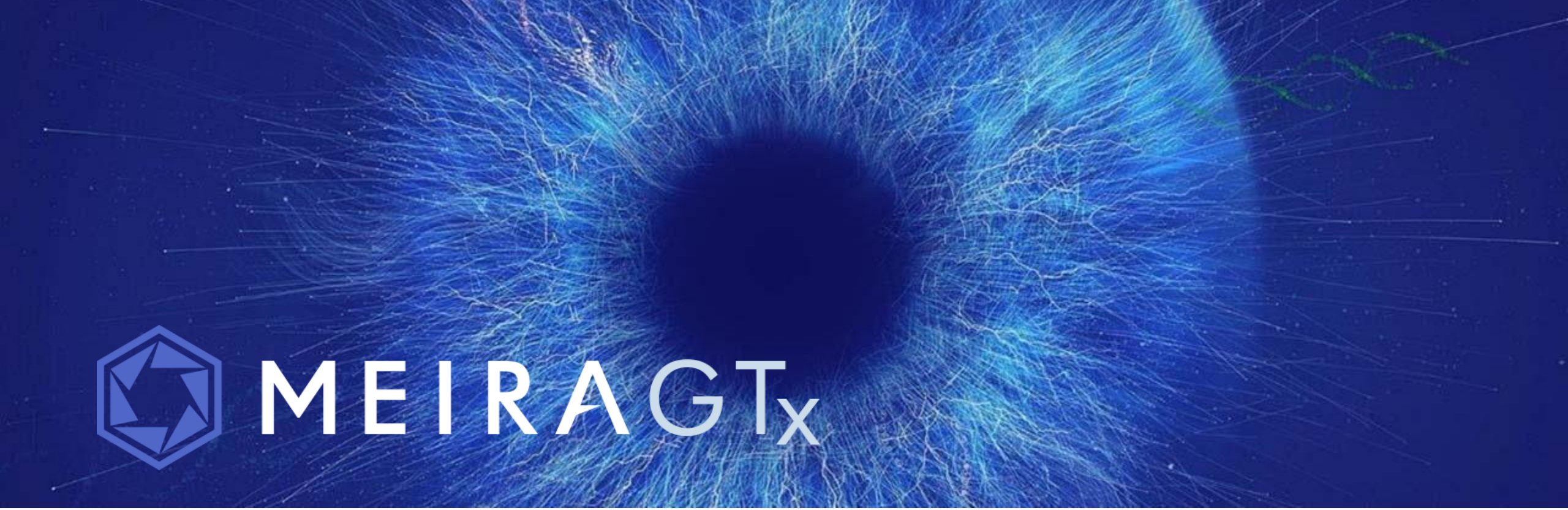


Corporate Presentation

April 2024

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, our ability to manufacture product candidates, potential milestone payments and the achievement of such milestones, and our pre-clinical and clinical data, reporting of such data and the timing of results of data, 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 transactions or priorities, bring product candidates to market, expansion of our manufacturing facilities and processes, successfully enroll patients in and complete clinical trials, accurately predict growth assumptions, recognize benefits of any orphan drug designations, retain key personnel or attract qualified employees, or incur expected levels of operating expenses; the impact of pandemics, epidemics or outbreaks of infectious diseases on the status, enrollment, timing and results of our clinical trials and on our business, results of operations and financial condition; failure of early data to predict eventual outcomes; failure to obtain FDA or other regulatory approval for product candidates within expected time frames or at all; the novel nature and impact of negative public opinion of gene therapy; failure to comply with ongoing regulatory obligations; contamination or shortage of raw materials or other manufacturing issues; changes in healthcare laws; risks associated with our international operations; significant competition in the pharmaceutical and biotechnology industries; dependence on third parties; risks related to intellectual property; changes in tax policy or treatment; our ability to utilize our loss and tax credit carryforwards; litigation risks; and the other important factors discussed under the caption “Risk Factors” in our 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 April 8, 2024.

MEIRAGTx

End-to-end Capabilities in Genetic Medicines

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

Clinical Pipeline

Diverse and advanced clinical programs:

- Multiple clinical programs, all post successful Phase 1 or Phase 2
- CNS, eye, salivary gland
- Local delivery
- Small doses
- Immune protected

GMP Manufacturing

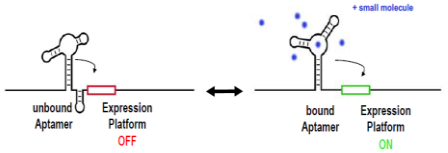
Flexible and Scalable

- 2 GMP facilities, commercial scale.
- Proprietary Platform Production Process – meets highest yield and full ratio in industry
- In-house Plasmid production for GMP
- Dedicated QC facility – analytics for commercial release and stability – commercial license
- Fill and Finish, warehouse and supply chain

Next Generation Vector Optimization

Potency, Safety, Dose, Immunogenicity

- Capsids - Cell Tropic, CNS, Eye, Liver, Muscle
- Promoters/enhancers: cell and level-specific, muscle, CNS, Liver, eye
- Vector sequence optimization – stability, durability, Immune protection, manufacturability



Transformative Gene Regulation Technology

Control of Genetic Medicines

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

Broad Pipeline of Transformative Gene Therapies:
Clinical programs across multiple TFAs

Product	Indication	Discovery / Preclinical	Phase 1/2	Phase 2	Phase 3
Salivary Gland					
AAV-AQP1	Xerostomia	*Orphan Drug*		*Pivotal*	
	Sjögren's Syndrome				
Neurodegenerative Disease					
AAV-GAD	Parkinson's Disease				
AAV-UPF1	ALS				
BDNF for Genetic Obesity – MC4R					
BDNF- MC4R	Metabolic				
Riboswitch Inducible Expression Programs					
GLP-1-GIP Myokine combinations	Metabolic				
Ribo-CAR-T	Oncology				
Other prevalent indications	Undisclosed				
X-Linked RP					
Botaretigene sparoparvovec[1]	X-linked RP	*PRIME, Fast Track, Orphan Drug*			lumeos XLRP study
Inherited Retinal Diseases					
AAV-RPE65	RPE65-Associated Retinal Dystrophy	*RPDD, Orphan Drug*			
AAV-CNGB3	Achromatopsia	*RPDD, PRIME, Fast Track, Orphan Drug*			
AAV-CNGA3	Achromatopsia	*RPDD, Fast Track, Orphan Drug*			
AAV-AIPL1	LCA4	Compassionate use under MHRA Specials License			
A007, A008	RDH12, Stargardt, KCNV2, GUCY2D				
Degenerative Ocular Diseases (non-inherited)					
	Wet & Dry AMD, Glaucoma, Uveitis				

[1] Remaining interests in program sold to Janssen in December 2023; MeiraGTx to receive up to an aggregate of $350.0 million upon achievement of milestones and will manufacture and supply commercial product for Janssen.

A Unique, Diverse and Inclusive Culture

MEIRAGTx

- 370+ full-time employees
- 55% female, 45% male
- Multiple locations globally
- 31 different nationalities represented

Strong Industry Partnerships

Janssen

MeiraGTx entered into an asset purchase agreement with Janssen, for the remaining interests in bota-vec for the treatment of XLRP

MeiraGTx will receive a total of **up to $415 million:**

- $130 million in upfront and near-term milestone payments
- Additional $285 million upon first commercial sales of bota-vec in U.S. & EU and manufacturing technology transfer
- MeiraGTx will manufacture and supply commercial product for Janssen at MeiraGTx's cGMP facilities

- J&J will be responsible for any royalty or milestone amounts that become payable on bota-vec to UCL Business plc (University College London)

sanofi

In October 2023, MeiraGTx received a **$30 million strategic investment** from Sanofi through sale of 4 million ordinary shares at $7.50 per share

- Sanofi received a Right of First Negotiation (ROFN) for MeiraGTx's phase 2 Xerostomia program, as well as for the use of MeiraGTx's Riboswitch gene regulation technology in certain targets:
  - Immunology and Inflammation (I&I), including IL-4 and IL-13
  - GLP-1 and other gut peptides for metabolic disease and obesity
  - Central Nervous System (CNS)

