which is being held from May 16-20, 2023, in Los Angeles, CA.

"Our presentations at this year's ASGCT Annual Meeting reflect the significant progress made in our novel gene and cell therapy platforms, including promoter discovery and development, manufacturing technology as well as several *in vivo* proof of concept efficacy studies using our riboswitch platform," said Alexandria Forbes, Ph.D., president and chief executive officer of MeiraGTx. "Our riboswitch gene control platform allows us to precisely control the expression of any gene in a tight dose response to oral small molecules and to control gene expression to a very high dynamic range, from undetectable at baseline to levels generally greater than the maximum expression of the unregulated vector expressing the same gene. Importantly, we are presenting data on *in vivo* dose dependent efficacy of our riboswitch in animal models. We demonstrate efficacy of vector-delivered human growth hormone, rescuing *B.little* mice by controlling hGH expression in a periodic fashion with an oral small molecule, and data demonstrating control of tumor burden by regulating anti-HER2 antibody in tight dose response to an orally dosed small-molecule inducer." Dr. Forbes continued, "We are also presenting data demonstrating precise regulation of CAR levels on CAR-Ts, with the unprecedented ability to intermittently switch CAR on to low receptor density levels, which results in increased CAR-T potency, decreased exhaustion markers and increased safety when directly compared to CAR-T with constitutively expressed CAR. These three examples, along with data on our promoter discovery platforms presented at ASGCT, provide support for the broad applicability of our gene regulation technology across multiple therapeutic targets for gene and cell therapy."

The posters will be available on the Posters and Publications page of the Company's website after the respective presentation session has concluded.

**The details of the poster presentations are below:**

**Poster #764** *Riboswitch-regulated chimeric antigen receptor (RiboCAR) enhances T cell activity*
**Session Date/Time:** 5/17/2023 12:00PM PT
**Session Title:** Wednesday Poster Session

Chimeric antigen receptor (CAR)-T cell therapy is a promising treatment for certain cancers and the level of CAR molecule expression is important for CAR-T cell activation, durability, and anti-cancer activities. RiboCAR is a synthetic riboswitch-based gene regulation system for precise regulation of CAR expression levels in CAR-T cell therapy via orally available small molecule. RiboCAR contains a synthetic mammalian ON riboswitch in the coding sequence of the CAR transgene, in which the aptamer functions as a sensor for a specific novel small molecule inducer.
We demonstrate that with a bioavailable small molecule inducer, CAR-T activity can be precisely tuned and "remotely" controlled *in vivo*. This precise control of CAR levels provides a system for improving the efficacy and durability of CAR-T as well as a safety mechanism for CAR-T cell therapy in comparison to current therapies with constitutively active CAR expression.

**Poster #1245:** *Towards Ultra Scale-down AAV Production in Microtiter Plates*
**Session Date/Time:** 5/18/2023 12:00 PM PT
**Session Title:** Thursday Poster Session

High-throughput screening methods have become an integral part of research and development in the biopharmaceutical industry due to their low cost, ease of operation, and high degree of parallelization. This study scaled down a transient transfection-based adeno-associated virus (AAV) production process from a 250 mL stirred tank reactor (STR) to a 24-deep square well (DSW) for serotypes AAV2, AAV5, and AAV8. A tightly controlled transfection step with sufficient mixing was identified as playing a decisive role in achieving scalable productivity, resulting in a reduction of the intra-plate coefficient of variance from 60% to under 30%, proving the suitability of the platform for large early-stage screening studies. These findings illustrate a viable method for high-throughput early-stage AAV process development.

**Poster #1277:** *Development of rationally designed CAG-based promoters for use in gene therapy*
**Session Date/Time:** 5/19/2023 12:00 PM PT
**Session Title:** Friday Poster Session

The promoter is an essential cis-regulatory element in any DNA-based gene therapy. It directly controls gene transcription and thereby therapeutic protein expression. Current gene therapy clinical trials mostly use cellular CAG or viral CMV promoters. To improve promoter efficacy we designed a series of 82 new CAG promoter variants by systematically introducing modifications to each of the promoter elements and testing them in different *in vitro* and *in vivo* models. In HEK293T cells, 67 CAG promoter variants were found to be stronger than the original CAG with the strongest promoter exhibiting a 13-fold improvement in potency. Two CAG promoter variants, based on improved *in vitro* activity and smaller size (~40% size reduction), were administered by tail vein injection into C57BL/6 mice. Expression in the liver improved by up to 4-fold compared to the original CAG promoter. Four MGTx variants are ~800 bp smaller than CAG but exhibit 15-fold higher expression in primary mouse hepatocytes. Our CAG promoter library provides promising options for the development of next-generation gene therapies.

