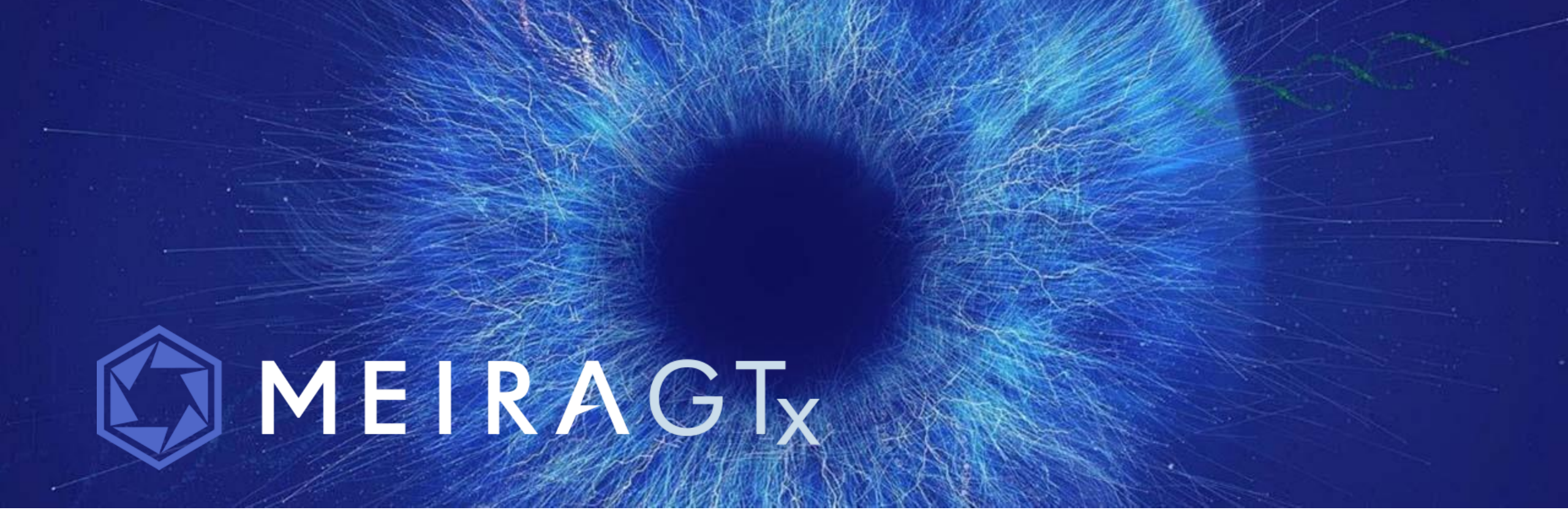


Corporate Presentation

May 2023

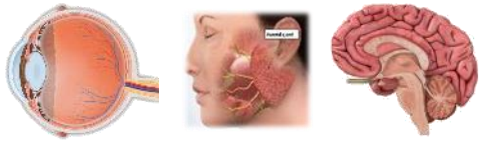
Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding our product development and anticipated milestones regarding our pre-clinical and clinical data and reporting of such data and the timing of results of data, including in light of the COVID-19 pandemic, as well as statements that include the words “expect,” “intend,” “plan,” “believe,” “project,” “forecast,” “estimate,” “may,” “should,” “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 most recent quarterly report on Form 10-Q or annual report on Form 10-K or subsequent 8-K reports, as filed with the Securities and Exchange Commission. These and other important factors could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management’s estimates as of the date of this presentation. 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 presentation. Unless otherwise stated or the context otherwise requires, the information herein is as of May 11, 2023.

MEIRAGTx

End-to-end Capabilities in Genetic Medicines

Broad pipeline with pivotal stage program | cGMP manufacturing | Comprehensive vector design | Gene regulation platform



Clinical Pipeline

Diverse advanced clinical programs:

- 6 clinical programs, all with positive Phase 1 or Phase 2 studies
- De-risked
- Local delivery of small doses
- Immune protected
- Human proof of concept
- CNS, eye, salivary gland

GMP Manufacturing

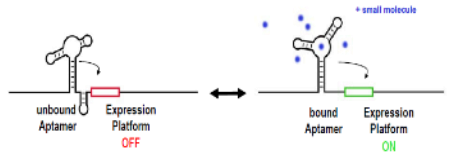
Flexible and Scalable

- 2 cGMP Facilities commercial scale
- Proprietary Platform Production Process – highest yield and full ratio in industry
- Plasmid production for cGMP
- Full analytics for commercial release and stability
- Fill and Finish

Next Generation Vector Optimization

Potency, Safety, Immunogenicity, Dose

- Capsids - Cell Tropic, CNS, Eye, Liver, Muscle
- Promoters; Regulatory Elements – cell and level specific, Muscle, Heart, CNS Liver, Eye
- Vector Sequence
- Immune Protection



Transformative Gene Regulation Technology

Control of Genetic Medicines

- Synthetic mammalian riboswitch
- >5000x dynamic range
- Multiple safe oral small molecules with good drug properties
- Precise dose response
- Any gene in any context
- Cell Therapy, Gene Editing, Gene Therapy

Broad Pipeline of Transformative Gene Therapies

Product	Indication	Discovery / Preclinical	Phase 1/2	Phase 3
Ocular				
Inherited Retinal Diseases				
Botaretigene sparoparvovec*[1] (janssen)	X-linked RP		*PRIME, Fast Track, Orphan Drug*	lumeos XLRP study
AAV-RPE65	RPE65-Associated Retinal Dystrophy		*RPDD, Orphan Drug*	
AAV-CNGB3* (janssen)	Achromatopsia		*RPDD, PRIME, Fast Track, Orphan Drug*	
AAV-CNGA3* (janssen)	Achromatopsia		*RPDD, Fast Track, Orphan Drug*	
AAV-AIPL1	LCA4	Compassionate use under MHRA Specials License		
A007, A008,	Undisclosed IRD Targets			
Degenerative Ocular Diseases (non-inherited)				
A006	Wet AMD (anti-VEGFR2)			
Neurodegenerative Disease				
AAV-GAD	Parkinson's Disease			
AAV-UPF1	ALS			
Salivary Gland				
AAV-AQP1	Xerostomia		*Orphan Drug*	
	Sjögren's Syndrome			
Other Pre-IND Programs				
Inherited Obesity (MC4R) / Neurodegenerative disease	AAV-BDNF			
Wilson Disease	AAV-ATP7B opti			
Small molecule riboswitch inducers				

* Co-development program with Janssen Pharmaceuticals
[1] Formerly referred to as AAV-RPGR

6 clinical-stage programs
Across multiple TFAs

2024
Anticipated BLA filing in XLRP

A Unique, Diverse and Inclusive Culture

MEIRAGTx

- 340+ full-time employees
- 55% female, 45% male
- 4 locations: US, UK, Netherlands, Ireland
- 31 different nationalities represented

Extensive Vector Engineering Toolkit (15 presentations at ESGCT 2022)

Gene Sequence Optimization

Control expression levels and cell specificity driving potency and safety

- Promoter-enhancer-intron-exon configuration
- Kozac sequence, 3', 5' and Poly A optimization
- Codon optimization – translation efficiency, immune regulation
- cDNA engineering/Protein Engineering

Gene Regulation Technology

Precise, specific, dose responsive control of genetic medicine levels

- Uses synthetic proprietary Riboswitch designed in mammalian cells
- High dynamic range
- In vivo applicable to antibodies, peptides, hormones, editing and cell therapy

Capsid Selection

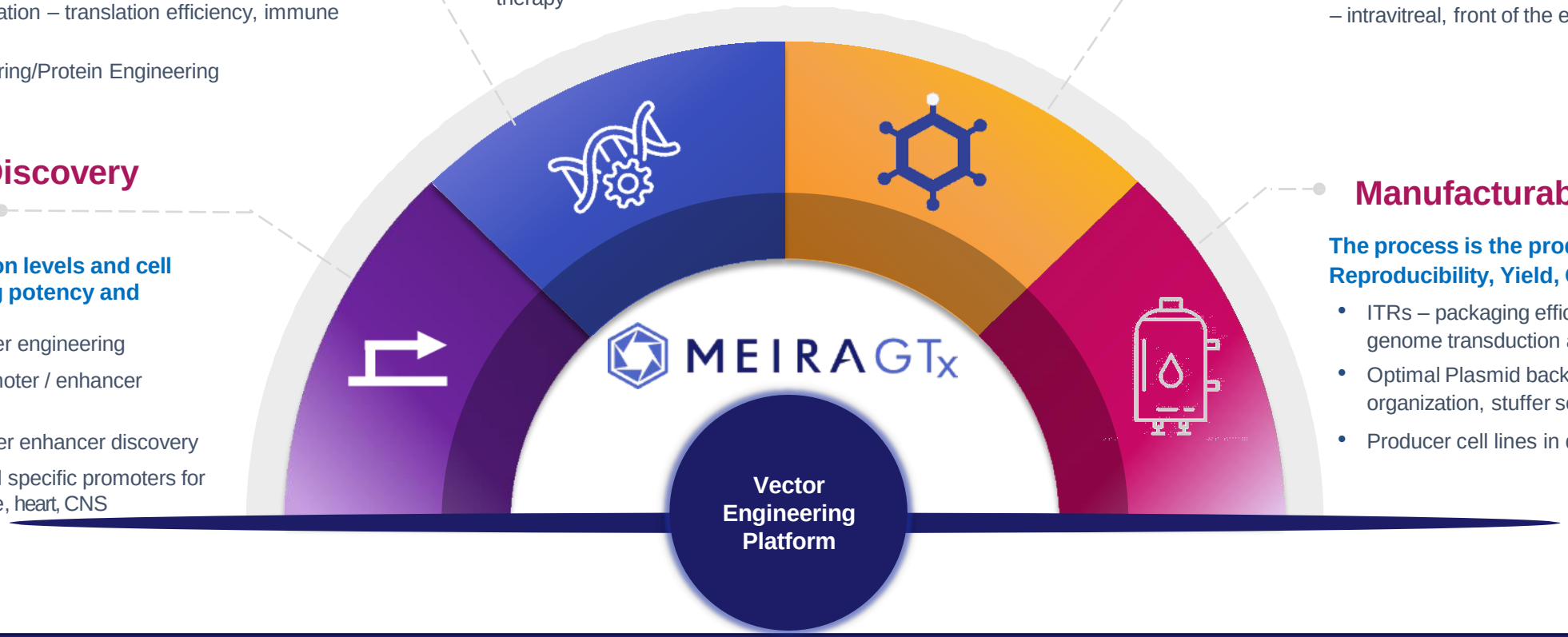
Tissue Tropism: Drives differential transduction efficiency and potency

- Proprietary capsids for the eye and CNS
- NHP screens for cell specific capsids ongoing – intravitreal, front of the eye, liver, CNS

Promoter Discovery Platforms

Control expression levels and cell specificity driving potency and safety

- Bespoke promoter engineering
- Large scale promoter / enhancer screening
- AI driven promoter enhancer discovery
- Strong, small cell specific promoters for eye, liver, muscle, heart, CNS



Manufacturability

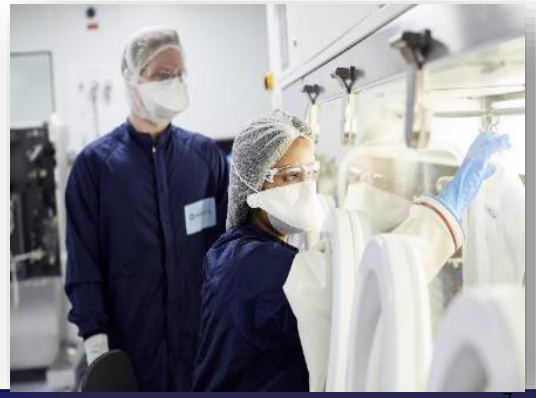
The process is the product: Safety, Potency, Reproducibility, Yield, Quality, Cost

- ITRs – packaging efficiency, impact on vector genome transduction and expression
- Optimal Plasmid backbone design – cap/rep organization, stuffer sequences
- Producer cell lines in development

Wholly-Owned, In-House, End-to-End cGMP Manufacturing

The most comprehensive viral vector manufacturing infrastructure in the industry, supported by robust know-how and patent estate

- In-house, commercial scale cGMP viral vector manufacturing – 2 facilities, London and Shannon, support commercial production
- In-house cGMP plasmid manufacturing - overcoming a significant supply chain bottleneck in the industry
- In-house QC, full analytics for commercial release and stability – essential to overcome global CRO deficiency in this area
- On-site Fill/Finish and Central Warehouse
- Experienced global regulatory team supporting 6 clinical programs Phase 2 and Phase 3
- Preparing for global commercial supply supporting BLA filing 2024



MeiraGTx Gene Regulation Technologies Enable Unprecedented Control of Genetic Medicine

Bespoke promoter transcriptional regulation combined with riboswitch regulation of mRNA processing allows for unprecedented control of gene expression in any cell therapy or gene therapy context

MeiraGTx Gene Regulation Technologies

Cis-Regulatory Elements (Promoters, Enhancers, Introns)

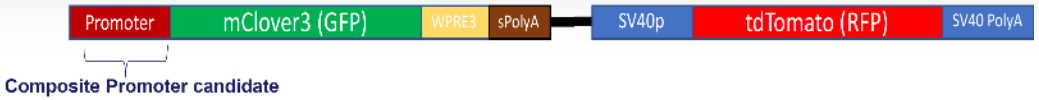
- Spatial control of gene expression - ubiquitous or tissue/cell-specific
- Control of expression levels
- Drives product potency and safety

Riboswitch Technology

- Precise control of expression levels in a dose-dependent manner
- Ability to switch off expression
- Bespoke small molecules
- 30 so far appear safe with good drug properties
- BBB-crossing, ocular, or systemic small molecule inducers

Multi-Platform Promoter Discovery Engine

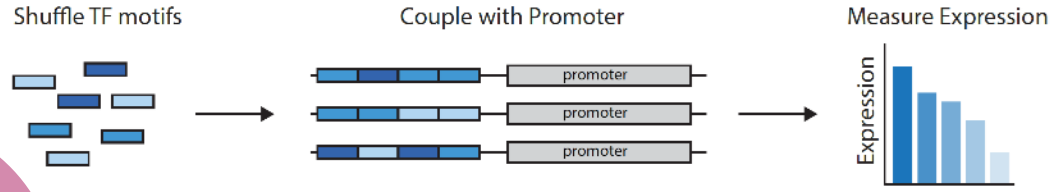
Rationally Designed Screens



- Composite promoters designed using selected core promoters combined with different cis-regulatory elements
- Cis-regulatory elements: either well-characterized or from genome-wide RNA-seq, ATAC-seq, and ChIP-seq datasets (e.g. ENCODE, FANTOM)
- More than 300 such rationally designed composite promoters with selected potency are in development at MeiraGTx

High-Throughput Transcription Factor Shuffling

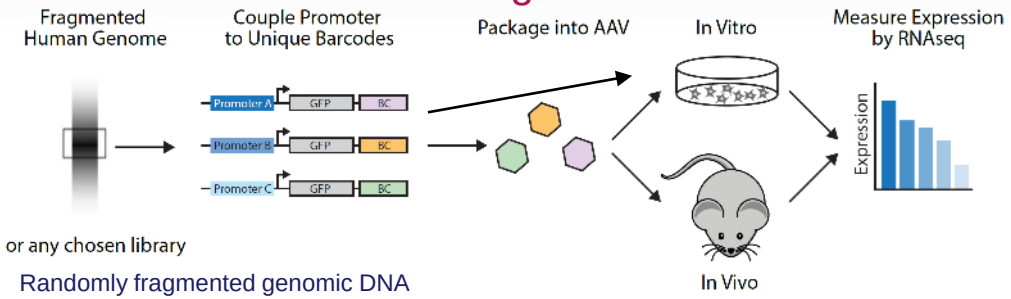
- Generation and screening of synthetic enhancers via cell specific transcription factor binding site (TFBS) shuffling



MEIRAGTx

Promoter Engineering Platforms

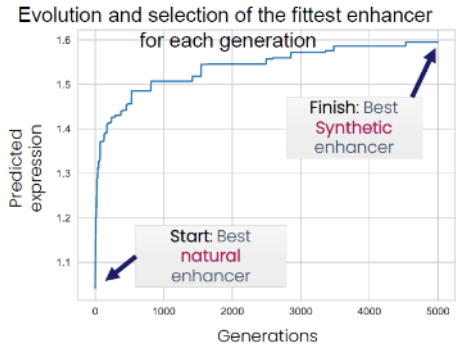
AAV-based or plasmid-based promoter screen using barcodes