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

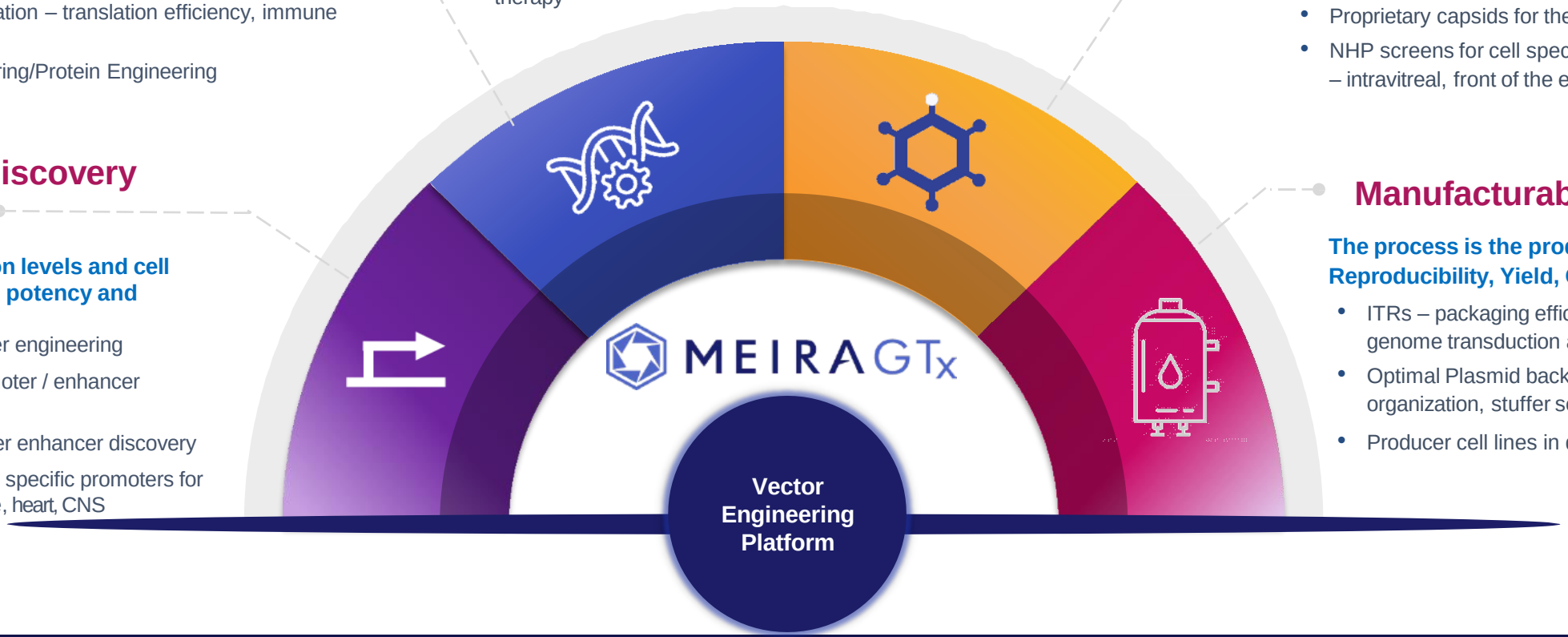
Tissue Tropism: Drives differential transduction efficiency and potency

- Immune evasion capsids
- Muscle tropic Capsids
- 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

Unique End-to-End Manufacturing Infrastructure and Production Process Fit For Commercial as well as Clinical Supply

- **2 GMP Viral Vector Production Facilities (London, UK and Shannon, Ireland):** single use philosophy; flexible and scalable within 1 week; fit for clinical through commercial supply (London 29,000 sq ft; and Shannon 150,000 sq ft).
- **Commercial QC Facility (Shannon):** Commercial and Clinical Licenses (HPRA) 2024 for full clinical and commercial release and stability, received Commercial license and then Clinical license 2023
- **Large-scale Plasmid Production for GMP (Shannon):** for GMP starting material, large capacity for potential commercial scale supply
- **In-House Fill and Finish, Warehouse, Supply Chain Infrastructure (London and Shannon):** prepared for commercial supply (RPGR; London and Shannon)
- **Stand Alone MSAT Dedicated Facility (London) :** >30 employees. Established over a period of 8 years with process development leveraging multiple capsids and vector genome combinations. Data lakes and AI driven process optimization for each new vector and capsid combination. Proprietary platform process for production with best-in-class yield and full-to-empty capsid ratios, fit to any new vector.
- **QC analytics development (London):** preclinical expertise leveraged for Phase 3 and commercial potency assay development as well as QC analytic development and transfer to GMP (AQP1 example of moving direct to pivotal from QC perspective).
- **Extensive CMC Regulatory Know How and Experience:** filed multiple CMC INDs and amendments for multiple products and comparability protocols with the FDA and 15 global agencies; cross referenced – tend to receive no questions driving delay for CMC (recent Pivotal discussion for 1st randomized study).
- **Specials License:** the only gene therapy manufacturing facility in the UK with a 'Specials License' allowing us to supply physician led studies outside of commercial clinical development for rare degenerative disorders with no other treatment options.

- **Reduced Cost of Goods: Process, Plasmid, Vector Production and QC**
- **Commercial process at IND; Saves 3-4 years for any AAV clinical development timeline from IND to commercial, allows potential for faster move to pivotal with expedited time to market**

MANUFACTURING

- ✓ Proprietary process with market-leading performance and adaptability across multiple AAV serotypes and genome sequences
- ✓ Eight years invested developing end-to-end manufacturing platforms for pre-clinical supply through commercial grade gene therapy products at-scale
- ✓ Extensive interactions with global regulatory bodies around CMC requirements from first-in-human, through pivotal studies, to BLA and commercialization
- ✓ Capabilities include manufacturing sciences, analytical services, GMP plasmid production, QC, fill/finish, warehousing, and distribution; allowing for turnkey operations
- ✓ Highly attractive location with deep local talent pool, proximity to potential customers and expansion capacity
- ✓ Modular construction and single use philosophy allows for significant expansion and scalable production in a range of batch sizes to fit development stage appropriate capacity needs
- ✓ Flexibility to accommodate manufacture of lentivirus and other viral vectors and vaccines if desired
- ✓ >200 FTEs across Manufacturing Production, QA, QC, MSAT/Process Development, Tech Transfer, Supply Chain, Engineering

Gene Regulation Technologies

MeiraGTx's Gene Regulation Technologies Enable Unprecedented Control of Genetic Medicine

Overlaying bespoke promoter regulation with riboswitch regulation allows for unprecedented control of the **timing, location, and level of gene expression**

Gene Regulation Technologies

Transcriptional Regulation (Promoters, Enhancers)

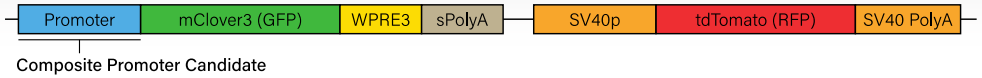
- Spatial control of gene expression - ubiquitous or tissue/cell-specific
- Control of expression levels
- Drives product potency and safety (through down-dosing of AAV)

Riboswitch Gene Regulation Technology

- Promoter independent regulation
- Tunable, dose-dependent control of expression
- BBB-crossing, ocular, or systemic small molecule inducers

MeiraGTx Multi-Platform Promoter Discovery Engine

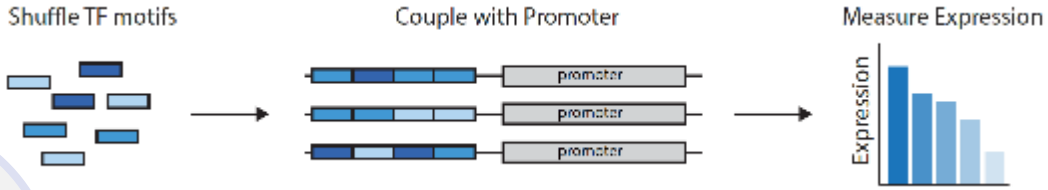
Rationally Designed Screens



- 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 700 such rationally designed composite promoters with selected potency are in hand at MeiraGTx

High-Throughput Transcription Factor Binding Site Shuffling

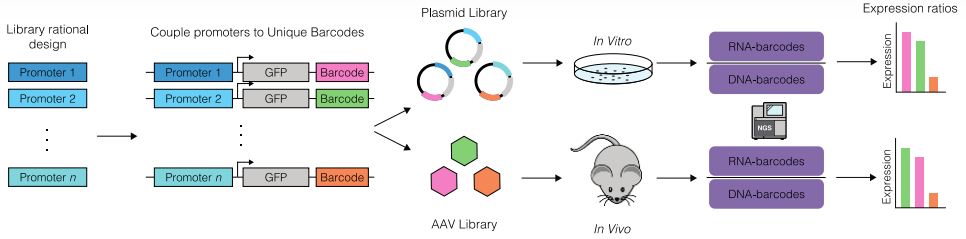
- Generation and screening of synthetic enhancers via cell specific transcription factor binding site (TFBS) shuffling