**Poster #1399:** *AAV-mediated riboswitch-controlled delivery of anti-HER2 antibody suppresses HER2-positive tumorigenesis*
**Session Date/Time:** 5/19/2023 12:00 PM PT

**Session Title:** Friday Poster Session

Controlled expression of delivered transgenes may be critical for optimized, safe, and effective genetic medicines. AAV-mediated gene transfer is a promising therapy for many diseases. However, excessive amounts of transgene from unregulated vectors may limit the breadth of applicability of gene therapy. A specific and precise mechanism for gene control via orally delivered small molecules with high dynamic range and gene expression at least as high as unregulated genes would provide a safe and effective gene therapy approach to a broad range of disease areas. We developed a regulated anti-HER2 antibody gene that addresses the potential safety concerns associated with excessive and long-term expression of therapeutic antibodies. The expression of the anti-HER2 antibody gene is controlled by riboswitch via a small molecule inducer. The induced anti-HER2 antibody is efficacious in suppressing HER2+ tumor growth and prolonging tumor-free survival in a dose-responsive fashion to the oral small molecule inducer. Our results indicate that synthetic mammalian riboswitch works efficiently *in vivo* and can provide precise control of therapeutic antibody expression, achieving high levels of antibody expression and rapid tumor suppression in a dose-dependent manner.

**Poster #1433:** *AAV-mediated, small molecule-riboswitch-controlled delivery of growth hormone rescues growth in GH-deficient B.little mice*
**Session Date/Time:** 5/19/2023 12:00 PM PT
**Session Title:** Friday Poster Session

AAV-mediated gene transfer holds promise as a therapy for various diseases, but unregulated protein expression from vectors can lead to unwanted side effects and reduced efficacy. We present the development of an optimized vectorized human growth hormone gene, whose expression is specifically and precisely in dose-response to a bespoke oral small molecules inducer via a synthetic mammalian riboswitch. Our gene expression platform utilizes a riboswitch, an RNA element that contains an aptamer as a sensor for a small molecule ligand/inducer. In the absence of the small molecule inducer *in vitro*, the growth hormone (GH) gene containing the riboswitch does not express growth hormone protein. In the presence of the small molecule inducer, growth hormone is robustly produced in a precise inducer dose-dependent manner. When the GH gene with riboswitch was delivered into the muscles of GH-deficient B.little mice via AAV-mediated local intramuscular injection, the oral small molecule inducer treatment resulted in increased body weight and body length of the mice. The improvement of the animal growth in B.little mice indicates that the induction of expression of growth hormone achieves a therapeutic level in these animals and demonstrates for the first time rescue of GH deficiency via the delivery of a small molecule inducer of a locally delivered gene therapy rather than repeated injection of exogenously produced synthetic growth hormone. Our data provide evidence that our riboswitch platform provides an efficacious and safe platform for delivering GH via gene expression control.

**Poster #1446:** *Development of in vitro neuronal cytotoxicity models for neurodegenerative disease gene therapy R&D*
**Session Date/Time:** 5/19/2023 12:00 PM PT
**Session Title:** Friday Poster Session

Neurological disorders such as Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS), and Frontal Temporal Dementia (FTD) are the second leading cause of death worldwide, with millions of new diagnoses each year. ALS alone affects 1 in 50,000 people per year worldwide, calling for increased demand for efficient therapies. Cytoplasmic mislocalization and the subsequent accumulation and aggregation of transactive response DNA-binding protein 43 kDa (TDP-43) is a hallmark of ALS and, in most cases, represents a reliable post-mortem diagnostic marker. We propose two cellular models of TDP-43-induced cytotoxicity mediated by adeno-associated virus (AAV) transduction. Primary cortical mouse neurons were transduced with AAV containing TDP-43 and cytotoxicity was tracked over time. Dose-dependent cytotoxicity, as well as changes in morphology, were observed in the TDP-43-transduced neurons. The same experiment was conducted using ReNcells, an immortalized human neural progenitor cell line. Treating ReNcells with AAV-TDP-43 resulted in dose-dependent cytotoxicity determined by LDH activity and AO/PI staining. Our data demonstrate that these *in vitro* models have the potential to be used in high throughput screens and functional potency assays for neuroprotective gene therapy development.