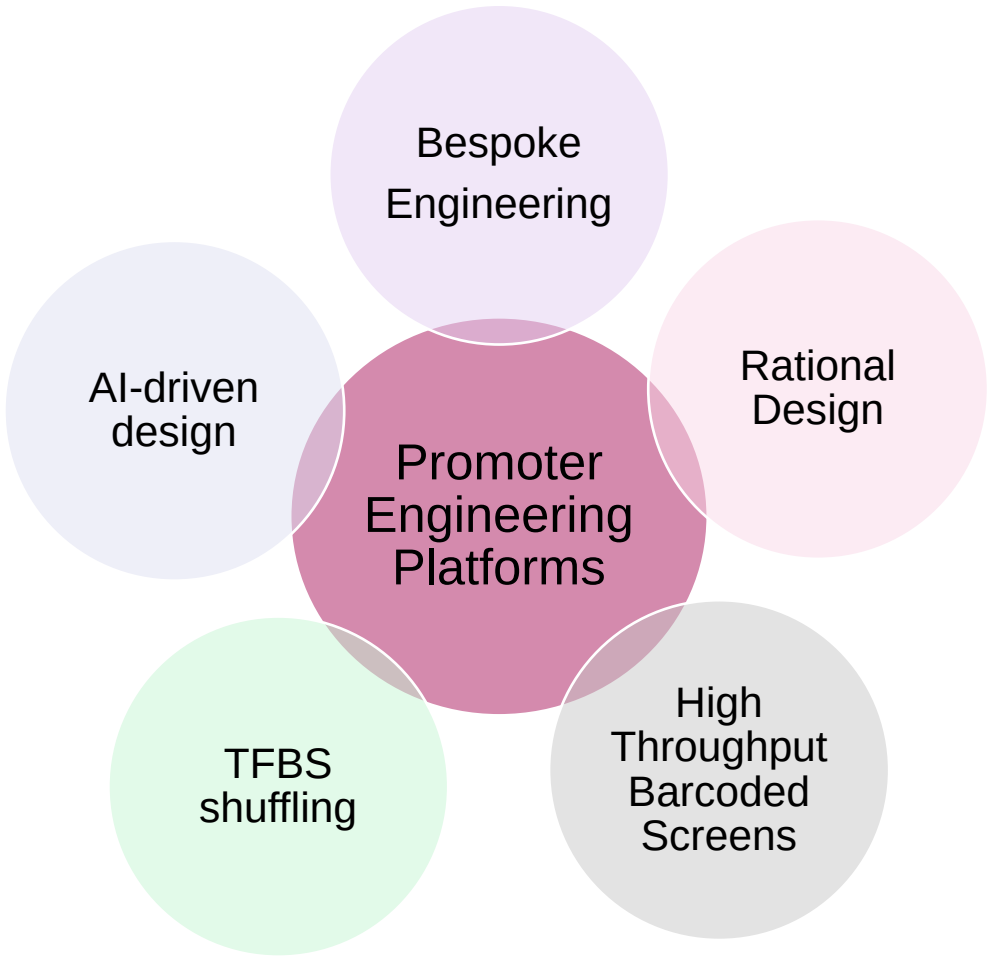
- Randomly fragmented genomic DNA
- All annotated human promoters
- All putative natural enhancers (ENCODE, FANTOM)
- Synthetic enhancers/promoters
- AI-driven library design

AI-driven Promoter Design and Evolution

1. AI model to predict promoter strength and optimize location of enhancer sequences
2. Genetic algorithm coupled with an AI model to evolve strong natural enhancers into stronger synthetic enhancers
3. In-silico mutation of selected promoters to speed discovery of stronger, smaller cell specific promoter variants



Multiple Promoter Engineering Platforms Yield Libraries of Strong, Small, Tissue Specific Transcriptional Regulatory Elements



Libraries of synthetic novel promoters with smaller size, greater strength, and better cell selectivity compared to CAG, CMV and natural cell-specific promoters

- Multiple ocular cell specific promoters for all cell types in the eye and with different strengths: e.g., the strongest known human pan-cone promoter
- >100 constitutive promoters up to 10-fold stronger than CAG and/or CMV
- Multiple muscle-specific promoters that are stronger than tMCK (currently used in clinical trials):
  - Synthetic muscle-specific promoter that is durable and up to 17-fold stronger than tMCK in mouse muscle in vivo
  - A 751 bp ubiquitous promoter is stronger in muscle than CAG
- >25 neuronal promoters up to 12x stronger than CAG in both human and mouse neuronal cell lines
- >30 liver promoters stronger than CAG and stronger than promoters currently used clinically (AAT, LP1, TBG). All smaller than CAG
- In silico screening and evolution of promoters via machine learning methods further enhances potency and cell specificity of promoters identified by other methods

Riboswitch Gene Regulation

Precise and Specific Control of Gene Activity with Bespoke Oral Small Molecules

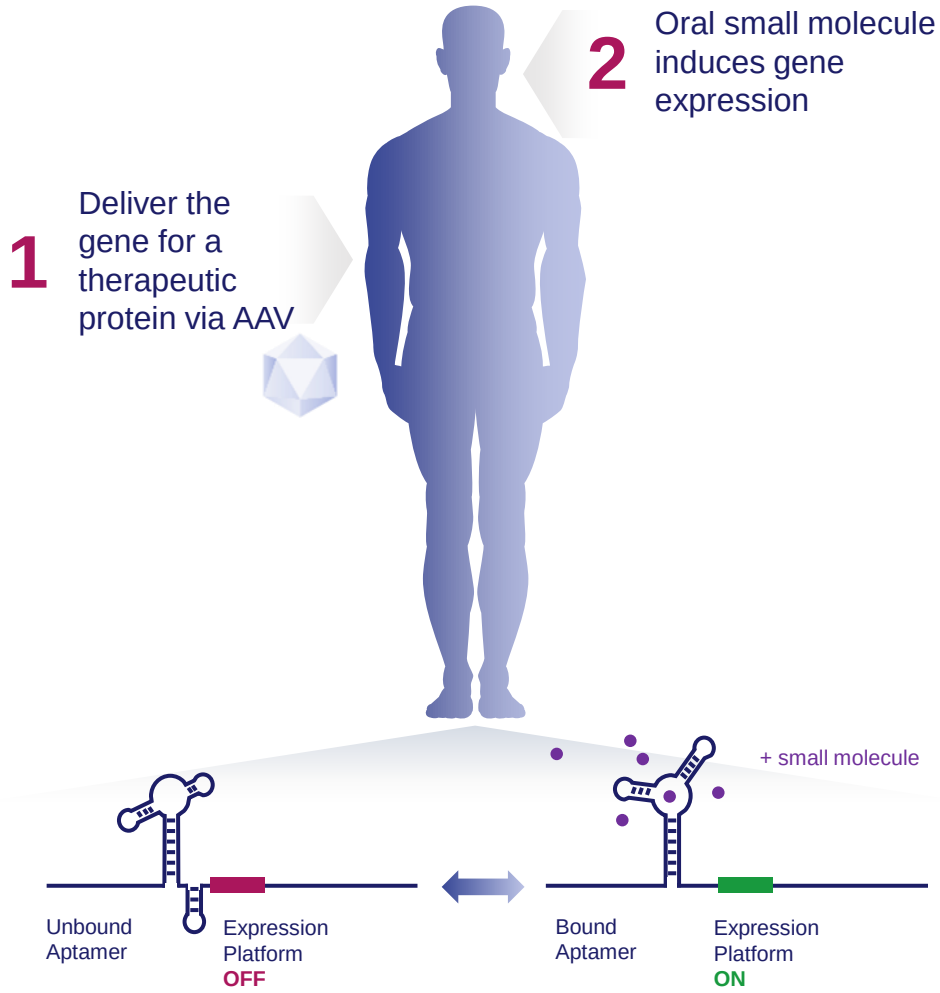
Riboswitch technology enables precise control of genetic medicine using bespoke orally-dosed inducers:

i. **Gene Regulation Cassette driven by novel mammalian Riboswitches**

ii. Only upon binding of an orally-delivered small molecule inducer, gene expression is specifically and robustly activated **in a precise dose-dependent manner** and at **unprecedented high dynamic ranges (>5000x)**

iii. Gene expression returns to basal levels upon clearance of the inducer

- ✓ Precise control of gene expression in response to small molecule dose
- ✓ It is not just an ‘on’ / ‘off’ switch, but a system for dose response of gene and cell therapies to oral drugs
- ✓ Can be coupled with any promoter - maintaining cell-specificity and potency
- ✓ Riboswitch can be applied to any transgene and any vector – for use in gene therapy, cell therapy, and gene editing



Riboswitch Unlocks the Potential of Genetic Medicine

Vectorized Biologics, Gene Replacement
Safety and Consistency of any genetic medicines

CNS expression of biologics – across the BBB
Gene Therapy delivered 1x within the BBB and activated using a small molecule that crosses the BBB

Cell Therapy
Controlled expression of CAR, cytokines, integrated ‘kill switch’

Short-lived Therapeutic Hormones and Peptides
Precise activation of naturally short-lived peptides and hormones; combinations of natural peptides regulated together

Ocular expression of therapeutic proteins
Tight control of expression in the eye with eye drop formulation

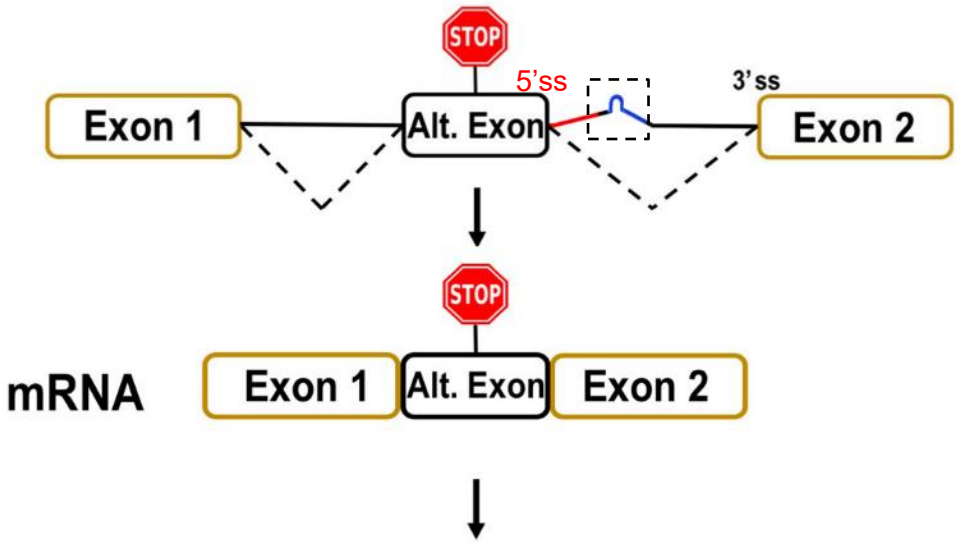
Tight regulation of Gene Editing
DNA or RNA editing e.g., Cas9 and CasRx

Passive and Active Vaccines with built-in capacity for Oral Small Molecule Boosters

Gene Regulation Cassette Driven by Splicing-Based Synthetic Mammalian Riboswitch

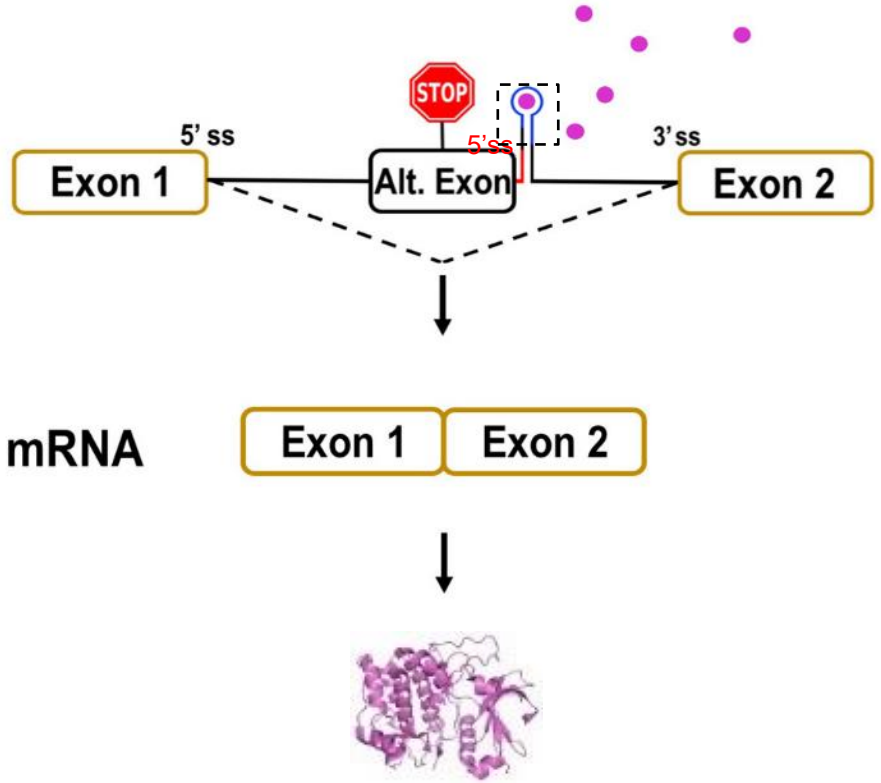
Riboswitch-mediated Modulation of alternative splicing
1:1 small molecule:mRNA

No Small molecule (OFF state)



no protein

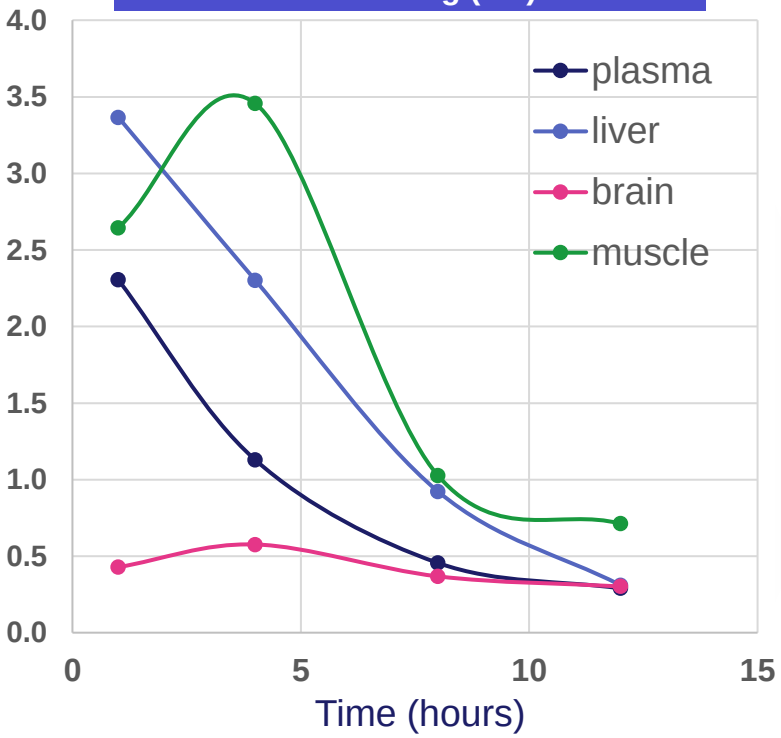
+ Small molecule (ON state)



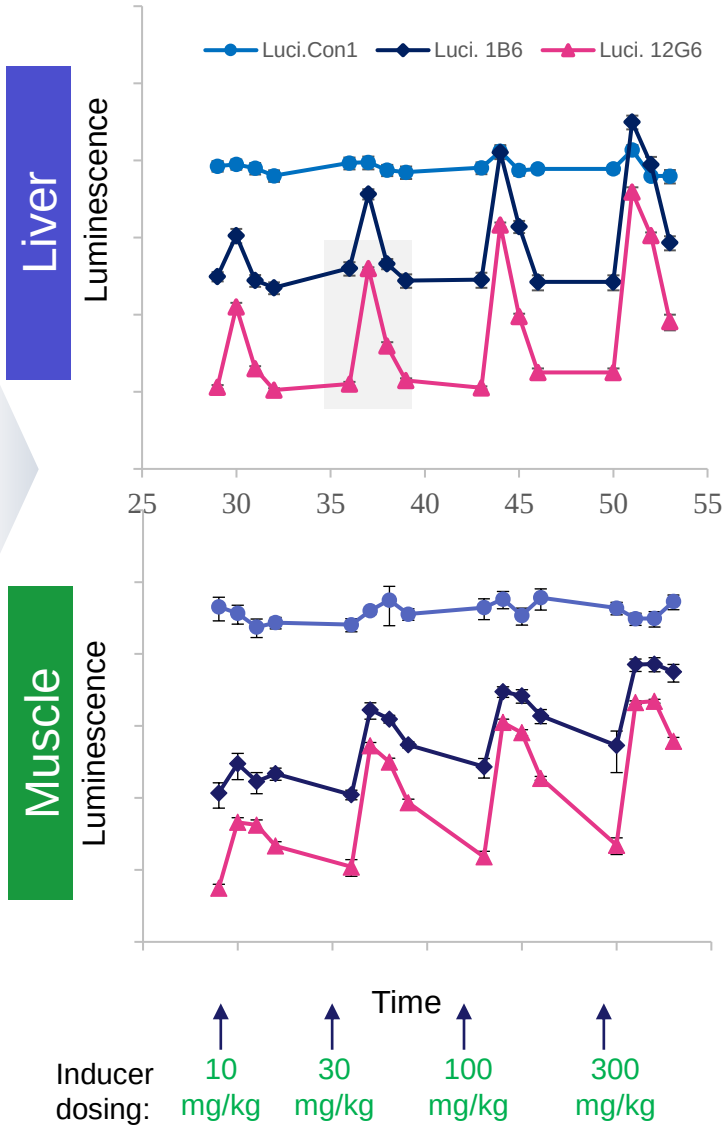
protein expressed

Riboswitch Regulates AAV-Mediated Transgene Expression in a Precise Dose Response to Oral Small Molecule Inducer