MEIRAGTx

Promoter Engineering Platforms

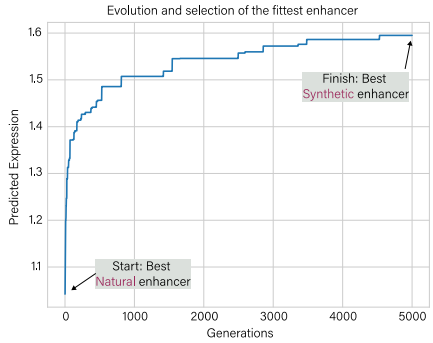
AAV-based or plasmid-based promoter screens using barcodes



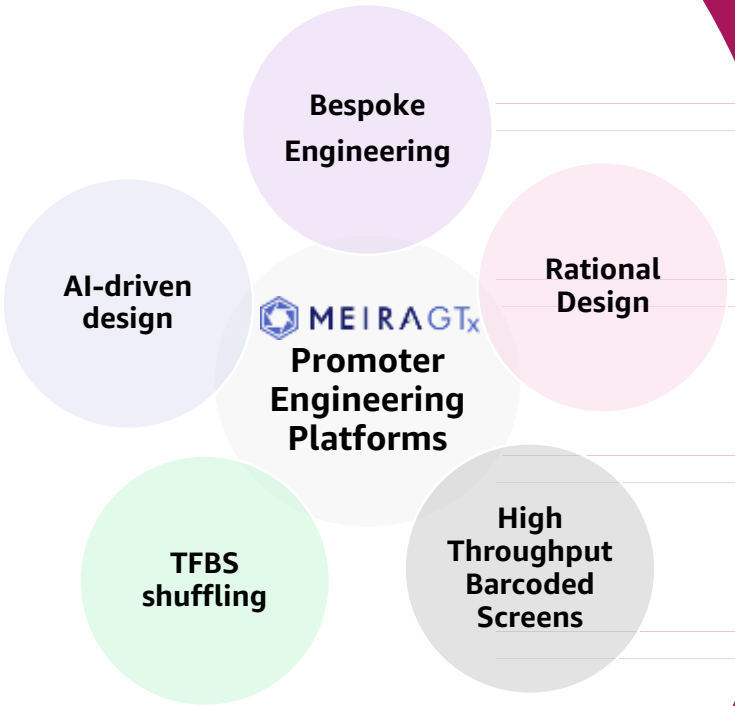
- Randomly fragmented genomic DNA
- All annotated human promoters
- All putative natural enhancers (ENCODE, FANTOM)
- Synthetic enhancers/promoters
- AI-driven library design

AI-driven Promoter Design and Evolution

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



MeiraGTx's Promoter Engineering Platforms Yield Extensive Libraries of Strong, Small, and/or Tissue-Specific Promoters



Ubiquitous Promoters	>100 promoters up to 15-fold stronger than CAG/CMV
Ocular Promoters	for multiple cell types in the eye e.g., the strongest known human pan-cone promoter
Muscle Promoters	Stronger vs. promoters used in the clinic: e.g., synthetic promoter 17x stronger than tMCK, in-vivo
Neuronal Promoters	Up to 12x stronger than CAG in both human and mouse neuronal cell lines
Liver Promoters	Stronger and smaller vs. promoters used in the clinic

Riboswitch Gene Regulation Technology: Precise and Specific Control of Gene Activity with Bespoke Oral Inducers

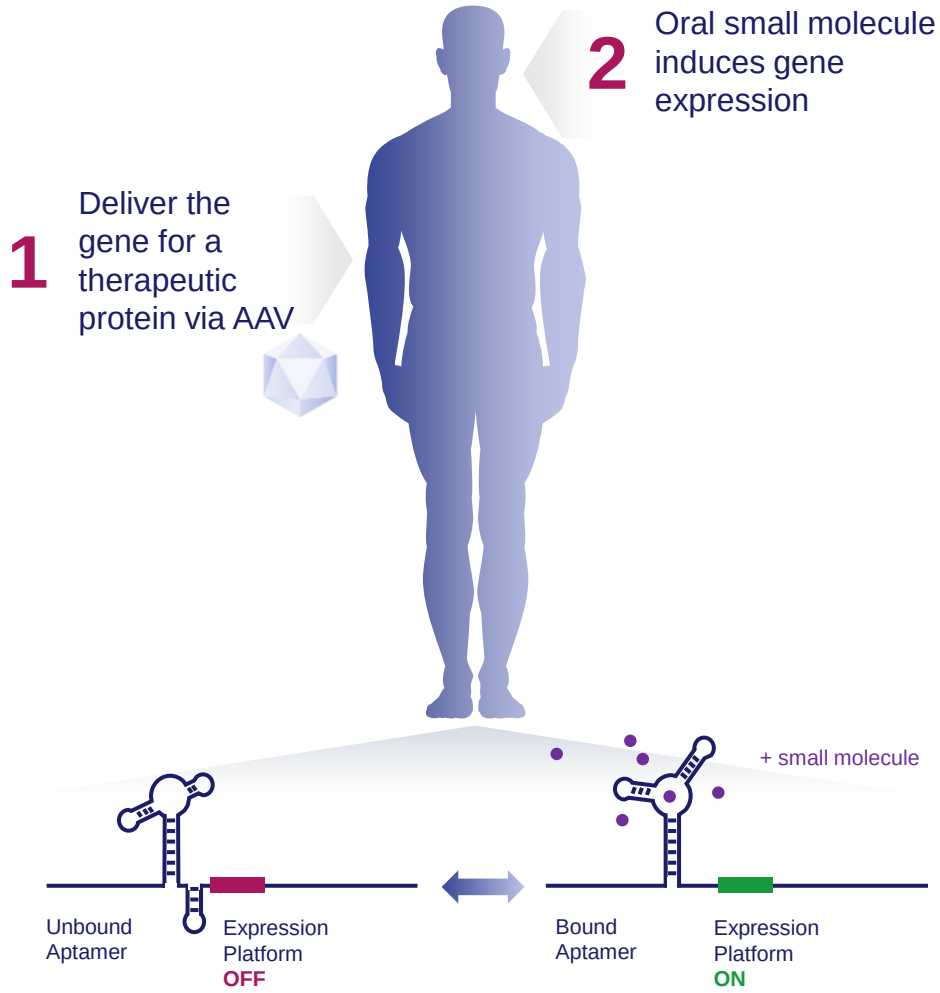
Riboswitch technology enables precise control of genetic medicine using bespoke orally-dosed inducers:

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’

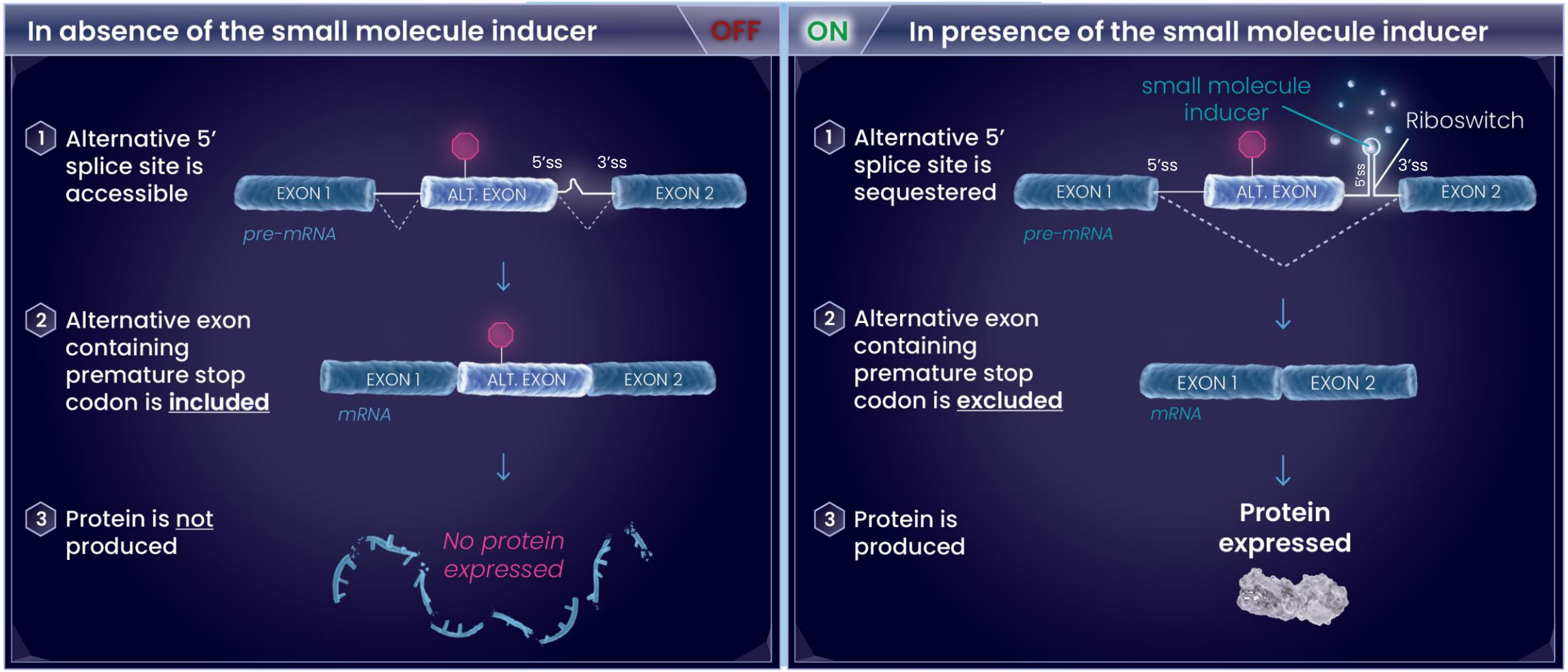
Short-lived Therapeutic Hormones and Peptides
Precise activation of naturally short-lived peptides and hormones; combinations of natural peptides regulated together