**Poster #1466:** *Identification of Novel Inflammation-Inducible Promoters Using a Hybrid-Barcoded SuRE$^{TM}$ Library*
**Session Date/Time:** 5/19/2023 12:00 PM PT
**Session Title:** Friday Poster Session

AAV-based gene therapy vectors are promising candidates for the treatment of inflammatory disease, resulting from a biological response of the immune system triggered by a variety of different factors. Regulatory elements, including promoters and enhancers, are engineered for use in AAV vectors to optimize the strength, kinetics, and specificity of transgene expression. The incorporation of promoters inducible by inflammation will help to reduce the risk of side effects due to overexpression of and/or continuous exposure to the anti-inflammatory therapeutic protein by such AAV vectors. The Survey of Regulatory Elements (SuRE) methodology was applied to identify new cis-regulatory elements in the human genome. The best-performing elements were combined with the NFkB-CMV promoter to generate a new barcoded library, consisting of ~40,000 new hybrid combinations, each of around 600 bp in size. The new barcoded hybrid library was subsequently used in a second round of screening in HT1080 cells. The best-performing hybrid elements were selected for further analysis in the context of the AAV2 genome upon plasmid transfection and AAV transduction, with luciferase as the reporter protein. Primary cells and different cell lines were used to determine the strength and inducible character of the new hybrid promoters. The expression profiles from plasmids and AAV viruses revealed a number of new hybrid promoter elements that displayed improved inducibility and/or higher expression under inflammatory conditions compared to the reference NFkB-CMV promoter.

**Poster #1499:** *Understanding the factors that influence capsid-column affinity and peak profile in AEX-HPLC to measure empty:full ratio*
**Session Date/Time:** 5/19/2023 12:00 PM PT
**Session Title:** Friday Poster Session

Anion exchange chromatography by HPLC is an analytical technique that can be used to determine the empty and full capsid content of adeno-associated viral (AAV) vector drug products. AEX columns have a positively charged resin which has a high affinity for negatively charged ions (anions). Under certain conditions, AAV capsids will bind to the column and the introduction of a salt gradient will alter the ionic strength, causing the bound empty capsids to elute first from the column shortly followed by full capsids. Developing a reproducible empty:full method can be challenging due to factors like sample preparation, mobile phase components, pH, conductivity, salt concentration, and temperature which influence the binding efficiency of AAV capsids onto the column and the elution of the empty and full capsids during the salt gradient. Data collected during the development of an AEX empty:full method demonstrates the effects of small method changes on capsid-column affinity and peak profile. AEX results are also compared to results of other orthogonal analytical techniques such as VG/VP ratio, AUC, cIEF, CryoEM, and mass photometry.

**Poster #1623:** *Multiple In Vitro Differentiated Skeletal Muscle Models for Screening of Synthetic Muscle Promoters for Gene Therapy*

**Session Date/Time:** 5/19/2023 12:00 PM PT
**Session Title:** Friday Poster Session

Gene therapy for inherited musculoskeletal disorders in skeletal muscle has been challenging due to the target's large size and the need for high systemic vector doses of adeno-associated virus (AAV) for therapeutic efficacy, which has resulted in dose-limiting toxicity and immunogenic responses. However, muscle tissue is an effective target for the therapeutic production of secretory proteins through the local delivery of viral vectors containing therapeutic transgenes. We established multiple *in vitro* differentiated myotube models of skeletal muscle for a more efficient evaluation of engineered muscle promoters for gene therapy and their characterization by transcriptomics and immunofluorescence analyses. We tested a set of in-house proprietary muscle promoters in these models and compared them against known reference muscle promoters currently used in clinical trials of AAV-delivered treatment for muscular dystrophies. Top performing candidates from our rationally designed compact muscle-based promoters were evaluated *in vitro* and *in vivo*, with our results showing higher transgene expression compared to reference muscle promoters. MGTx-M24, a top candidate demonstrated higher potency *in vivo* than promoters used in clinical trials, which validates the relevance of our models. Collectively, these results show we have established a robust platform to screen engineered promoters for applications to skeletal muscle gene therapies.

**About MeiraGTx**

MeiraGTx (Nasdaq: MGTX) is a vertically integrated, clinical stage gene therapy company with six programs in clinical development and a broad pipeline of preclinical and research programs. MeiraGTx has core capabilities in viral vector design and optimization and gene therapy manufacturing, and a transformative gene regulation platform technology that allows precise, dose-responsive control of gene expression by oral small molecules with dynamic range that can exceed 5000-fold. Led by an experienced management team, MeiraGTx has taken a portfolio approach by licensing, acquiring, and developing technologies that give depth across both product candidates and indications. MeiraGTx's initial focus is on three distinct areas of unmet medical need: ocular diseases, including both inherited retinal diseases as well as large degenerative ocular diseases, neurodegenerative diseases, and severe forms of xerostomia. Though initially focusing on the eye, central nervous system, and salivary gland, MeiraGTx plans to expand its focus to develop additional gene therapy treatments for patients suffering from a range of serious diseases.

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 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 the COVID-19 pandemic 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, 2023, 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