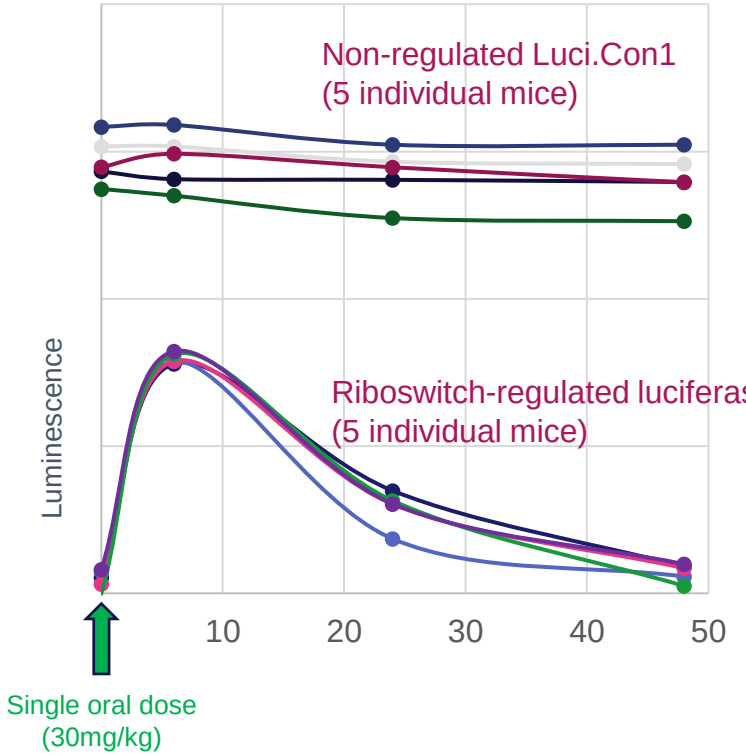
Inducer tissue concentration after P.O. dosing (uM)



- Tissue distribution of orally delivered small molecule indicates short term accumulation in muscle while exit from liver is straight down
- This is directly reflected in the different profiles of expression in the liver and muscle, respectively



Liver transgene induction following a single inducer dosing 30 mg/kg PO

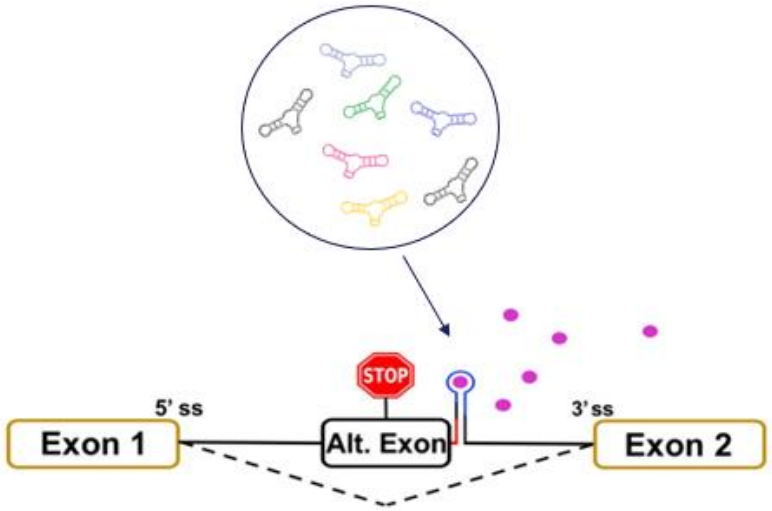


- On a mouse by mouse basis, expression in response to small molecule inducer is tightly controlled based on small molecule dose compared to unregulated expression from constitutively active construct

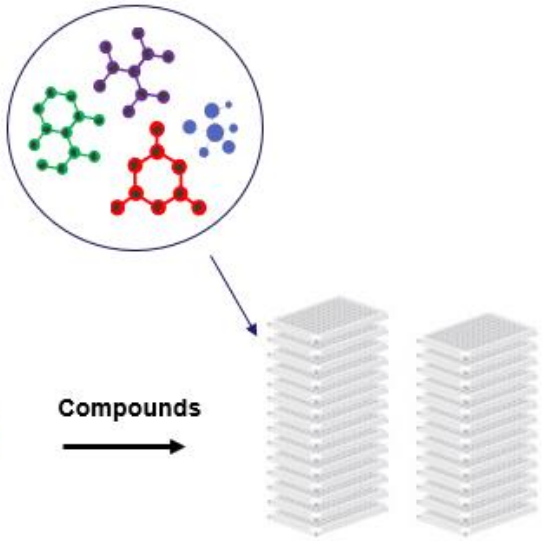
High Dynamic Range Regulation Cassette Allows Screening for RNA-Small Molecule Functional Binding within Mammalian Cells

Large aptamer libraries screened expression cassette

- Randomized aptamer sequence
- Site directed mutagenesis



Small molecule libraries screened against selected aptamer containing riboswitches



Mammalian cell culture

The gene is expressed **ONLY** when a small molecule binds an aptamer and drives hairpin formation and splicing

Assay readout: gene expression ON

Current status of small-molecule screening:

- Small libraries designed to improve potency and pharmaceutical properties
- ~150 Compounds have been screened
- 27 compounds demonstrated high potency and good ADME/PK properties
- 10 Compounds have gone or are going through rodent non-GLP tox studies.
- 2 compounds were identified to be BBB penetrant, with a brain:plasma ratio > 3 and are currently going through non-GLP PK and Tox studies
- 5 compounds demonstrated high eye exposure levels when dosed orally - are currently going through non-GLP PK and Tox studies
- Two compounds are in pre-clinical development: one compound completed GLP tox studies, and another will complete GLP tox this year. Both showed good safety profile in non-GLP rat, dog, and NHP studies.
- **Most advanced candidate entering IND enabling studies in 2023**

Therapeutic Genes Currently Vectorized, Optimized, and Regulated by Riboswitch Technology

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (ophthalmology)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
- Anti-HER2
- Anti-IL4Ra

Cell Therapy

- Ribo-CAR

Therapeutic Hormones / Cytokines / Peptides

- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon etc.

Gene/RNA Editing Nucleases

- Cas9
- CasRx

[Watch the MeiraGTx Gene Regulation R&D Day Presentation and Replay Here]

Therapeutic Genes Currently Vectorized, Optimized, and Regulated by Riboswitch Technology

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (ophthalmology)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
- Anti-HER2
- Anti-IL4Ra

Cell Therapy

- Ribo-CAR

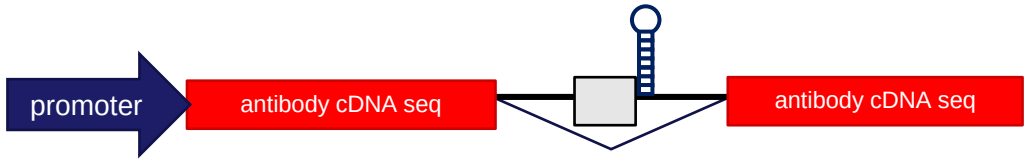
Therapeutic Hormones / Cytokines / Peptides

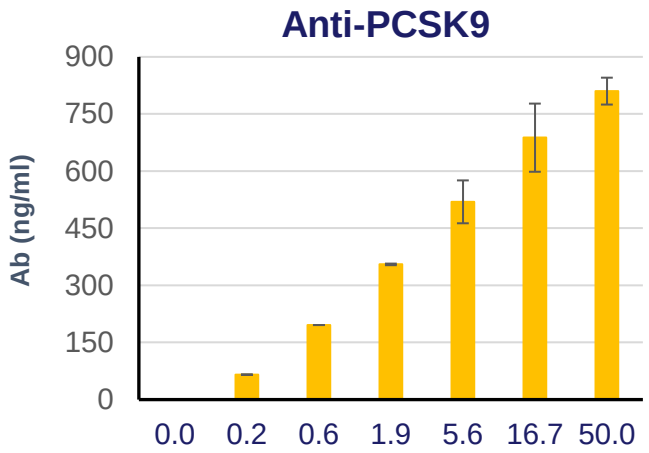
- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon etc.

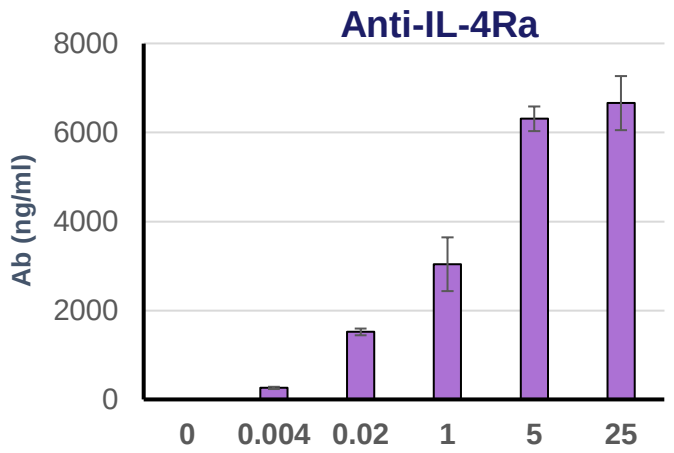
Gene/RNA Editing Nucleases

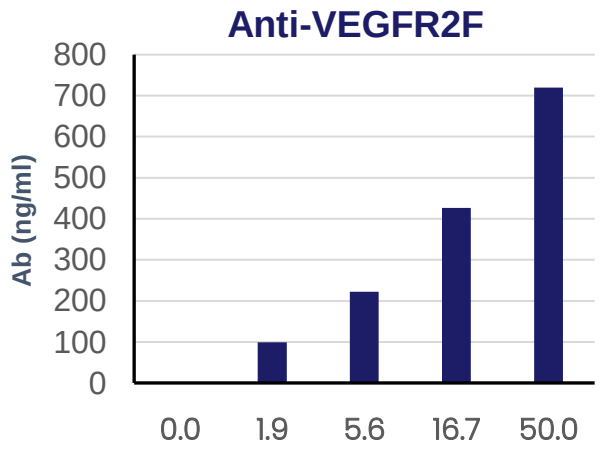
- Cas9
- CasRx

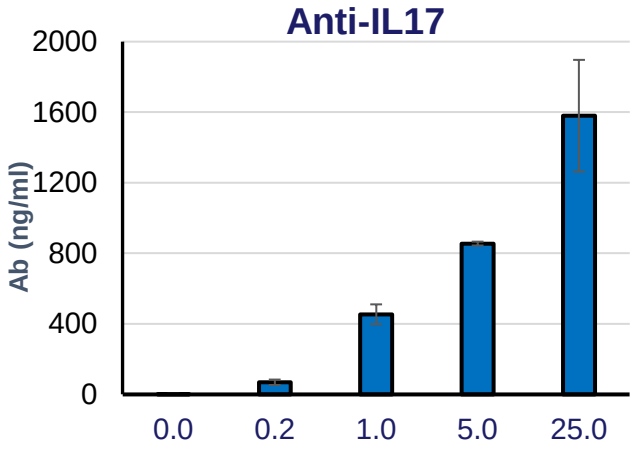
Riboswitch Tightly Regulates Expression of Therapeutic Antibodies in Precise Dose Responsive Fashion

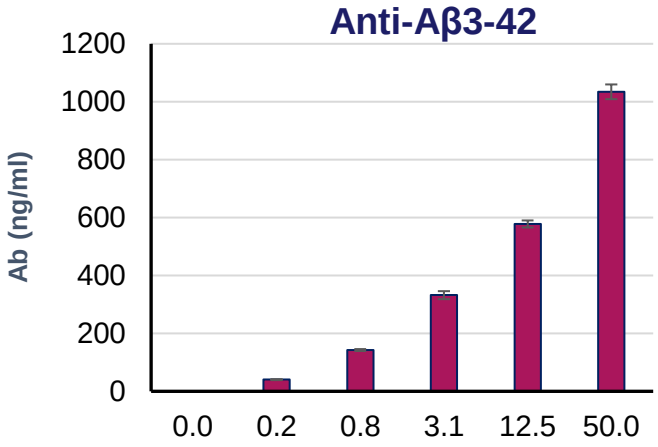


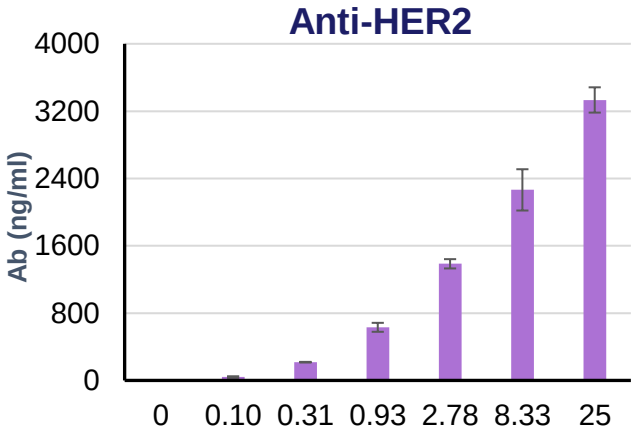












Small molecule inducer (µM)

Gene Regulation Applied to Cell Therapy: CAR-T Proof of Concept

MEIRAGTx

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (ophthalmology)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
- Anti-HER2

Cell Therapy

- Ribo-CAR

Therapeutic Hormones / Cytokines / Peptides

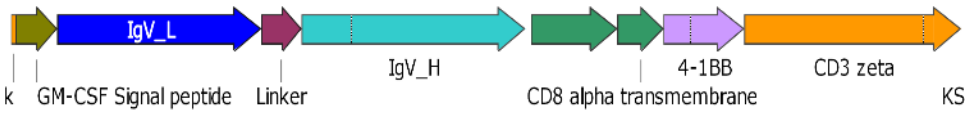
- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon etc.

Gene/RNA Editing Nucleases

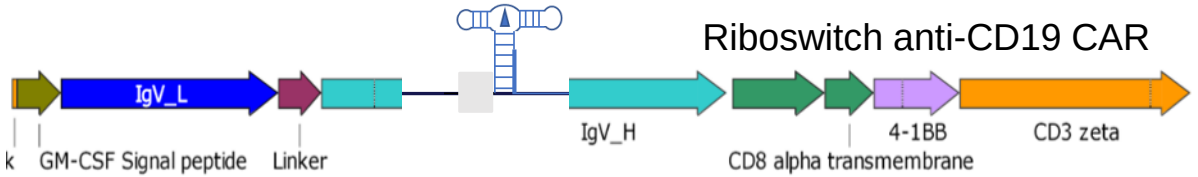
- Cas9
- CasRx

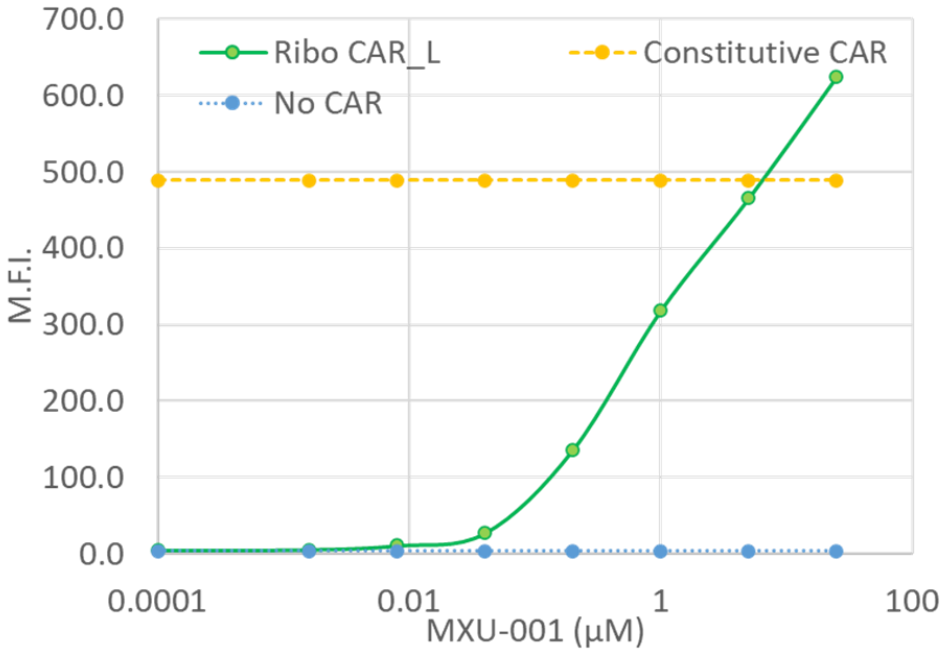
Novel MXU-001 Riboswitch Regulates Chimeric Antigen Receptor Cell Surface Expression in HEK 293 cells