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

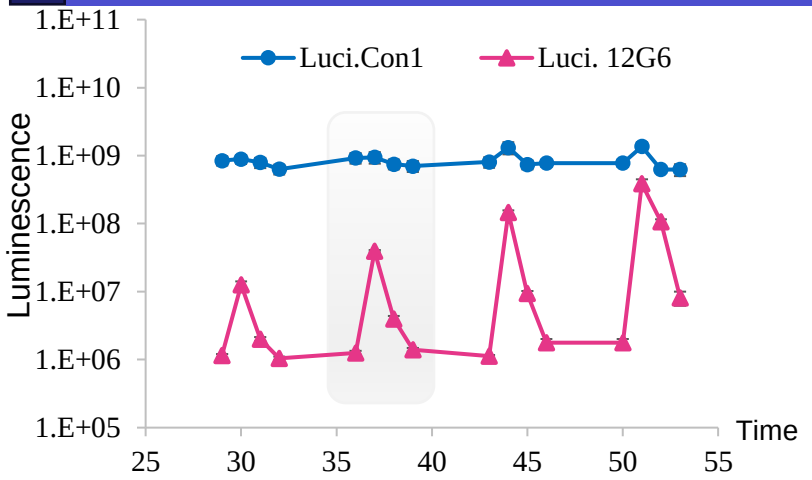
Passive and Active Vaccines with built-in capacity for Oral Small Molecule Boosters

Gene Regulation Cassette Driven by Splicing-Based Mammalian Synthetic Riboswitch

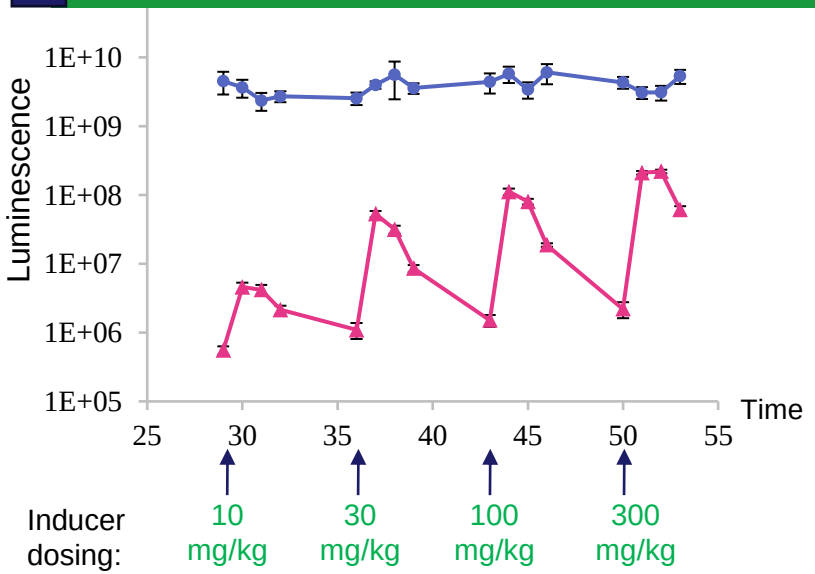


Regulation Cassette Precisely Controls AAV-Mediated Transgene Expression in Response to Oral Small Molecule Inducer

A Liver Expression of constitutive and regulated luciferase



B Muscle expression of constitutive and regulated luciferase



- **Luci.Con1**: constitutive expression – no regulation cassette
- **Luci.12G6:** identical construct to Luci. Con1 but with regulation cassette

Liver Expression: tail vein injection AAV-luciferase

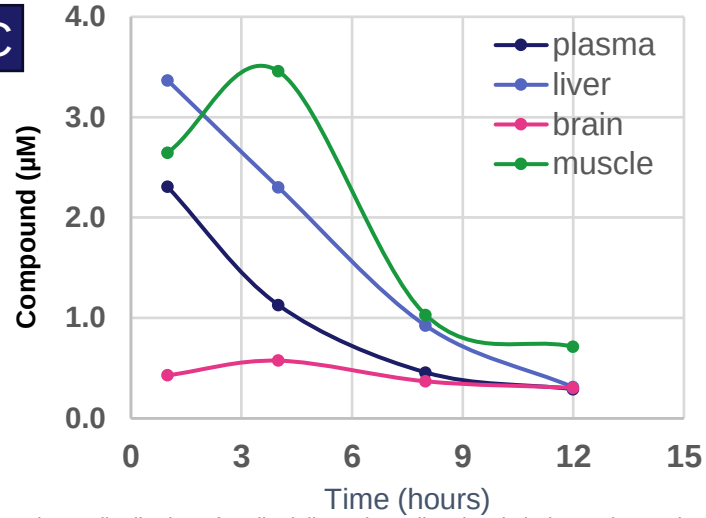
Muscle Expression: direct intramuscular injection of AAV-Luciferase

- Single oral dose of small molecule results in dose responsive expression of Luciferase from Luci. 12G6 in comparison to constitutive expression with Luci con1 in both tissues (**Figures A and B**)
- However, the shape of the curve of luciferase induction shows tissue-specific response to the differential tissue biodistribution following a single oral dose of the small molecule (shown in **Figure C**) sharp peak for liver (blue) vs. slow accumulation and then exit from muscle (green).
- **Figure D** illustrates the restriction of expression with small molecule dosing.

Figure D shows individual mice from the 30mg/kg dose – indicated by the gray box in Figure A.

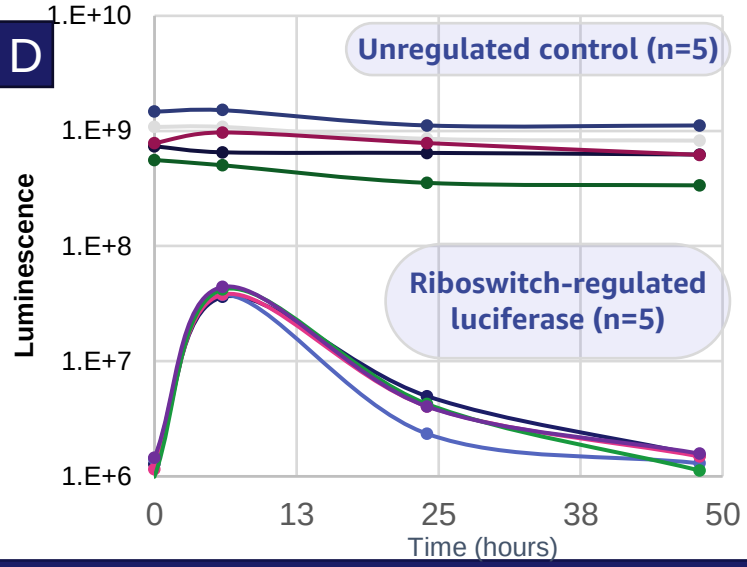
- On a mouse-by-mouse basis there is about 0.4 log range of expression between mice from constitutively active construct.
- In contrast, induced expression in response to oral inducer is tightly controlled, expression is limited by the dose of the oral small molecule such that each mouse receiving the same oral dose expresses the same level of luciferase.

C



- Tissue distribution of orally delivered small molecule inducer shows short term accumulation in muscle, whereas clearance from liver is linear. This is directly reflected in the different profiles of regulated luciferase expression in the liver and muscle (Figures A and B)

D

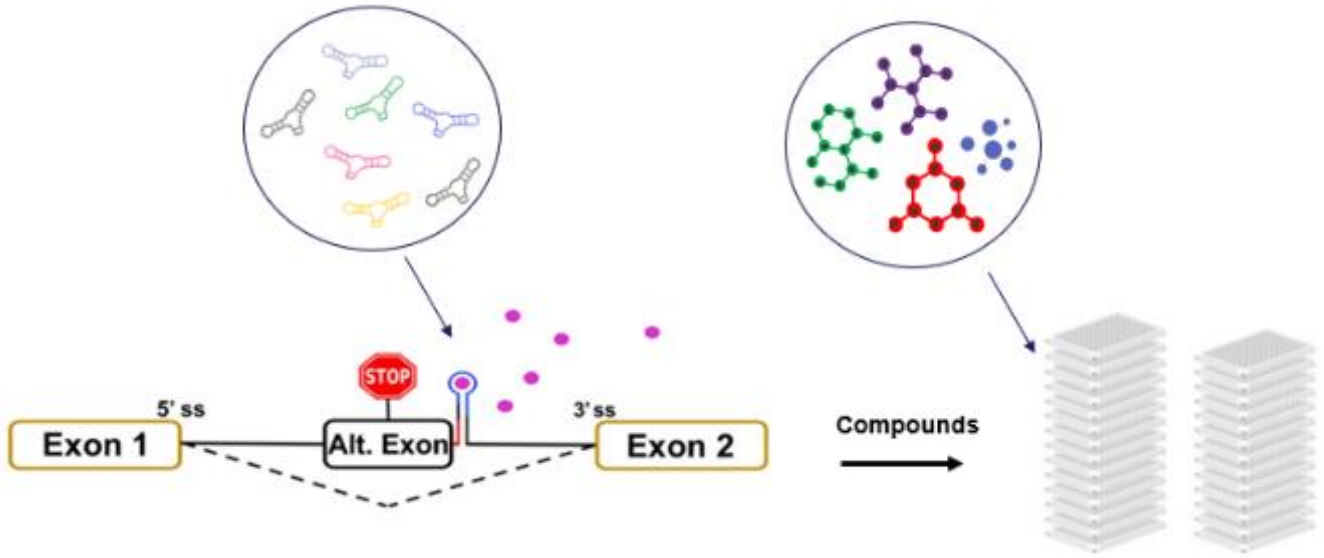


High Dynamic Range Regulation Cassette Allows Screening for RNA-Small Molecule Functional Binding in Mammalian Cells

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
- ~250 Compounds have been screened
- 42 compounds demonstrated high potencyy; >30 compounds tested demonstrated good ADMET/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 desired ADMET/PK properties
- 5 compounds demonstrated high eye exposure levels when dosed orally
- 3 compounds are in pre-clinical development: one compound completed GLP tox studies, and two others will complete GLP tox in 2024. All showed good PK/safety profile in non-GLP rat, dog, and NHP studies.
- **Most advanced candidate entering IND enabling studies in 2024**

Riboswitch Control System Drives Precise Dose Response Expression of Multiple Therapeutic Proteins: Vectorized Antibodies, Peptides and Hormones in vivo as well as Receptors in Cell Therapy and DNA and RNA targeting Nucleases

Therapeutic Antibodies

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

Cell Therapy

- Ribo-CAR:
  - Anti-CD19
  - Anti-PSMA
  - Anti-mesothelin
  - Anti-HER2

Therapeutic Hormones / Cytokines / Peptides

- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon
- Myokines
- Adipokines – leptin
- Orexin

Gene/RNA Editing Nucleases

- Cas9
- CasRx

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
- Anti-Myostatin

Cell Therapy

- Ribo-CAR:
  - Anti-CD19
  - Anti-PSMA
  - Anti-mesothelin
  - Anti-HER2

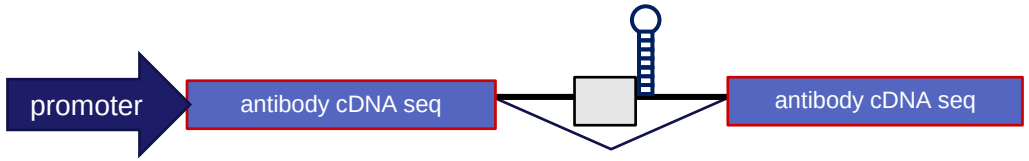
Therapeutic Hormones / Cytokines / Peptides

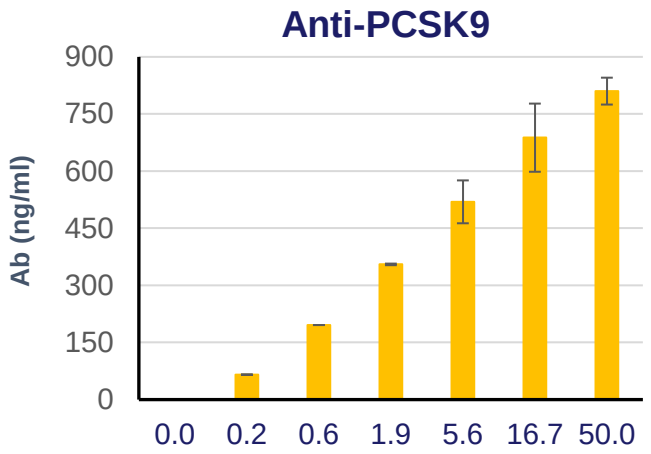
- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon
- Myokines
- Adipokines – leptin
- Orexin

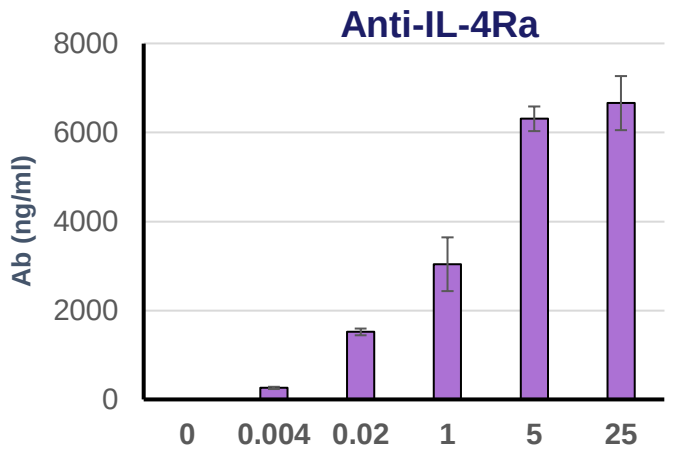
Gene/RNA Editing Nucleases

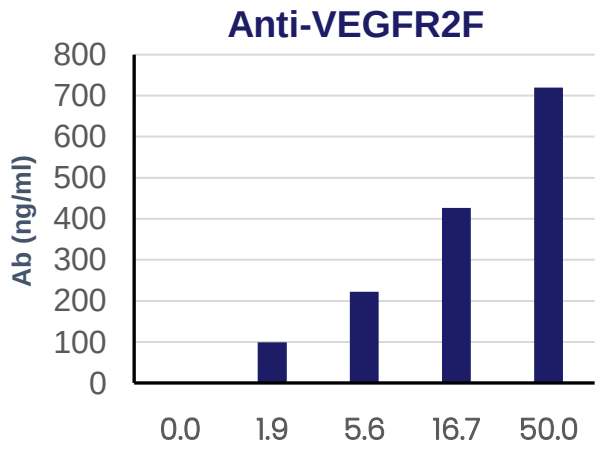
- Cas9
- CasRx

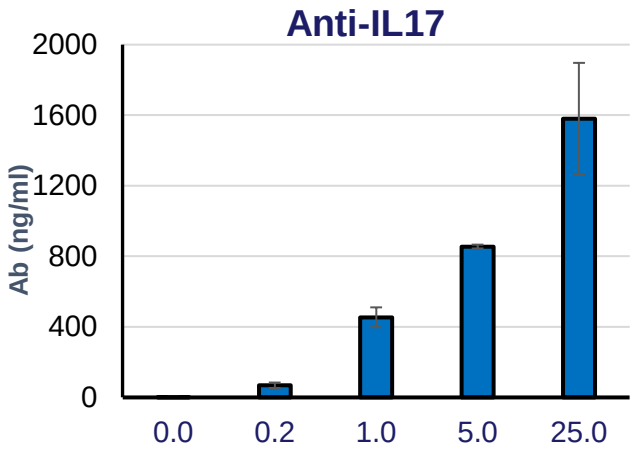
Riboswitch Tightly Regulates Expression of Therapeutic Antibodies in Precise Dose Responsive Fashion