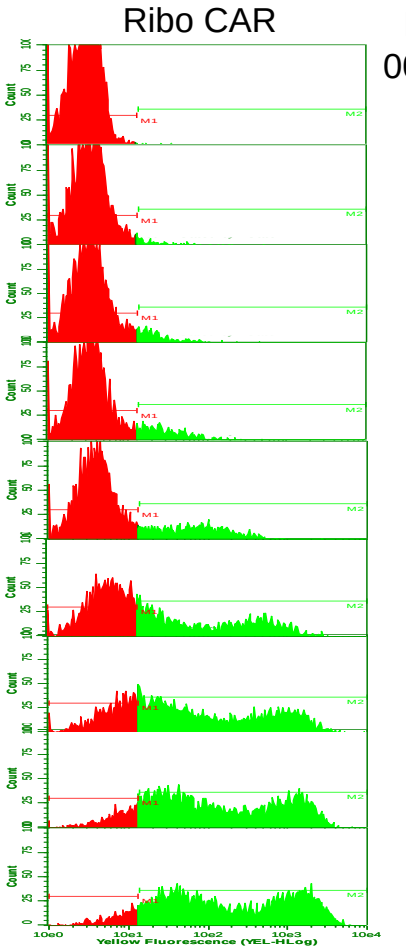
Constitutive anti-CD19 CAR



Riboswitch anti-CD19 CAR







MXU-001(µM)

mock

0

0.0016

0.008

0.04

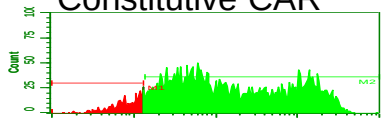
0.2

1

5

25

Constitutive CAR



- HEK 293 cells were transfected with CAR constructs
- Transfected cells were treated with MXU-001 at different doses
- HEK 293 cells were stained with anti-FMC63 antibody 48 hours after transfection
- CAR expression was measured by Flow cytometry
- **CAR expression was induced by MXU-001 in dose-dependent manner**
- **Induction of CAR expression with MXU-001 can exceed expression of constitutive CAR**

Therapeutic Genes Currently Vectorized, Optimized, and Regulated by Riboswitch Technology

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (ophthalmology)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
- Anti-HER2

Cell Therapy

- Ribo-CAR

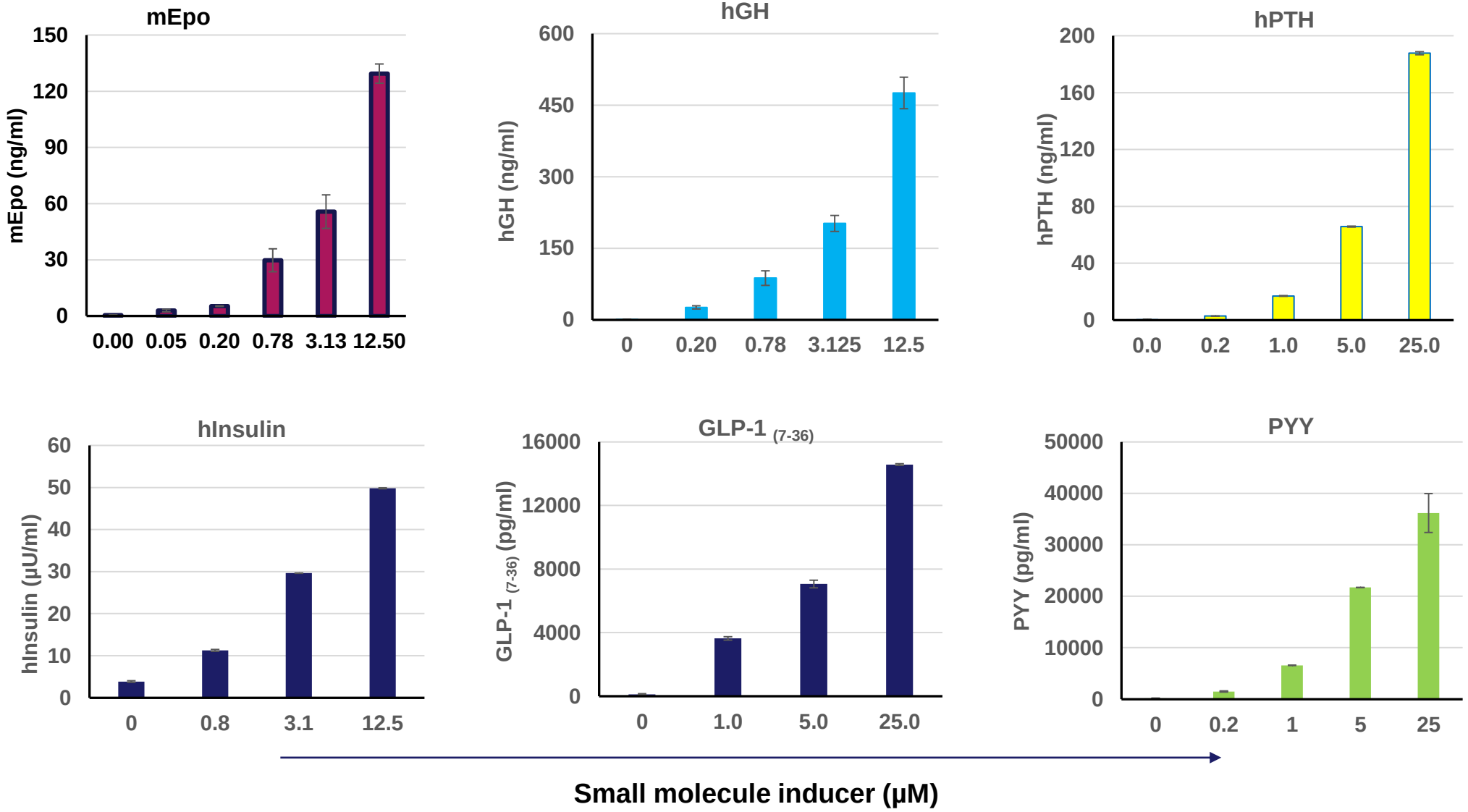
Therapeutic Hormones / Cytokines / Peptides

- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon etc.

Gene/RNA Editing Nucleases

- Cas9
- CasRx

Tight Dose Response Control of Expression of Vectorized Peptides and Hormones



Therapeutic Genes Currently Vectorized, Optimized, and Regulated by Riboswitch Technology

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (ophthalmology)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
- Anti-HER2

Cell Therapy

- Ribo-CAR

Therapeutic Hormones / Cytokines / Peptides

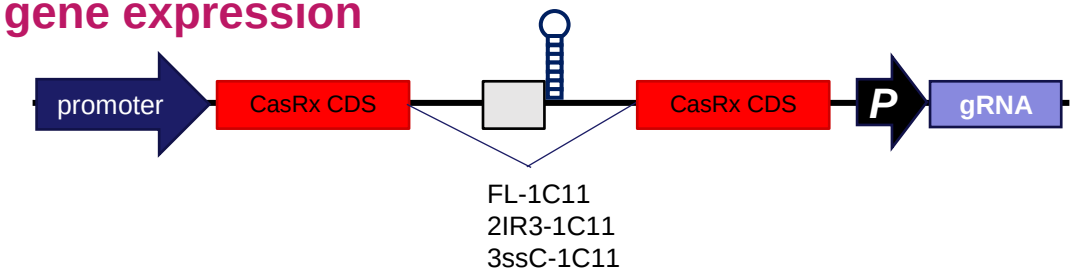
- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon etc.

Gene/RNA Editing Nucleases

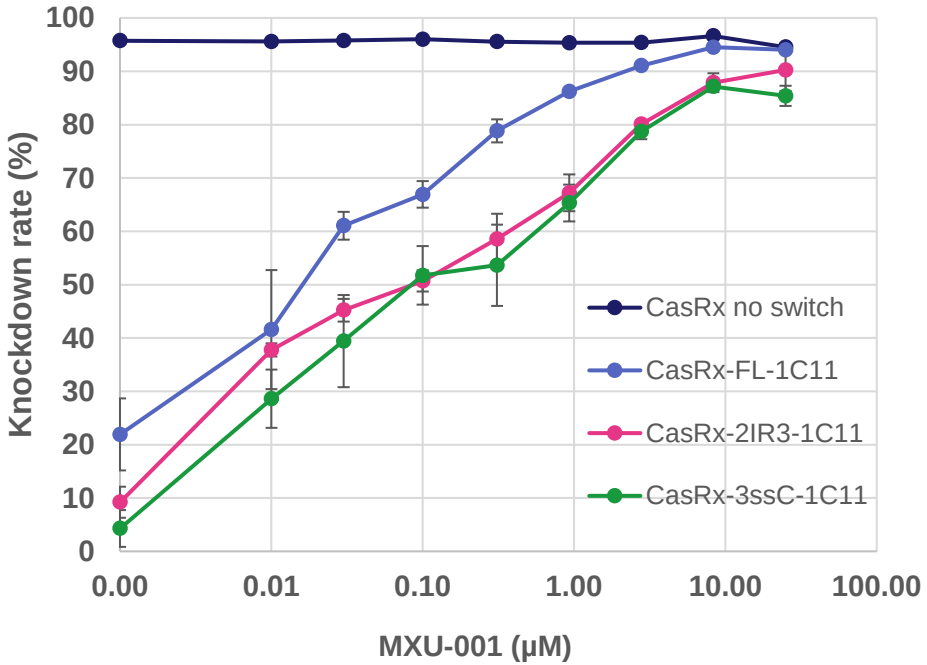
- Cas9
- CasRx

CRISPR-CasRx: Further Reduction of Basal Level of Expression with Intron Sequence Changes to Provide Unprecedented Regulation of Nucleases

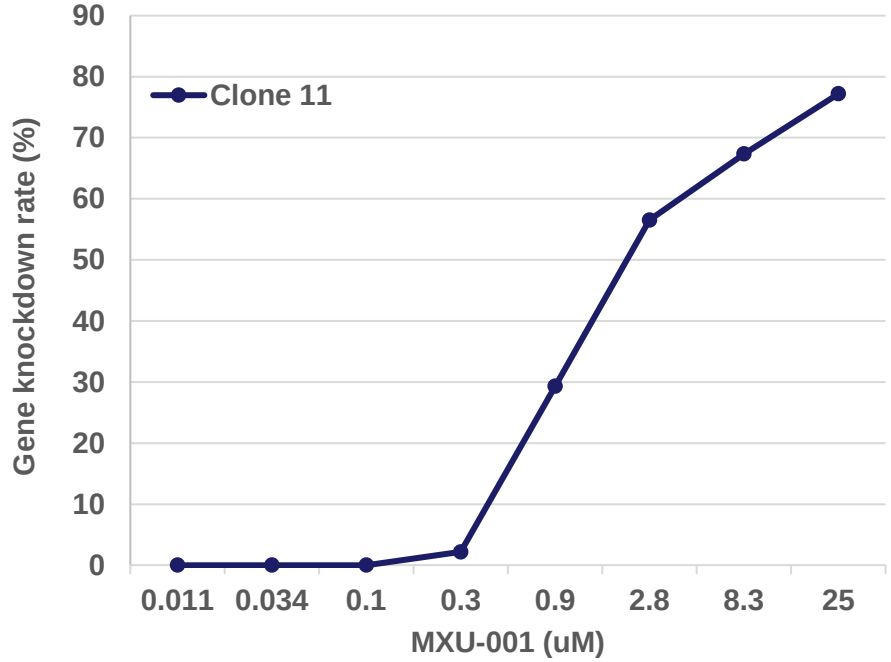
Use of intron sequence modification in the regulation cassette to achieve activation from undetectable basal level of gene expression



In transiently transfected HEK 293 cells



In stably transfected HEK 293 cells with CasRx-3ssC-1C11

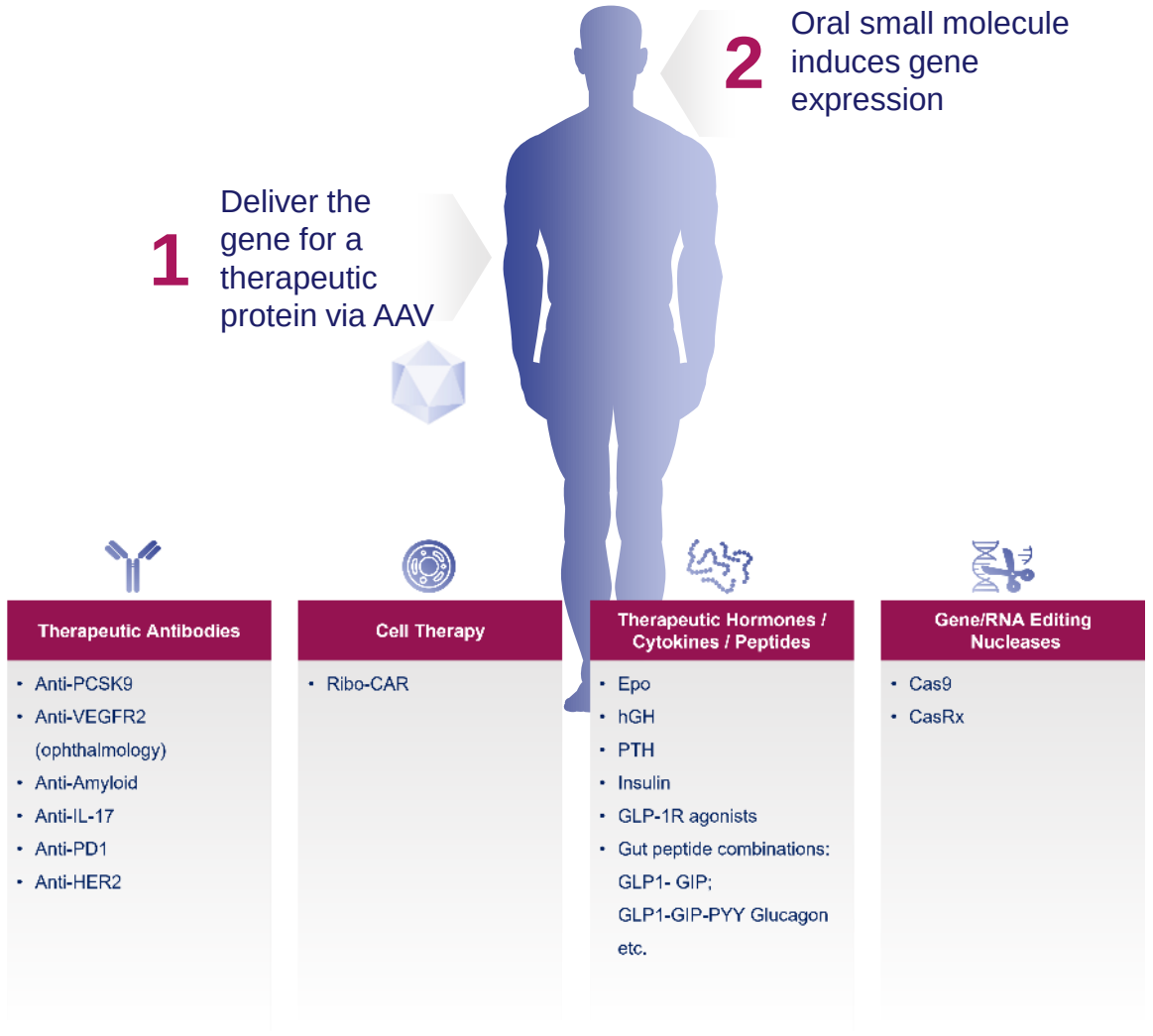


- RNA knockdown is induced by MXU-001 in dose dependent manner
- CasRx-3ssC-1C11 has the lowest basal activity of CasRx
- Zero basal activity of CasRx in cells stably expressing the CasRx-3ssC-1C11 in the absence of inducer (right side graph)

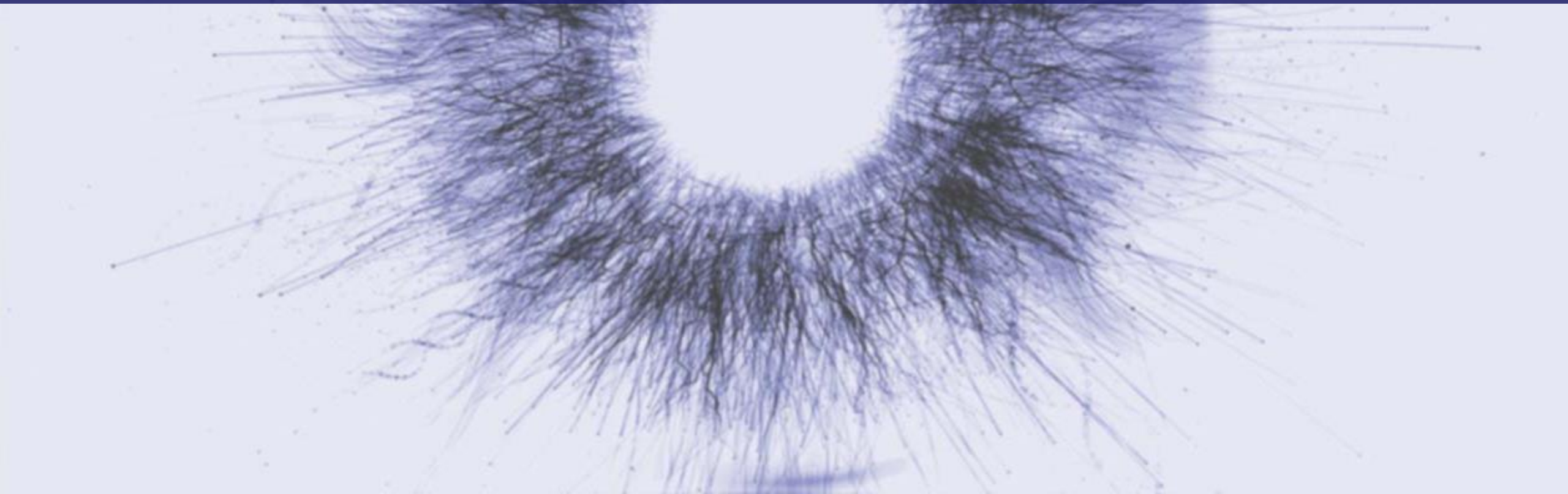
Summary

Riboswitch technology enables, for the first time, precise control of cell & gene therapies using orally-dosed inducers