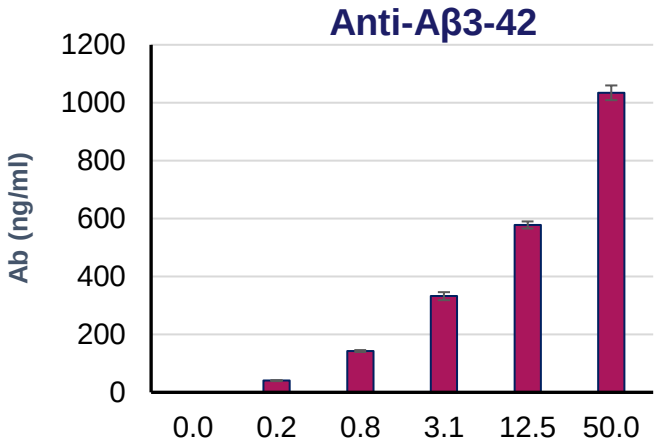


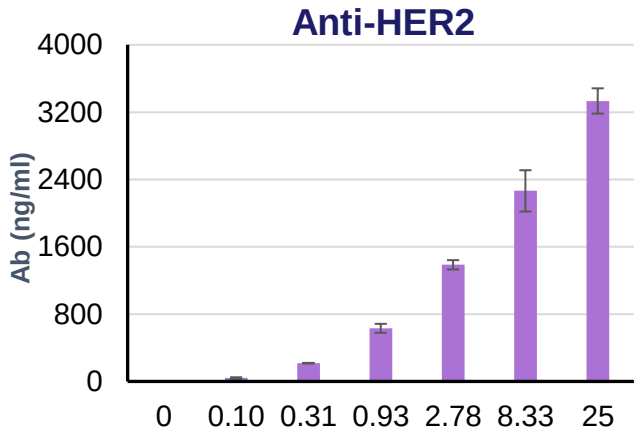








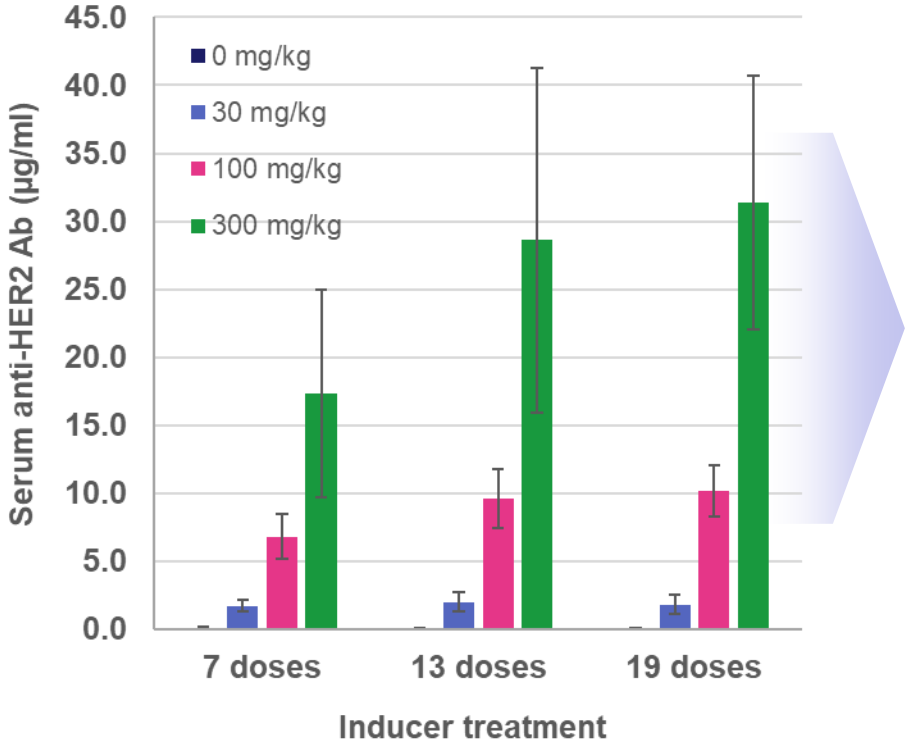




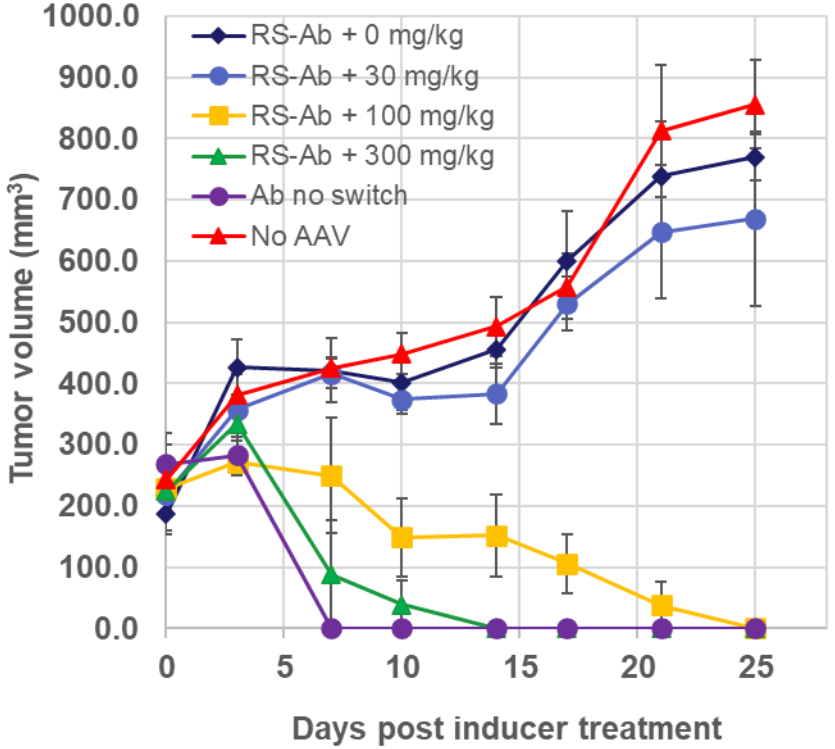
Small molecule inducer (µM)

Example: Riboswitch-Regulated anti-HER2 Antibody Expression, in-vivo

Dose-dependent anti-HER2 antibody expression



Dose-dependent suppression of HER2⁺ tumor



- Mice (n=5) were injected with AAV vector containing anti-HER2 Ab with ($4.1x10^{10}$ vg/mouse) or without riboswitch.
- 4 weeks post AAV delivery, 5×10^6 Calu-3 tumor cells were inoculated into mice (n=5) subcutaneously.
- 7 days post tumor cell inoculation, mice were treated with riboswitch small molecule inducer MXU-001 at the indicated doses.
- Riboswitch controlled anti-HER2 antibody inhibited tumor growth and halted tumor progression in response to small molecule inducer treatment.

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
- Anti-Myostatin

Cell Therapy

- Ribo-CAR:
  - Anti-CD19
  - Anti-PSMA
  - Anti-mesothelin
  - Anti-HER2

Therapeutic Hormones / Cytokines / Peptides

- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1-GIP-PYY Glucagon
- Myokines
- Adipokines – leptin
- Orexin

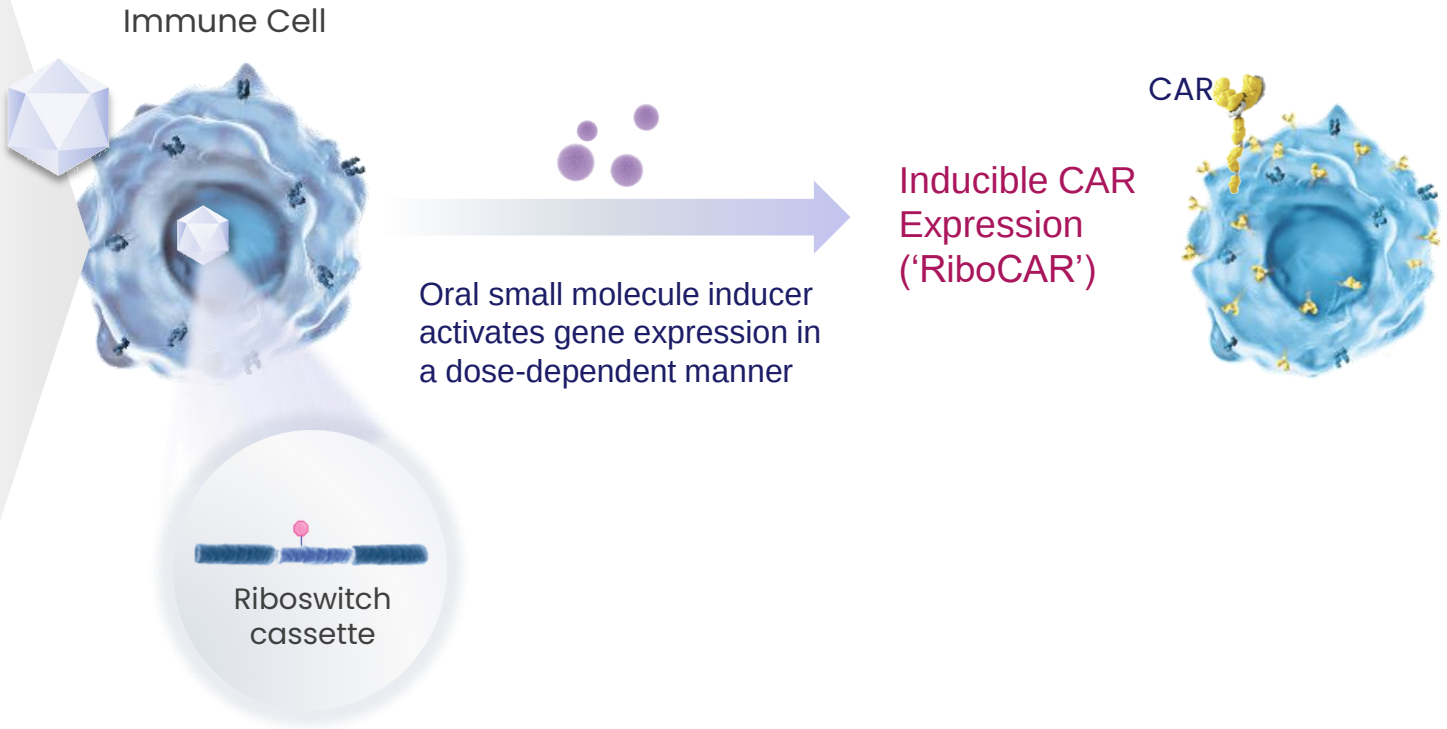
Gene/RNA Editing Nucleases

- Cas9
- CasRx

Riboswitch-Regulated Cell Therapies

Riboswitch-controlled cell therapies address key limitations of this therapeutic class, providing significant improvements in immune cell activity as well as important safety features.

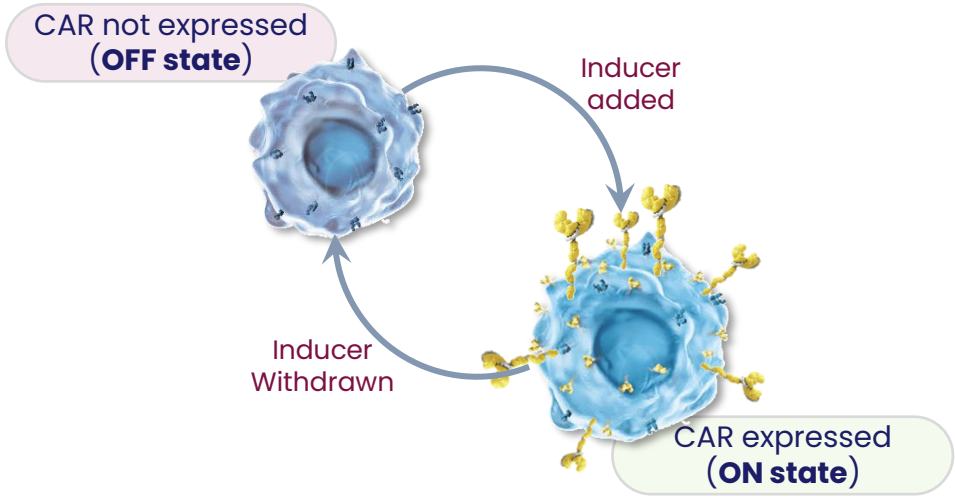
- T-cells are engineered with a riboswitch-containing expression cassette
- The riboswitch cassette can regulate proteins that activate or modulate immune cell function (e.g. CAR, cytokines, chemokines)
- Alternatively, the riboswitch cassette can regulate proteins that induce programmed cell death (e.g. apoptotic proteins) to eliminate cells if needed



Inducible Control of Chimeric Antigen Receptor (RiboCAR) May Improve The Safety & Efficacy of CAR–T Therapy

The ability to control cell therapies once infused into the patient overcomes key limitations of current generation cell therapies and drives increased potency at reduce cell doses:

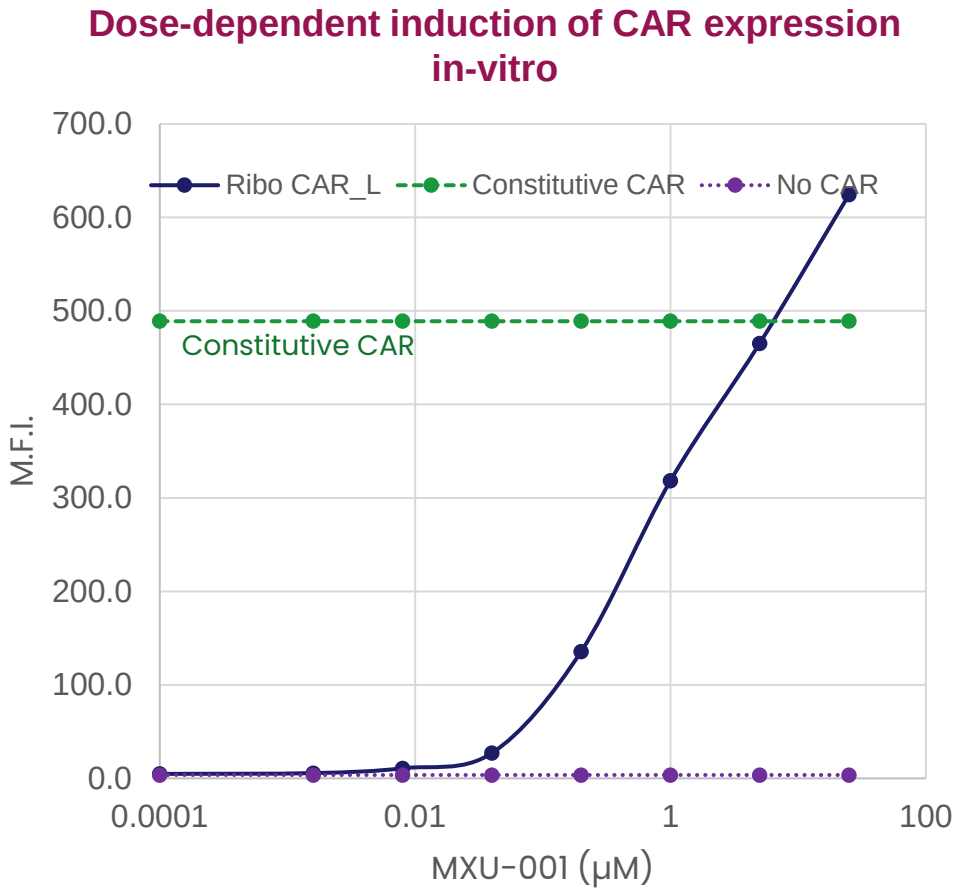
- Constitutive expression of CAR can lead to T-cell exhaustion and reduced persistence due to tonic signaling, limiting anti-tumor response and contributing to resistance to CAR-T therapy
- In clinical settings, patients receiving CAR-T therapies enriched in high density constitutive CAR were shown to have significantly worse clinical outcomes in several hematological malignancies[1].