- Precise dose-responsive control of genetic medicine levels by novel small molecules
- Can be coupled with any promoter - maintaining important cell-specificity and potency
- Can be applied to any transgene and any vector – for use in gene therapy, cell therapy, and gene editing
- Libraries of small molecules specifically designed to match synthetic aptamers, with different drug properties
- Genes regulated with intron splicing cassettes generally can express at levels higher than the unregulated transgene
- Regulated expression compared to constitutively expressed target gene may improve activity and potency of the gene



Ocular Pipeline



Industry-Leading Toolkit for Ophthalmology Gene Therapy

Ophthalmology Toolkit:

- Retinal organoid technology
- Increased Potency
  - Promoter engineering - enhanced potency and activity – strong cell specific and ubiquitous promoters from MeiraGTx promoter discovery platform
  - Regulatory elements, enhancers, introns, polyA and ITR
  - Kozak and Codon optimization
- Intravitreal delivery: Capsid selection
  - Proprietary intravitreal capsids in NHP head-to-head testing
  - Ongoing NHP directed evolution screen for capsids for different parts of the eye
- Reduced immunogenicity
  - Design elements to reduce innate immune response
  - Codon Optimization
  - Manufacturing: potential alternative to plasmid DNA - linear DNA, mini-circles
  - Multiple study experience to optimize steroid regimen
- Suprachoroidal Delivery**:** 3 devices in development

Large ophthalmology indications in development:

- Wet AMD – two novel potent mechanisms
- Dry AMD – transformative rod-to-cone technology
- Glaucoma
- Uveitis

Strategic Collaboration with Janssen in the IRD Space

MEIRAGTx

MEIRAGTx

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Clinical Development

- Janssen and MeiraGTx collaborate to advance botaretigene sparoparvovec*, AAV-CNGB3, AAV-CNGA3 through clinical development
- Janssen responsible for 100% of costs

Janssen Commercial Infrastructure

- Janssen has worldwide exclusive commercial rights to botaretigene sparoparvovec*, AAV-CNGB3, AAV-CNGA3 and specific future IRD programs
- IRD portfolio benefits from worldwide reach of Janssen commercial infrastructure
- MeiraGTx receives 20% untiered royalty
- MeriaGTx is the commercial manufacturer for IRD products

Pre-Clinical IRD Research

- Collaboration leverages MeiraGTx vector engineering technologies to develop gene therapy treatments for multiple IRDs
- Janssen can opt-in to receive exclusive rights to develop & commercialize programs from research collaboration
- Janssen pays majority of research costs, and pays 100% development costs after opt-in. MGTx receives milestones and high teens untiered royalty

Manufacturing and Process Development

- Janssen accesses MeiraGTx advanced manufacturing capabilities with clinical & commercial supply agreements
- Joint development of AAV manufacturing technologies to expedite and optimize development
- MeiraGTx commercial manufacturing for Janssen-partnered IRD programs

MeiraGTx retains global rights to all non-inherited ocular programs
e.g., Wet AMD, Dry AMD, Glaucoma, Uveitis

* Formerly referred to as AAV-RPGR

AAV-RPGR: Gene Therapy for Treatment of X-Linked Retinitis Pigmentosa: Pivotal Phase 3 Study Lumeos ongoing

Disease Overview

Retinitis Pigmentosa (RP)

- A group of IRDs which represents the most common genetic cause of blindness
- X-linked RP is the most severe form of RP and accounts for 10-15% of RP patients

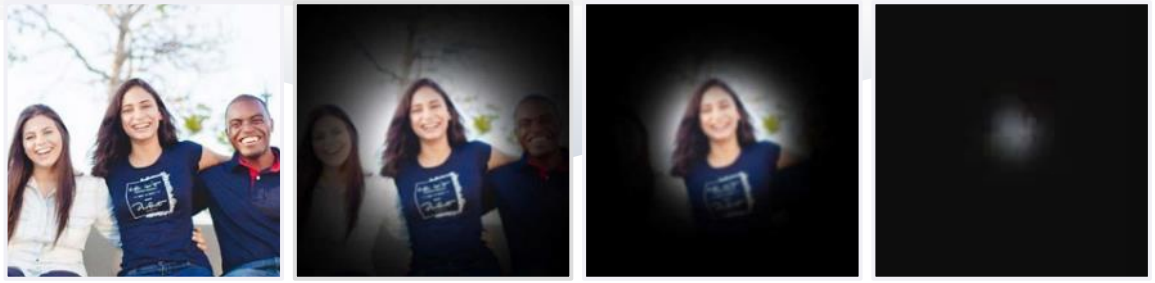
Disease progression

- Loss of night vision
- Progressing into tunnel vision
- Blindness in 4th decade

Prevalence

- ~1/40,000
- Total patients in US, EU5, Japan: ~20,000

Patient Experience:



Product: Botaretigene sparoparvovec | Stage: Clinical

Developed to deliver stable transgene sequence to rod and cone photoreceptors, driving expression of a functional RPGR protein, resulting in rescue of photoreceptor function and consequently improving vision

Optimized RPGR ORF15 transgene

Selective deletion in highly repetitive purine-rich region of RPGR ORF15 stabilizes the transgene, resulting in expression of functional protein with correct photoreceptor localization

AAV5 capsid

Efficiently delivers vector genome to both rods and cones

Human rhodopsin kinase promoter (hRKp)

Photoreceptor-specific promoter restricts expression of transgene to photoreceptor cells

Summary: 12-Month Dose Escalation Data from Ongoing Phase 1/2 Study of AAV-RPGR in Patients with XLRP

Significant vision improvement sustained 12 months after treatment

- Meaningful improvement from baseline in retinal sensitivity across multiple metrics and modalities in low and intermediate dose cohorts
- Meaningful improvement from baseline in vision-guided mobility in low and intermediate dose cohorts (mobility testing undertaken at 9-month timepoint)
- Statistically significant improvements from baseline compared to untreated eyes in low and intermediate dose cohorts

AAV-RPGR was generally well tolerated, with a favorable safety profile

- Most AEs were ocular, anticipated due to the surgical procedure, transient and resolved without intervention

» **For full details + data presented on XLRP at the 2022 American Academy of Ophthalmology, click here**

Ph1/2 AAV5-RPGR (Botaretigene Sparoparvovec) Gene Therapy Trial in RPGR-associated X-linked Retinitis Pigmentosa (XLRP).

lumeos XLRP study

Phase 3 Lumeos study ongoing and enrolling

MEIRAGTx

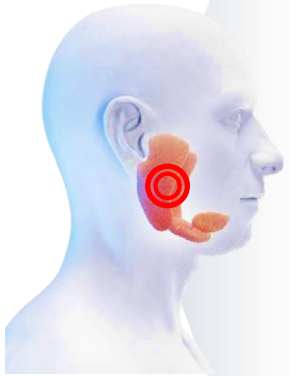
Salivary Gland Pipeline:

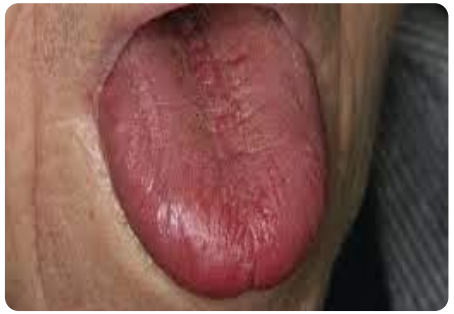
AAV-hAQP1 Gene Therapy for Treatment of Radiation-Induced Xerostomia (RIX)

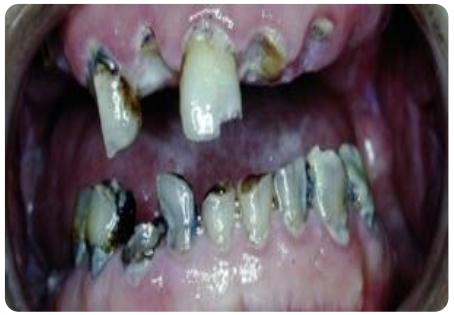
Radiation-Induced Xerostomia: An Irreversible and Severely Debilitating Condition

Disease Overview

- Radiation-Induced Xerostomia (RIX) is one of the most frequent complications of radiation therapy for head and neck cancer
- 85% of radiation-treated patients experience reduced saliva production, of whom 40% have persistent Grade 2/3 RIX. Estimated over 170,000 patients in the US.
- Persistent Grade 2/3 (moderate to severe) RIX is an irreversible and severely debilitating condition.







Patients experience severe symptoms as a result of reduced saliva:

- ❑ Difficulty eating, chewing, and swallowing
- ❑ Difficulty speaking / speech abnormalities
- ❑ Uncontrollable dental caries with severe tooth decay and periodontal disease
- ❑ Inability to wear dentures
- ❑ Oral pain and throat pain
- ❑ Harmful changes in oral flora
- ❑ Burning mouth sensation in 40% of patients

There Are No Effective Treatment Options for Grade 2/3 RIX

Standard of Care for RIX:

1. **Lifestyle changes:** e.g., water consumption, gum chewing. Provide limited benefit, particularly for Grade 2/3 RIX patients.
2. **Topical agents:** e.g., artificial saliva - provide short-term benefit and are disliked by patients
3. **Oral medication:** 75% of grade 2 & 3 RIX patients are treated with sialogogues to increase saliva flow (pilocarpine or cevimeline) however efficacy is limited and these are poorly tolerated.
   - Do not improve salivary gland function
   - Majority of patients experience side effects, including flushing, upset stomach, and sweating (20% experience grade 3/4 SAE)
   - Require chronic, frequent dosing (x3 times daily) with limited efficacy
   - Contraindicated in a variety of conditions

- No effective treatment options available
- Current therapies provide limited efficacy and poor tolerability with only partial symptomatic relief
- ~83% of grade 2 & 3 patients do not respond or do not tolerate currently available treatments
- **AAV-hAQP1 has the potential to provide meaningful benefit in symptoms of moderate to severe RIX and to be the first disease-modifying therapy for RIX**

Large Patient Population with Significant Unmet Need

Large indication with no effective treatments:

- There are currently >170,000 long term (i.e. 2 years post radiation treatment) grade 2/3 RIX patients in the US alone[1,2,3]
- 54,000 new cases of head and neck cancer per year in the US with >15,000 new persistent grade 2/3 RIX patients each year[1,2,3]
- Patients are in the healthcare system in remission for head and neck cancer and seeing physicians at least annually
- Low dose, low cost of goods, large market for gene therapy
- Opportunities for label extension beyond grade 2/3 RIX – e.g., Sjögren's syndrome

Prevalence (US)

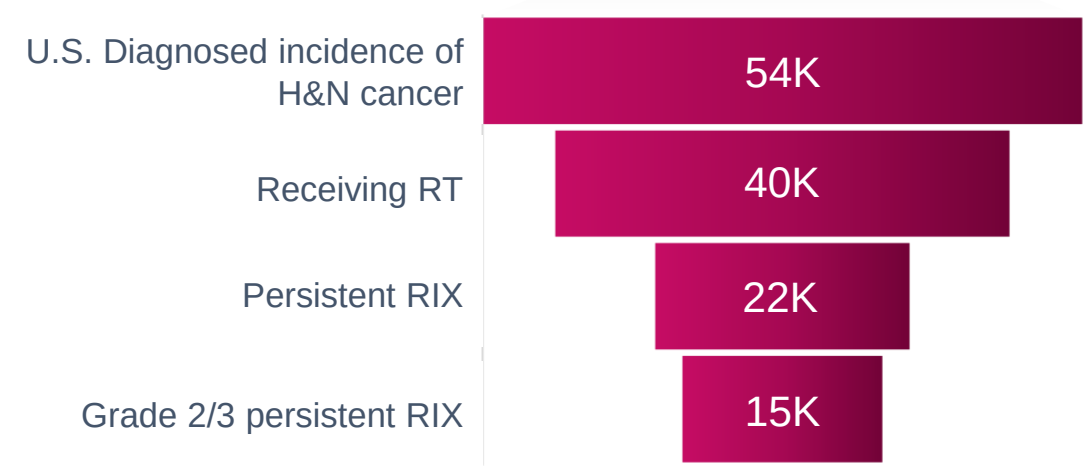
170K

Grade 2/3 RIX patients in the US

Incidence (US)

15K

New cases of grade 2/3 RIX annually in the US

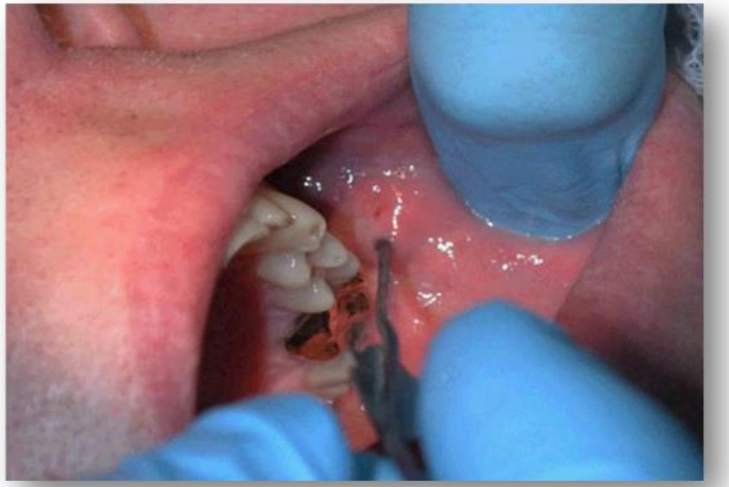


[1] SEER, Cancer.net
[2] Marta GN et al (2014). Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol. 110(1):9-15
[3] Jensen S.B., et al. (2010). A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer. 18(8):1039-1060

AAV-hAQP1 Approach: A One-time, Outpatient Treatment with Disease-Modifying Potential

Therapeutic Approach

- AAV-hAQP1 introduces the human aquaporin 1 gene (hAQP1) directly to salivary gland cells, rendering them permeable to water and increasing saliva output
- AQP1 forms a channel that increases the permeability of the salivary gland epithelium, permitting water to flow into the intra-ductal space
- AAV-hAQP1 is a one-time treatment with the potential to restore salivary function in patients with intractable RIX



AAV-hAQP1 is delivered locally to the parotid gland in a minimally invasive, brief, one-time outpatient procedure

» **Outpatient treatment** | Simple, minimally invasive procedure, with no need for anesthesia. ENTs and many dentists/oral surgeons already trained in this procedure

» **Local administration, small volume** | avoiding potential safety risks associated with high dose / systemic exposure of AAV

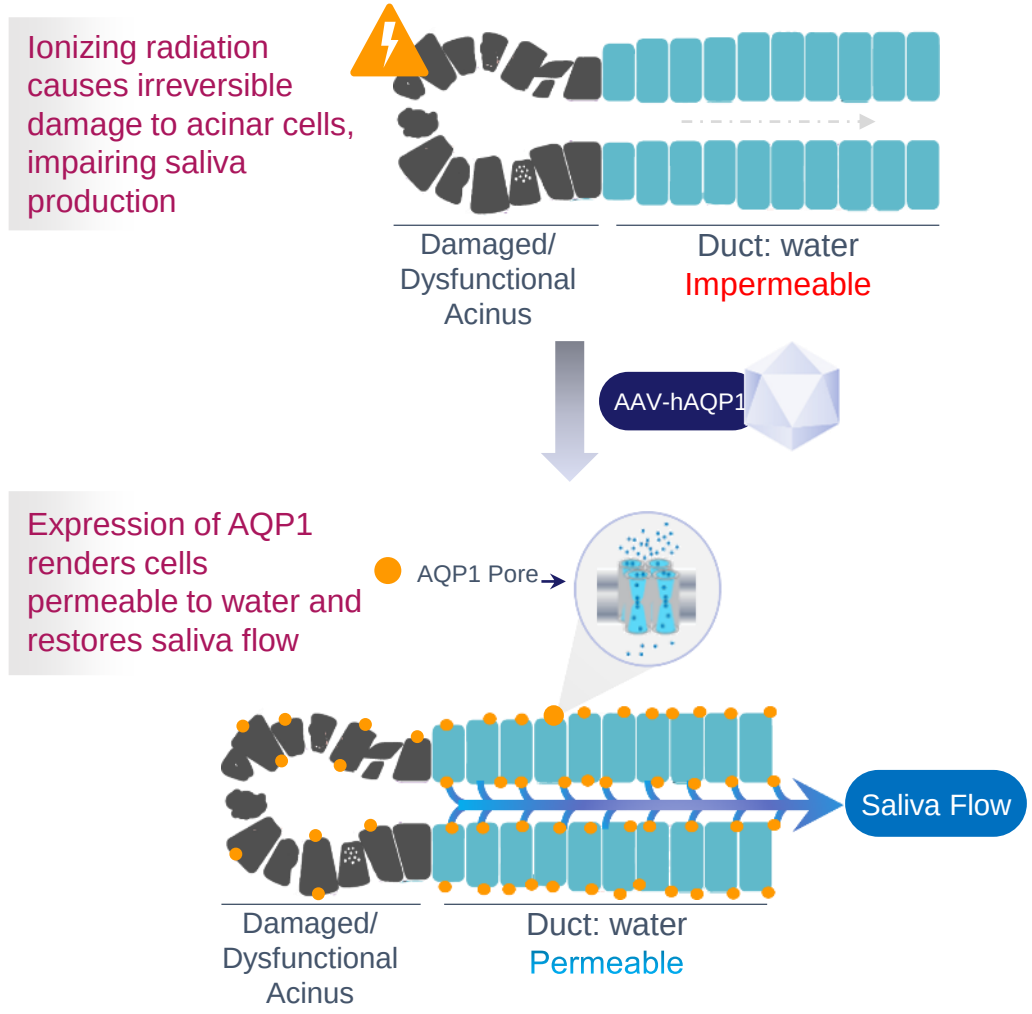
» **One-time therapy** | Well tolerated by patients, with durable efficacy

» **Disease Modifying** | Results in durable change in gland physiology and function – allowing water to flow through otherwise damaged impermeable glands

AAV-hAQP1: Mechanism of Action

Proposed Mechanism of Action:

- In normal salivary glands, water flows through polarized water channels located in the basal membrane of acinar cells into the lumen of the salivary duct
- Acinar cells are particularly vulnerable to Ionizing radiation used to treat head and neck cancer. Acinar cell death and disorganization of the polar monolayer due to IR treatment can result in chronic inability to produce saliva
- Expression of the water channel, Aquaporin 1 (hAQP1), via viral vector delivery into the salivary gland duct, renders duct cells and surviving acinar cells permeable to water
- **AQP1 allows water to flow into the salivary duct and out to the oral cavity to moisten the mouth**



Salivary Hypofunction and Xerostomia

- **Hyposalivation: Objective measure** of saliva production – assessed by collecting absolute whole saliva volume produced over time
- **Xerostomia: Subjective feeling** of dry mouth – assessed using patient reported outcome measures (PROs)
- Relationship between Xerostomia and Saliva Production:
  - Xerostomia symptoms are associated with reduction in saliva production
  - Xerostomia severity (or PRO score) is not directly correlated with an absolute volume of saliva production
- Both objective (salivary flow rate), and subjective (patient-reported) measures were assessed in the MeiraGTx phase 1 study

Key PRO endpoints in Xerostomia:

Global Rate of Change Questionnaire (GRCQ)

- Patients are asked if there is a change in their symptom of Dry Mouth
- They may reply, “Better”, “Worse”, or “About the Same”
- If patients reply “Better” or “Worse”, they are asked to quantify the change on a 7-point scale with the maximum score of 7 and ”a very important change” and 1 being the minimum
- A 2-point change is “large enough to be important” to the patient
- Anything 3 points or greater is considered a substantial improvement over standard of care and “transformative” by KOLs

Xerostomia Questionnaire (XQ)

- 8 symptom-specific questions wherein the patient rates each symptom from 0 (not present) to 10 (worst possible)
- Responses are summed (0-80), providing an overall measure of disease burden
- An improvement (decrease) of 8 points (or 10%) or more is considered clinically meaningful
- A decrease in score of 10 or greater is considered a substantial improvement over standard of care and “transformative” by KOLs

MGT016 AQUAx Phase 1 Study Design

Study Design

- Open label, multi-center, dose escalation study (4 sites in the US and Canada)
- One-time administration of AAV-hAQP1 to one (unilateral) or both (bilateral) parotid glands
- Four dose escalating cohorts with 3 participants per cohort (n=12 for unilaterally treated and n=12 for bilaterally treated)
- All participants are followed for 1-year post-treatment and then enrolled in long-term follow-up study for a total of 5 years

Primary Endpoint

- Safety

Secondary Endpoints

- Patient reported measures of xerostomia symptoms:
  - Global Rate of Change Questionnaire (GRCQ)
  - Xerostomia Questionnaire (XQ)
- Whole saliva flow rate

Cohort	Dose
Single gland injection	
1	1×10^{11} vg/gland
2	3×10^{11} vg/gland
3	1×10^{12} vg/gland
4	3×10^{12} vg/gland
Bilateral gland injection	
1b	3×10^{10} vg/gland
2b	1×10^{11} vg/gland
3b	3×10^{11} vg/gland
4b	1×10^{12} vg/gland

MGT016 AQUAx Phase 1 Study Overview

Study Status:

- Enrollment completed in the four unilateral treated cohorts (n=12). Data is available out to 12 months post-treatment.
- Enrollment completed in the four bilateral treated cohorts (n=12). Data is available out to 6 months post-treatment (12-month data for full bilateral cohort will be available by end of Q1/2023).

Safety Summary:

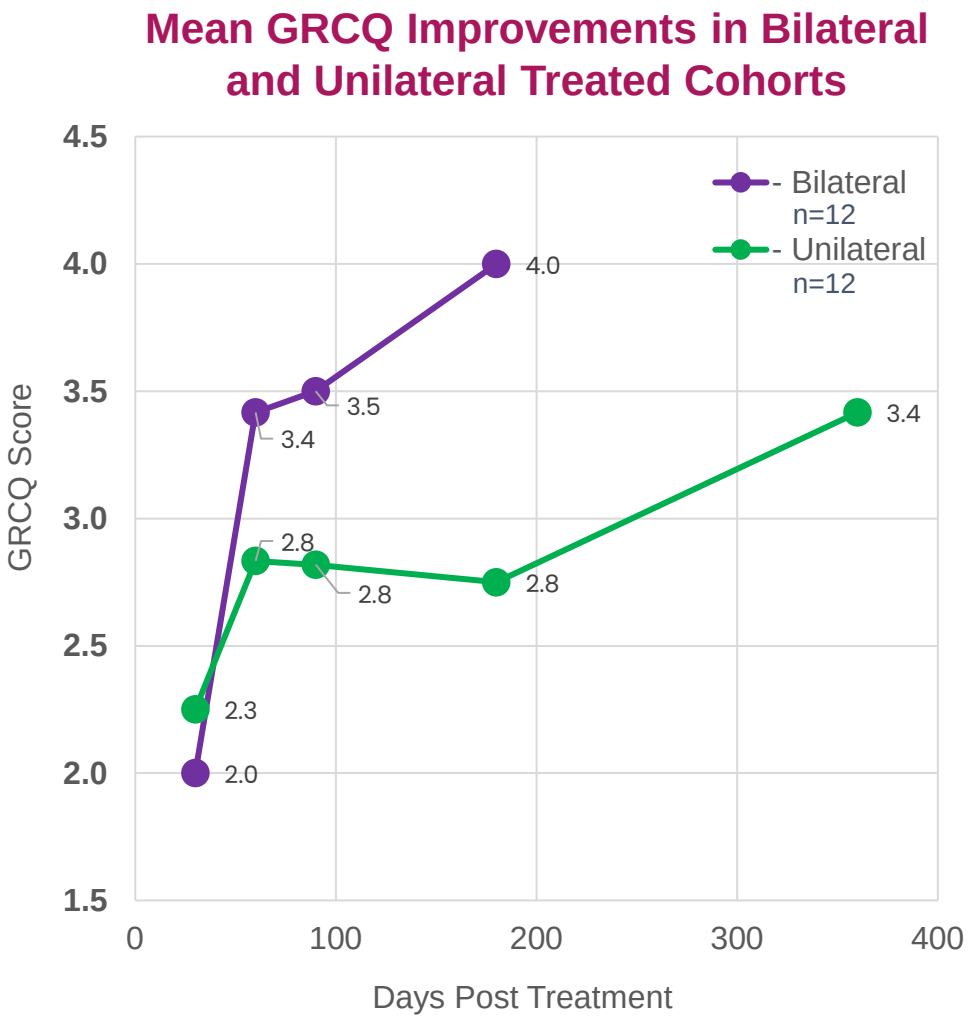
- AAV-hAQP1 treatment was safe and well tolerated at each dose tested
- No dose-limiting toxicities or drug-related serious adverse events

Efficacy Findings:

- Improvements observed in both of the patient reported assessments of xerostomia symptoms, GRCQ and XQ, in both unilaterally and bilaterally treated cohorts at 12- and 6-months post treatment, respectively
- Improvements in salivary flow were seen in both the unilateral as well as bilateral cohorts
- To date (December 2022) - durability was seen in the 3 participants reaching 2 years post treatment and the 1 participant reaching 3 years

Click here for MeiraGTx's December 2022 Clinical Update Presentation from the Phase 1 AQUAx Trial

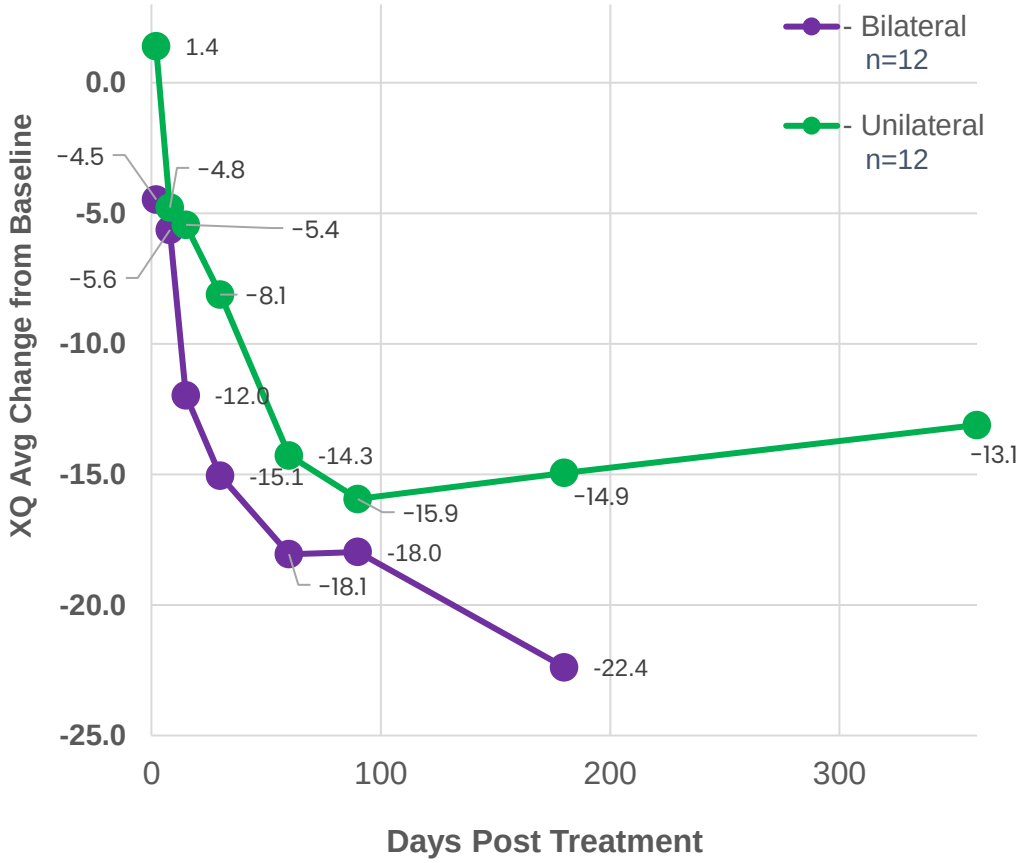
Clinically-Meaningful Improvements in Xerostomia Global Rate of Change Questionnaire (GRCQ)



- For all treated participants including bilateral and unilateral (n=24), 18/24 or 75% reported dry mouth as 'better' with a clinically meaningful score of 2 or more. Greater average improvement was reported by participants treated bilaterally compared to those treated unilaterally.
- 8/12 participants in the unilateral group and 10/12 patients in the bilateral group reported improvement in symptoms of dry mouth at 6- and 12-months, respectively. No participant reported worsening of xerostomia symptoms.
- 4 participants in the unilateral group and 3 participants in the bilateral group rated the change in xerostomia symptoms as "very important improvement" (i.e., the highest possible GRCQ score of 6 or 7).
- **Durable effect**: in the unilateral group, improvements in xerostomia symptoms were maintained in 3 patients who reached the 2-year assessment point; 1 participant reached the 3-year assessment and the maximum score of 7 was maintained.

Xerostomia Questionnaire (XQ): Clinically Meaningful Improvements in Both Unilateral and Bilateral Groups

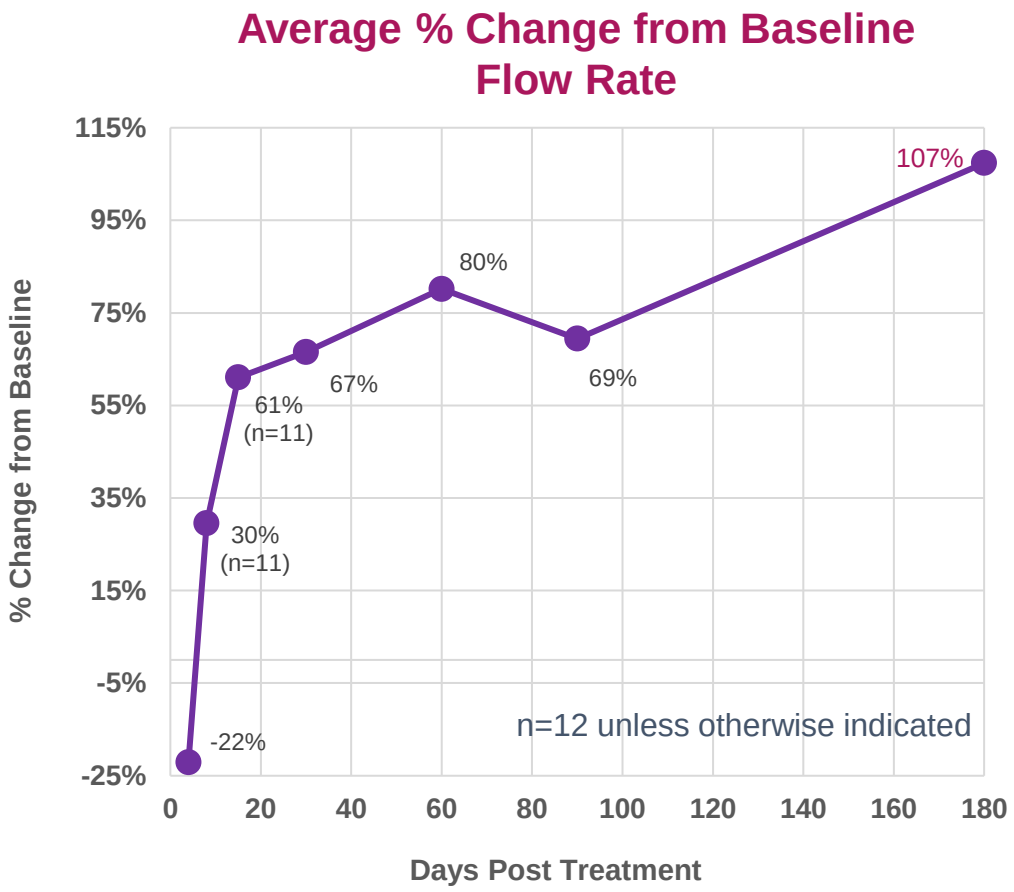
XQ improvements in Bilateral and Unilateral Treated Cohorts



- In the Xerostomia Questionnaire (XQ), a decrease of ≥8 points is considered clinically meaningful, whereas a decrease of ≥10 is considered a substantial improvement over standard of care and "transformative" by KOLs
- In both treatment groups, XQ scores improved (declined) >8 points soon after treatment, and >10 points within ~2 months after treatment
- Unilateral patient group: 13-point average improvement from baseline at 12 months
- Bilateral patient group: 22-point average improvement from baseline at 6 months
- As seen with GRCQ, the degree of improvement was greater in bilateral compared to unilateral treated cohorts

» The level of benefit reported by patients based on the XQ scale is considered transformative by KOLs

Normalization of Unstimulated Whole Saliva Production Rate Following AAV-hAQP1 Treatment



- Meaningful increase in unstimulated whole salivary flow was seen in bilateral treated patients (whole unstimulated saliva samples were not collected from unilateral patients)
- The mean % change from baseline was >100% at 6 months. This is clinically meaningful as a 50% reduction in whole saliva volume is associated with xerostomia symptoms.
- The overall unstimulated whole saliva flow rate improved to an average of 0.4 mL/min which is within the normal range for unstimulated whole saliva production - which is 0.3-0.4 mL/min.
- If flow rate of unstimulated saliva is below <0.1-0.2mL/min, then salivary hypofunction is generally diagnosed with associated xerostomia[1].
- Based on both absolute unstimulated whole saliva change as well as the overall % change from baseline – the improvement in unstimulated salivary flow in bilaterally-treated participants is of clinically meaningful size.

[1]Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies: ISOO/MASCC/ASCO Guideline; Mercadante et al; *Journal of Clinical Oncology* 39, no. 25 (September 01,2021) 2825-2843

Summary of Clinical Data: Improvements in Two Xerostomia PROs and Increase in Saliva Production Following AAV-hAQP1 Treatment

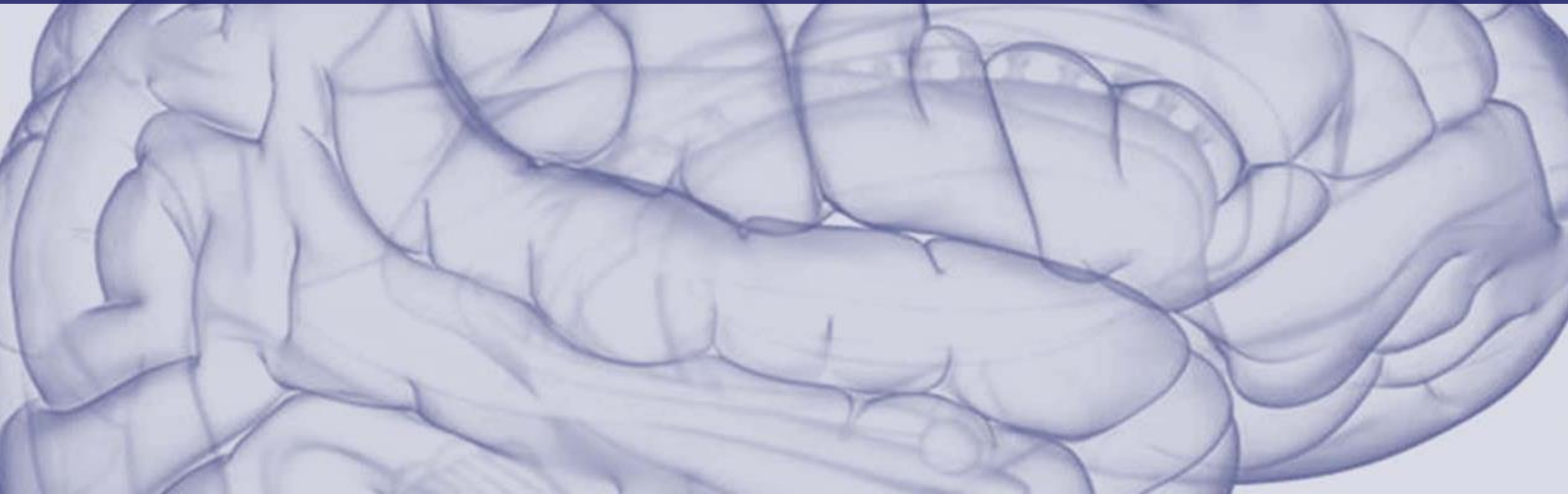
Summary of Clinical Data:

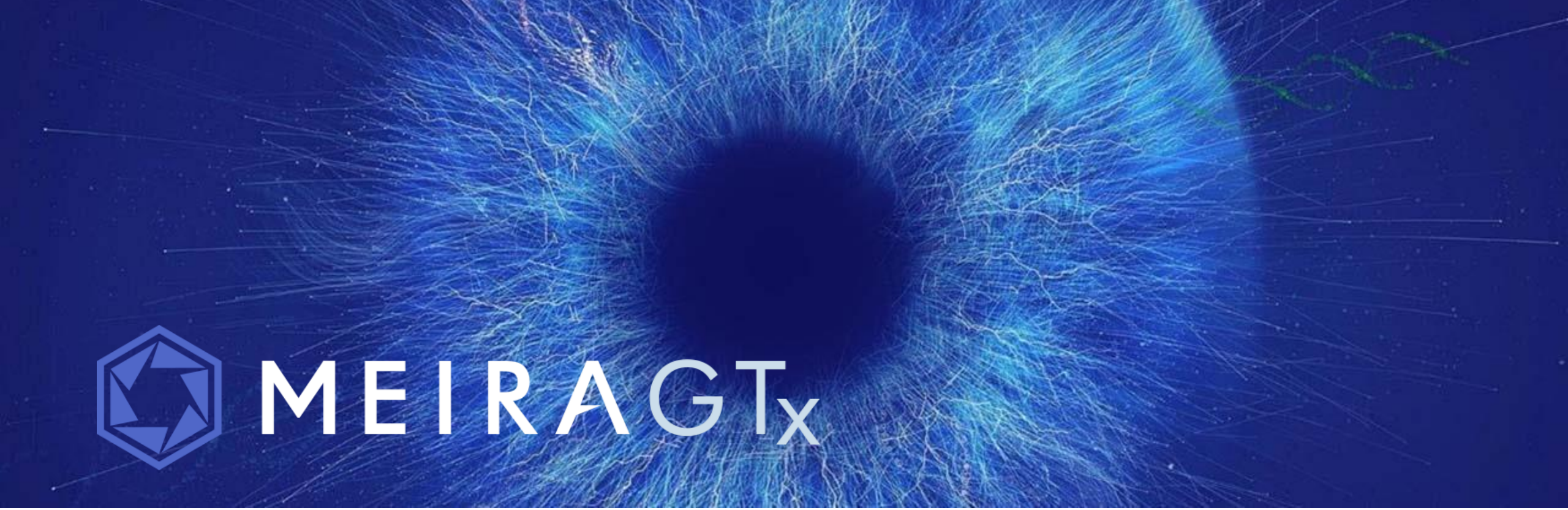
- Meaningful improvements in xerostomia symptoms were reported by participants across both unilateral and bilateral treatment cohorts
- 75% of all participants treated with AAV-hAQP1 (18/24) reported improvement in xerostomia symptoms that they considered important on the Global Rate of Change Questionnaire (GRCQ)
- Using the Xerostomia Questionnaire (XQ), 71% (17/24) reported an improvement of >8 points (clinically meaningful), and 67% (16/24) had an improvement of ≥10 (considered transformative by KOLs)
- Mean unstimulated whole saliva flow rate in bilaterally-treated patients improved >100% vs. baseline at 6 months, providing an objective efficacy measure
- Across assessments, greater improvements were observed in bilaterally treated participants compared to those treated unilaterally
- Interim long-term follow-up data show durable efficacy after 2+ years of follow up; salivary gland cells are very slowly dividing, supporting the potential for one-time therapy

AAV-hAQP1 Program HIGHLIGHTS

- ✓ **AAV-hAQP1 has the potential to become the standard of care for long-term, grade 2/3 radiation-induced xerostomia patients based on its disease-modifying mechanism and meaningful improvements in both objective and subjective outcome measures.**
- ✓ **One-time, minimally-invasive delivery of a single, small, and local dose. Expected to provide durable long-term benefit in this large population of severely affected patients with no other effective current treatment options.**
- » AAV-hAQP1 is a one-time, minimally invasive treatment delivered through an outpatient cannulation procedure that ENTs and dentists trained in oral medicine are familiar with
- » AAV-hAQP1 treatment for grade 2/3 xerostomia is a large commercial opportunity given the high unmet need, large prevalent/incidence patient population – with no effective therapies and no other known disease-modifying treatments in the clinic
- » AAV-hAQP1 uses a small locally delivered dose, with low associated COGS - providing flexibility to support a range of sustainable price points for patients and payors
- » Additional data from the AQUAx study can be found here
- » A phase 2, randomized, double-blind, placebo-controlled study is planned to initiate 1H 2023

Neuroscience Pipeline





AAV-GAD: A First-in-Class Gene Therapy for Treatment of Parkinson's Disease

AAV-GAD Program HIGHLIGHTS

AAV-GAD is the only gene or cell therapy:

- To meet primary efficacy endpoint in a randomized, blinded multi-center Phase 2 trial compared to sham
- With an imaging biomarker supporting efficacy which correlates with clinical outcome
- With a routine and brief surgical procedure that requires minimal OR time and no general anesthesia
- Improvement in off-medication clinical ratings, ON time without dyskinesia and complications of medical therapy and without declines in neuropsychological function or speech
- Consistency in clinical outcomes and imaging results between phase 1 and phase 2

AAV-GAD could be accessible to more patients than current standard of care:

- Non-dopaminergic strategy: potentially applicable to large patient population not adequately treated with currently available therapies
- Unlike DBS, AAV-GAD does not require specialized post-op care or in-dwelling hardware

Status

- Clinical bridging study ongoing with material manufactured at MeiraGTx using an optimized commercial process. Randomized sham-controlled study with 2 doses. Completion of enrollment anticipated in 2H 2023
- Global regulatory interactions around pivotal design ongoing – with potential global pivotal study in 2024

Parkinson’s Disease

Disease Overview

- Parkinson’s Disease (PD) is a progressive neurodegenerative disease characterized by degeneration of dopaminergic neurons involved in motor control
- PD primarily manifests as a movement disorder, with cardinal features being tremor, bradykinesia and rigidity
- Current treatments may have benefit for several years; however, the majority of patients suffer loss of efficacy, increased side effects and toxicity over time, without good alternative therapeutic options.

10M
Parkinson’s patients worldwide

$52B
Estimated economic burden of PD in the US

1. Yang G. Economic Burden and Future Impact of Parkinson's Disease. Lewin Group Report (2019)

Current Standard of Care Leaves Significant Unmet Need:
Most patients become refractory to dopamine treatment, and few are eligible or willing to undergo in-dwelling deep brain stimulation (DBS)

MEIRAGTx

Increasing Severity of PD

Levodopa

1st line therapy

Combination Therapy

Dopamine agonists or enzyme inhibitors may be added on top of Levodopa

Provides symptom relief for the first 3-5 years after diagnosis

Deep Brain Stimulation (DBS) Surgery

If PD progresses or patients are refractory, surgical treatments such as DBS may be prescribed

Clinically effective in some late-stage patients

Remaining Unmet Need

- Treatment effect wears off over time, requiring increasingly higher doses and dosing frequency (up to 6-10x times daily) to control motor symptoms
- Long-term use of levodopa is associated with motor complications, including levodopa-induced dyskinesia and motor fluctuations
- ~50% of patients stop responding adequately to oral therapies within 5 years of diagnosis

- Only a fraction of those in need get DBS
- Factors limiting adoption of DBS:
  - Multiple surgeries under general anesthesia needed for complete system installation
  - Infection risk
  - Proximity to expert center and need for multiple adjustments over months to optimize therapy
  - Off-target effects of stimulation on white matter tracts cause adverse effects (ex. speech deterioration in 15% of patients)

AAV-GAD Gene Therapy for Parkinson's Disease

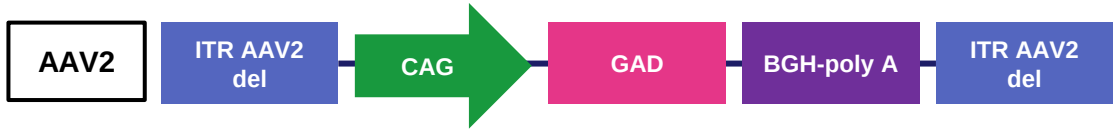
Approach

- AAV-GAD delivers a functional copy of the Glutamic Acid Decarboxylase (GAD) gene locally into the sub-thalamic nucleus (STN)
- GAD converts glutamate (excitatory neurotransmitter) to GABA (inhibitory neurotransmitter) to alleviate PD-associated hyperexcitation of the STN

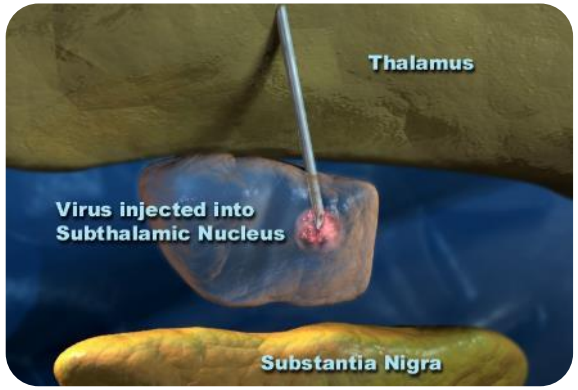
Localized delivery of AAV-GAD directly into the STN | local delivery of very small dose avoids safety risks associated with high dose/broad exposure of AAV in CNS and provides site-specific changes in neurotransmitter activity.

Standard and brief surgical procedure (same target site as DBS) | no need for general anesthesia, well-known surgical route for administration, many highly trained surgeons in this technique.

One-time therapy | does not require device implantation or frequent follow-ups for tuning stimulation - significantly lowering treatment burden and improving patient access



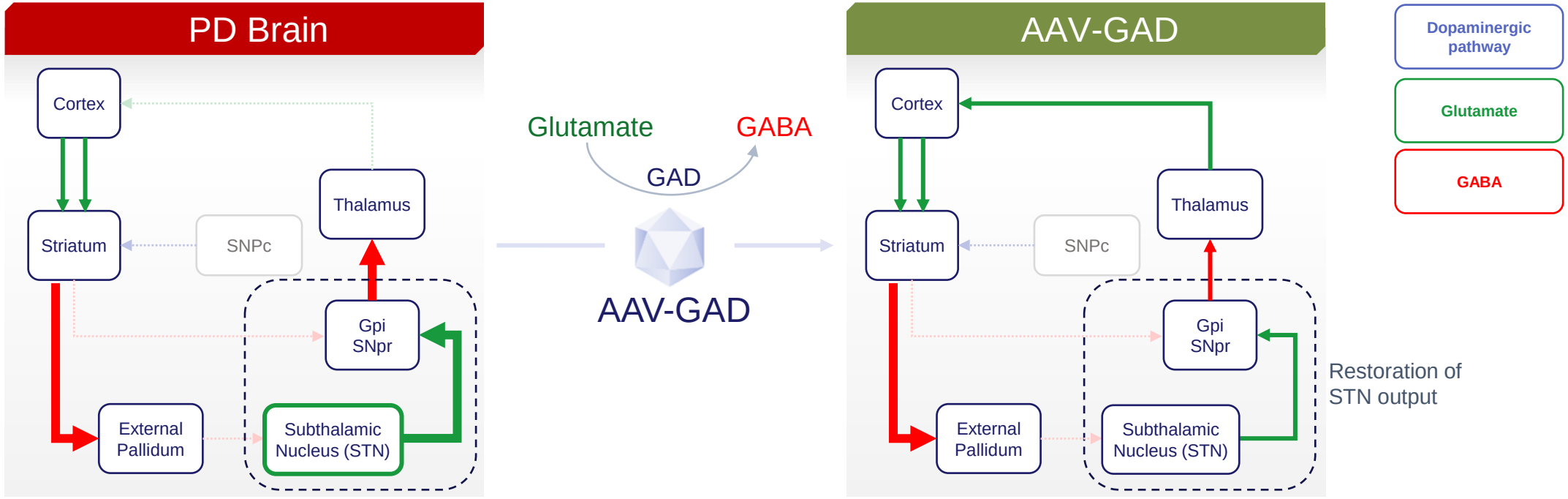
The Glutamic Acid Decarboxylase (GAD) gene is delivered locally to the STN to increase production of GABA only at the specific site that is required for alleviating PD related motor symptoms



Status:

- Positive clinical data from two controlled studies (see publications)
  - Phase 1: unilateral, dose escalation study
  - Phase 2: bilateral, sham controlled study
- Ongoing, sham controlled 'bridging' study using GMP material manufactured with commercial ready process in-house at MeiraGTx

Mechanism of Action:
Circumvents the Need for Dopamine Input to Suppress STN Hyperactivation, Resulting in Improved Motor Function



- In PD, loss of dopaminergic neurons in the substantia nigra (SNPc) results in decreased GABA input to the STN.
- As a result of decreased GABA input, the STN is hyperactivated.
- This results in uncontrolled activation of the basal ganglia output nuclei (Gpi, SNpr), which then act to continually repress the activity of the thalamus – leading to the motor symptoms of PD.

- AAV-GAD, delivered directly to the STN, results in conversion of glutamate (excitatory neurotransmitter) to GABA (inhibitory neurotransmitter) locally in the STN.
- Increased GABA and reduced glutamate output of the STN, releases the Gpi and SNpr inhibition of the thalamus, leading to restored cortical activity and improved motor function.
- **Self-limiting autoregulation:** STN neurons express $GABA_A$ receptors, which inhibit further release of GABA upon increase in extracellular GABA levels.

AAV-GAD Has The Potential to Address Major Unmet Medical Needs in PD

Current Therapies

Medical Treatment (e.g. L-Dopa)

- Treatment effect of dopaminergic therapies wears off over time, requiring increasingly higher doses and dosing frequency
- Long-term use is associated with complications such as levodopa-induced dyskinesia and motor fluctuations
- Approx. 50% of PD patients stop responding adequately to oral therapy within 5 years

Surgical Treatment - Deep Brain Stimulation (DBS)

- DBS requires multiple invasive surgeries at specialized centers
- Requires general anesthesia
- Safety concerns, such as infection, speech deterioration in 15% of patients, have further limited widespread adoption
- While most patients become refractory to dopamine treatment, few are eligible or willing to undergo in-dwelling deep brain stimulation
- Limited utilization due to these issues exacerbated for many by limited access to repeat visits at expert centers

MEIRAGTx | AAV-GAD

- ✓ One-time therapy
- ✓ The only gene therapy to meet primary efficacy endpoint in a Phase 2, randomized, controlled study
- ✓ Non-dopaminergic strategy: AAV-GAD targets the STN, bypassing dysregulated dopamine signaling - allowing treatment of patients who are not adequately controlled by L-Dopa
- ✓ Standard and brief surgical procedure without need for general anesthesia
- ✓ Does not require frequent follow-ups or device implantation
- ✓ Available to patients residing in areas far from surgical centers
- ✓ No cognition or speech AEs observed in clinical trials, likely due in part to avoiding general anesthesia and AAV-GAD restriction to STN without effect on nearby white matter tracts

Results From Phase 1, Dose Escalation Study of AAV-GAD

Study Design

Single-arm, open-label, dose escalation study of unilateral subthalamic administration of AAV-GAD in patients with PD (n=12)

Safety:

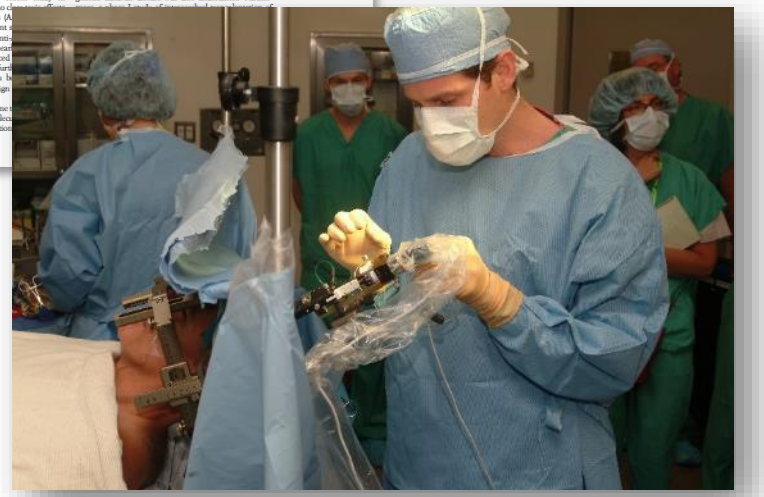
- AAV-GAD was safe and well tolerated, with no adverse events related to the gene therapy
- No abnormalities were noted on postsurgical MRIs up to 1 year
- No evidence of adverse events in the perioperative period and for at least 1 year after treatment (most patients followed up for >2 years)
- No evidence of vector-related immunity

Efficacy findings:

- Significant improvements in motor UPDRS scores, predominantly on the side of the body contralateral to surgery, were seen as early as 3 months after therapy and persisted to 12 months (latest follow-up)
- PET scans revealed a substantial improvement in thalamic metabolism that was restricted to the treated hemisphere
- Correlation found between clinical motor scores and brain metabolism in the supplementary motor area

Articles

Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial



Kaplitt MG et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet. 2007;369:2097-2105

Results From Phase 2, Randomized, Double-Blind, Sham-Controlled, Multi Center Study of AAV-GAD

Study Design

- Randomized (n=45,1:1) double-blind study of bilateral STN AAV-GAD against sham control in patients with advanced Parkinson's disease
- Primary endpoint: improved off-medication UPDRS score at 6 months

Safety:

- AAV-GAD was safe and well tolerated with no SAEs related to the therapy
- Other adverse events were mild or moderate, likely related to surgery and resolved
- Worsening of PD was reported in 35% of sham patients vs. 0% of AAV-GAD, further supporting efficacy

» AAV-GAD is the only interventional study with gene or cell therapy in PD to meet the primary clinical endpoint compared to sham control

Efficacy findings (summary):

» Study met primary endpoint: UPDRS motor score improvement vs. sham at 6 months; Improvements persisted at 12 months

» Significantly greater responder rate in AAV-GAD treated group (50%) compared with sham (14.3%)

» Improvements in secondary outcome measures, including ON time across one year (no change in sham at any time point)

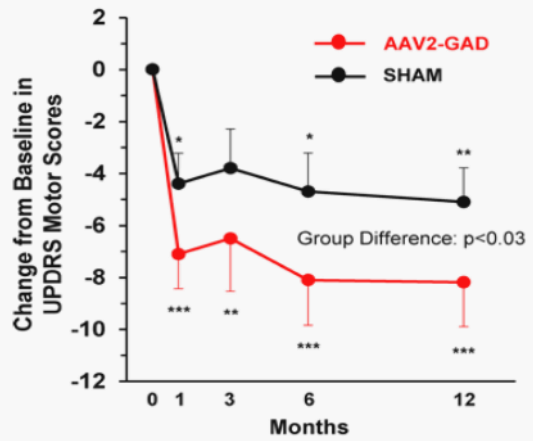
» Significant reduction in medication complications at 6 and 12 months (UPDRS 4) in AAV-GAD group (no change in sham at any point)

» Consistent with MOA, FDG-PET imaging showed significant metabolic decrease/improvement in several brain regions of AAV-GAD patients, not observed in the sham group

- *LeWitt PA. AAV2-GAD gene therapy for advanced Parkinson's Disease: a double-blind, sham-surgery controlled, randomized trial. Lancet Neurology. 2011; 10(4):309-19.*
- *Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133*

Results from Phase 2 Study: Significant Improvements Following AAV-GAD Treatment Compared to Sham Control

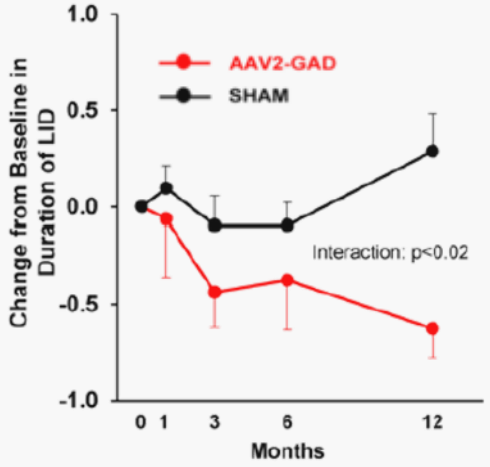
Significant improvements in UPDRS motor scores



*p < 0.05, **P < 0.01, ***p <0.001

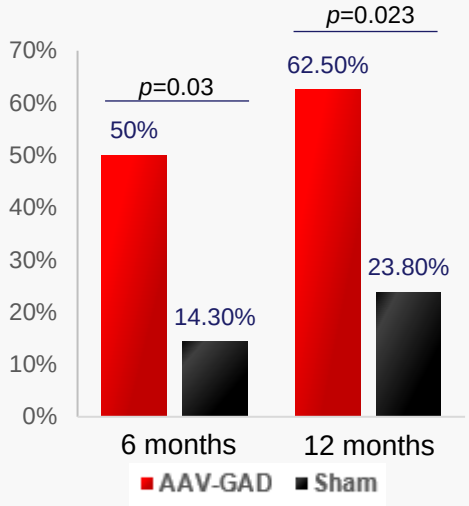
- Met primary outcome measure: improvement in UPDRS 3 motor scores vs. sham at 6 months
- Improvements in the AAV-GAD group were observed at all time points

Reduction in duration of levodopa-induced dyskinesia



- Significant improvement in drug-induced dyskinesia at 12 months relative to baseline in the AAV-GAD group (vs. no change in the sham group)

Significantly greater responder rate (≥9 points UPDRS)



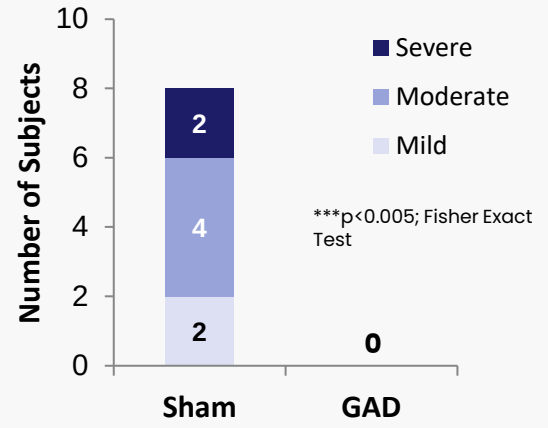
- Significantly greater responder rate in the AAV-GAD group vs. sham group at 6 and 12 months

- *LeWitt PA. AAV2-GAD gene therapy for advanced Parkinson's Disease: a double-blind, sham-surgery controlled, randomized trial. Lancet Neurology. 2011; 10(4):309-19.*
- *Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133*

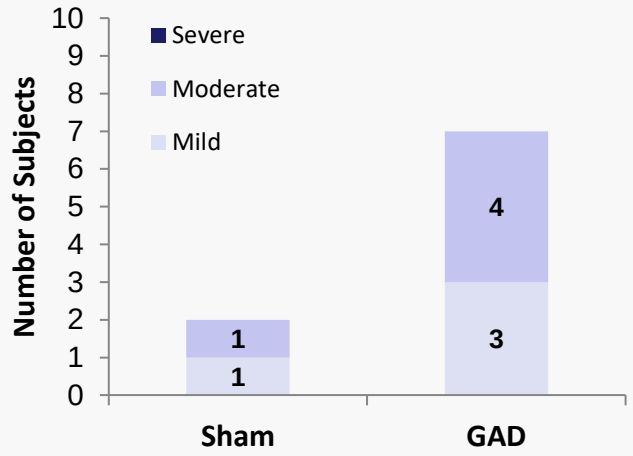
Treatment Very Well Tolerated; Overall Significant Improvement Compared to Sham in Safety, Related to Worsening Parkinson's

Adverse Events Over 12 Months (20% or Greater Frequency)

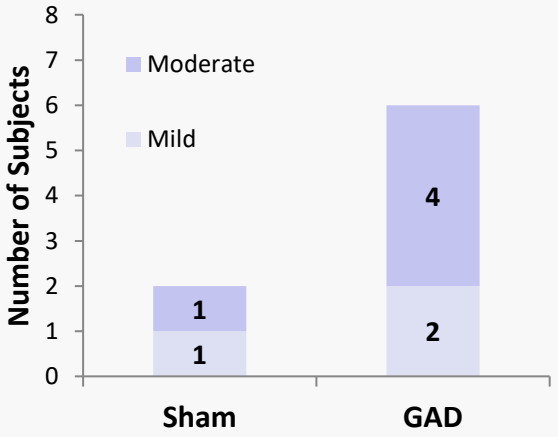
Worsening of Parkinson's Disease



Headache



Nausea



Serious Adverse Events* (Number of Subjects)

	Sham	GAD
Intestinal obstruction		1
Accidental drug overdose		1
Prostatitis		1
Delusion, Hallucination Parkinson's Disease worse	1	

*All SAEs occurred 4-12 months post-surgery and all resolved

Novel Biomarker for Clinical Efficacy of AAV-GAD:
AAV-GAD related changes in basal ganglia circuitry highly correlated with improved motor symptoms

FGD-PET (Fluorodeoxyglucose positron emission tomography):

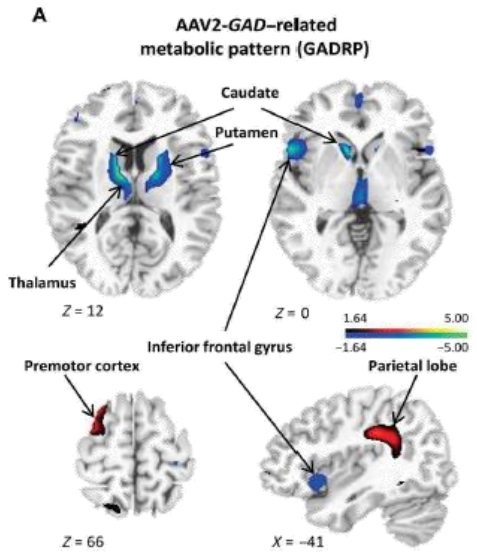
- Neurons metabolize glucose proportionate to their level of activity
- FDG-PET measures regional metabolism of radioactive glucose to determine changes in activity

FDG-PET can be utilized to evaluate brain physiology in multiple ways:

- Patient screening (exclusion of atypical parkinsonism or indeterminate patterns)
- Measure metabolic changes in specific brain regions of interest
- Determine interactions between brain regions during disease progression
- Determine interactions between brain regions as a biomarker of response to therapy

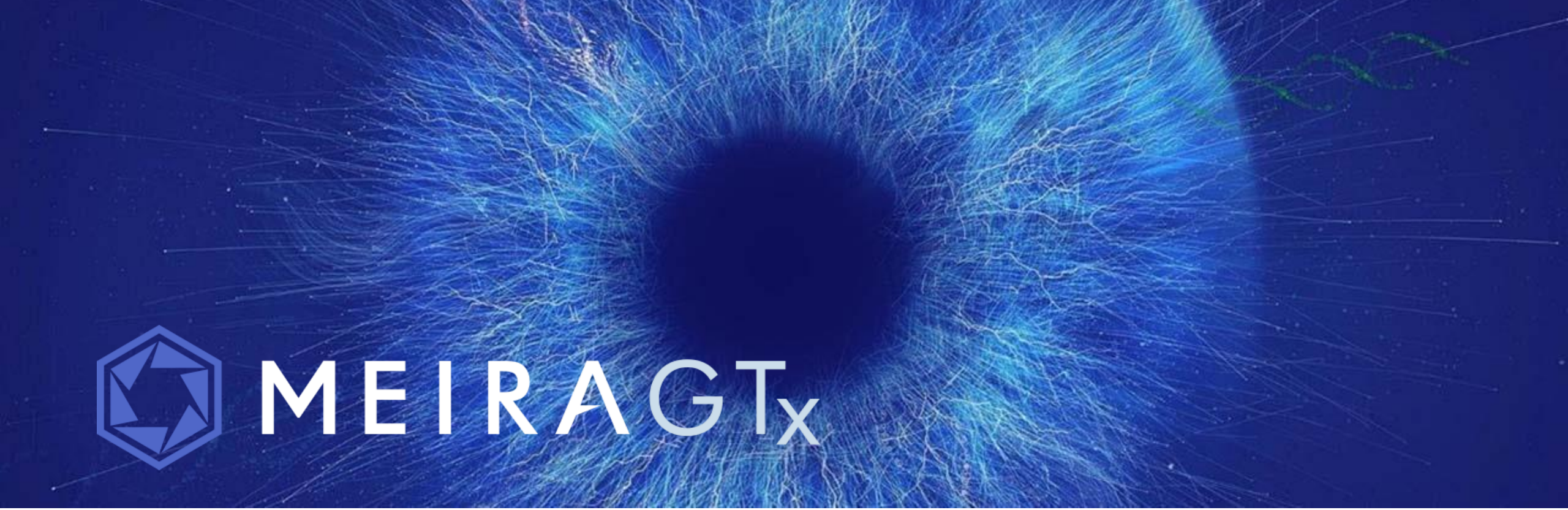
FDG-PET Based Biomarker for clinical effect - GADRP:

- Patients treated with AAV-GAD developed unique treatment-dependent polysynaptic brain circuit: “GAD-Related Pattern” (GADRP)
- Statistically significant correlation between improvement in UPDRS motor ratings and GADRP ($p < 0.009$)
- This treatment-induced brain circuit offers a way to differentiate true treatment-driven responses from placebo responses
- AAV-GAD is the first gene therapy for PD to have an objective imaging biomarker that correlates with clinical improvement



- AAV-GAD treatment-dependent polysynaptic brain circuit
- Reflects formation of new polysynaptic functional pathways linking the STN to motor cortical regions
- Correlation between improvement in UPDRS motor ratings and GADRP expression ($p < 0.009$)

Niethammer M. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. Sci. Trans. Med. 2018; 10(469). pii: eaau0713



AAV-UPF1: A First-in-Class Gene Therapy for Treatment of Amyotrophic Lateral Sclerosis (ALS)

MEIRAGTx

AAV-UPF1 Program HIGHLIGHTS

AAV-UPF1 is a novel gene therapy for ALS with the potential to treat both familial and sporadic ALD (>95% of patients):

- UPF1 is a novel therapeutic target for ALS discovered in an unbiased genetic screen in yeast and validated in multiple in-vitro and in-vivo models of ALS
- AAV-UPF1 targets an underlying cellular defect of ALS – RNA metabolism and homeostasis. UPF1 is known to play a central role in RNA regulation, including in Nonsense-Mediated Decay (NMD).
- In-vivo studies in multiple rodent models of ALS (TDP43, FUS and C9orf72) have demonstrated the ability of AAV-UPF1 to reduce motor neuron death and ameliorate ALS-like symptoms related to limb strength and mobility
- Uses a proprietary capsid (AAV2-retro), which demonstrated favorable transduction of upper and lower motor neurons

Status:

- Vector optimization completed – reduced size for enhanced packaging efficiency, and improved potency over original academic construct
- Initiation of IND-enabling studies planned for 2023

Amyotrophic Lateral Sclerosis (ALS)

Disease Overview

- ALS is a severe, progressive neurodegenerative disease affecting motor neurons.
- Early symptoms of ALS include muscle weakness or stiffness. Gradually, all voluntary muscles are affected. Most ALS patients die from respiratory failure, typically within 3 to 5 years from symptom onset.
- Only 5-10% of ALS cases are inherited, familial ALS (fALS).
- In the majority (>95%) of ALS patients, both fALS and sALS, cytoplasmic mis-localization and aggregation of the proteins TDP43 or FUS can be detected.

MeiraGTx is developing a first-in-class gene therapy with the potential to address **both** sporadic and familial forms of ALS (>90% of ALS patients)

AAV-UPF1: A First-In-Class Gene Therapy for ALS

Approach

- **Therapeutic target: UPF1**
- First protein in the nonsense-mediated decay (NMD) pathway, involved in other RNA processing and quality control pathways
- UPF1 was identified in an unbiased yeast gain-of-function screen as protective against TDP43- and FUS-induced cellular toxicity
- Since then, the protective role of UPF1 in ALS has been validated by MeiraGTx as well as independent research groups in multiple disease models:
  - In-vivo TDP43 neonate rat model
  - In-vivo TDP43 adult rat model
  - in-vivo FUS mouse model
  - In-vivo C9orf72 mouse model
  - Drosophila C9orf72 model
  - Primary rodent neurons – FUS and TDP43
  - iPSC derived neurons – TDP43 and C9orf72

AAV-UPF1:

» Targets an underlying cellular defect driving the disease – RNA metabolism

» Has potential to address **both** familial and sporadic forms of ALS (>90% of patients), as well as potentially FTD

» Validated in multiple in-vivo and in-vitro models, in the context of AAV


MEIRAGTx