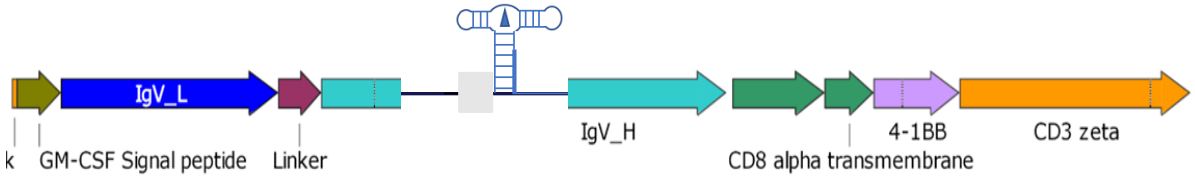


In vitro and *in vivo* work using riboswitch-controlled CAR (RiboCAR) provides evidence that **temporal control of CAR signaling has a significant impact on potency, reduces exhaustion and can mitigate the potential for toxicity**

[1] CAR density influences antitumoral efficacy of BCMA CAR T cells and correlates with clinical outcome (Science Advances, 2022)

Riboswitch Regulation of Chimeric Antigen Receptor (CAR) Cell Surface Expression in HEK293 Cells

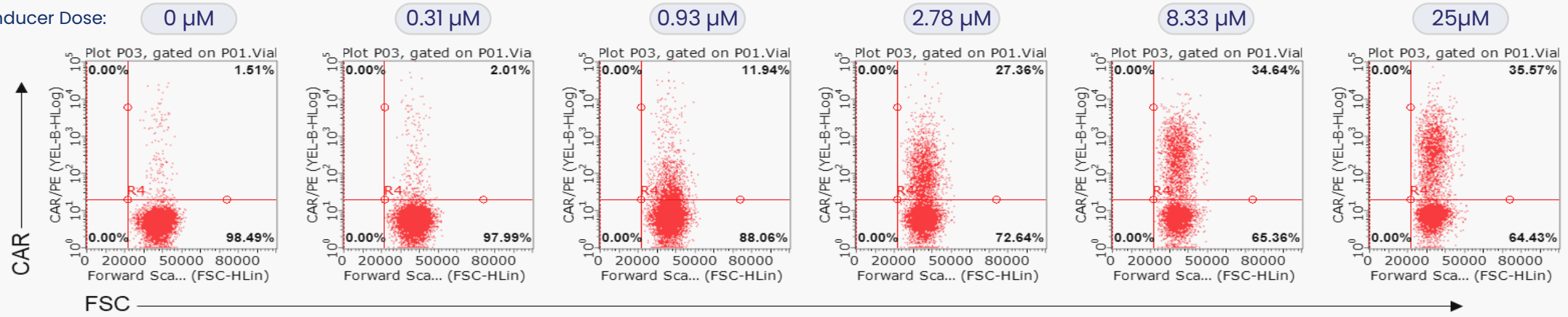




- HEK293 cells transfected with different riboswitch-regulated CAR constructs were treated with MXU-001 inducer at increasing doses
- In the absence of the small molecule inducer, no CAR expression was detected
- CAR expression is induced in a dose-dependent manner
- CAR expression levels surpass those of constitutive (non-regulated) CAR even at low doses of the small molecule activator

In Primary Human T-Cells: RiboCAR-T Cells Express CAR in a Precise Dose-Response to Small Molecule Inducer

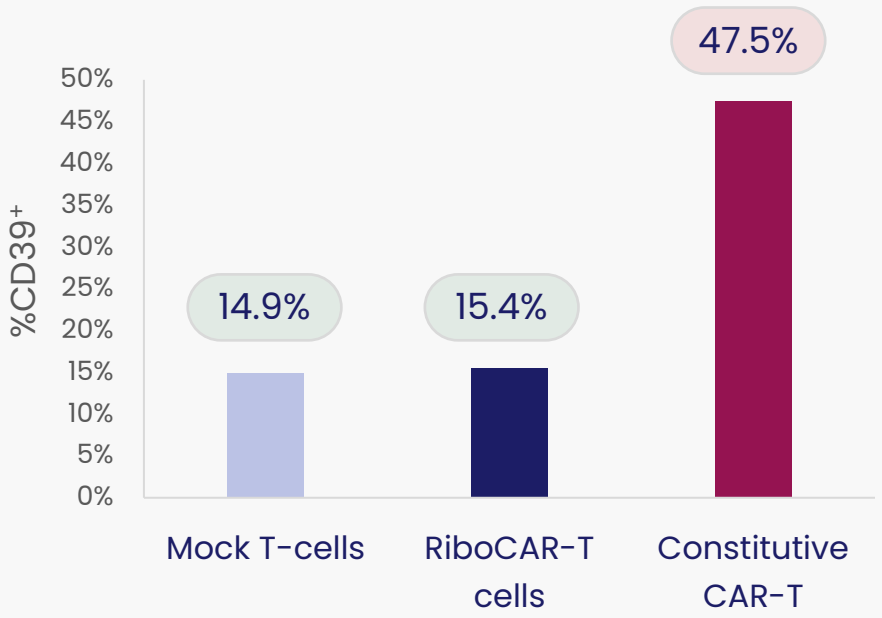
Dose dependent expression of CAR in RiboCAR-T cells in response to riboswitch inducer



- In human primary T-cells, RiboCAR was targeted to TRAC locus by CRISPR/cas9-mediated knock-in
- CAR was not expressed in in the absence of the small molecule inducer during in vitro expansion
- CAR expression was induced in a dose-dependent manner by the small molecule inducer treatment in human primary T cells

Riboswitch Controlled CAR-T Cells Exhibit Significantly Reduced Exhaustion vs. Constitutive CAR-Ts

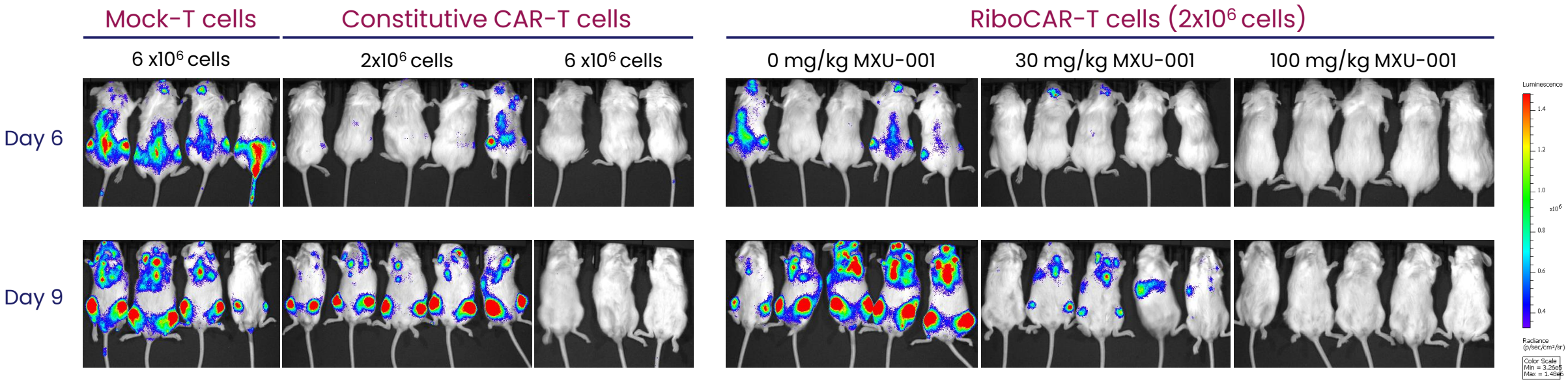
Induced primary RiboCAR-T cells exhibit reduced exhaustion markers (CD39) vs. ConstCAR-T (25µM MXU-001 inducer)



- T-cell Exhaustion is a critical issue in cell therapy using resulting from the constitutive expression of CARs
- Exhausted CAR-T cells exhibit decreased proliferative capacity, impaired anti-tumor activity, and attenuated persistence[1].
- RiboCAR T-cells exhibit significantly lower levels of the exhaustion marker, CD39, vs. constitutive CAR
- In parallel, these cells with regulated CAR show increased potency compared to constitutive CAR in in-vitro and in-vivo models

1) Zhu X, Li Q, Zhu X. Mechanisms of CAR T cell exhaustion and current counteraction strategies. Front Cell Dev Biol. 2022 Dec 8

Riboswitch-Controlled RiboCAR-T Cells Outperform Constitutive CAR-T Cells in anti-Tumor Activity, *in-vivo*



- $1x10^6$ Raji-ffLuc cells were injected into NSG mice; 4 days later, mice were treated with the indicated CAR-T cells.
- Mice received daily oral dosing with the small molecule inducer at the indicated doses, starting the day before RiboCAR-T cell injection.
- Tumor growth was monitored every 3 days using bioluminescence imaging.
- The dose of RiboCAR-T cells ($2x10^6$ cells) with 100 mg/kg of the small molecule that resulted in complete tumor killing was 1/3 of the dose required using Constitutive CAR-T cells ($6x10^6$ cells) with the same CAR knocked into the same locus.

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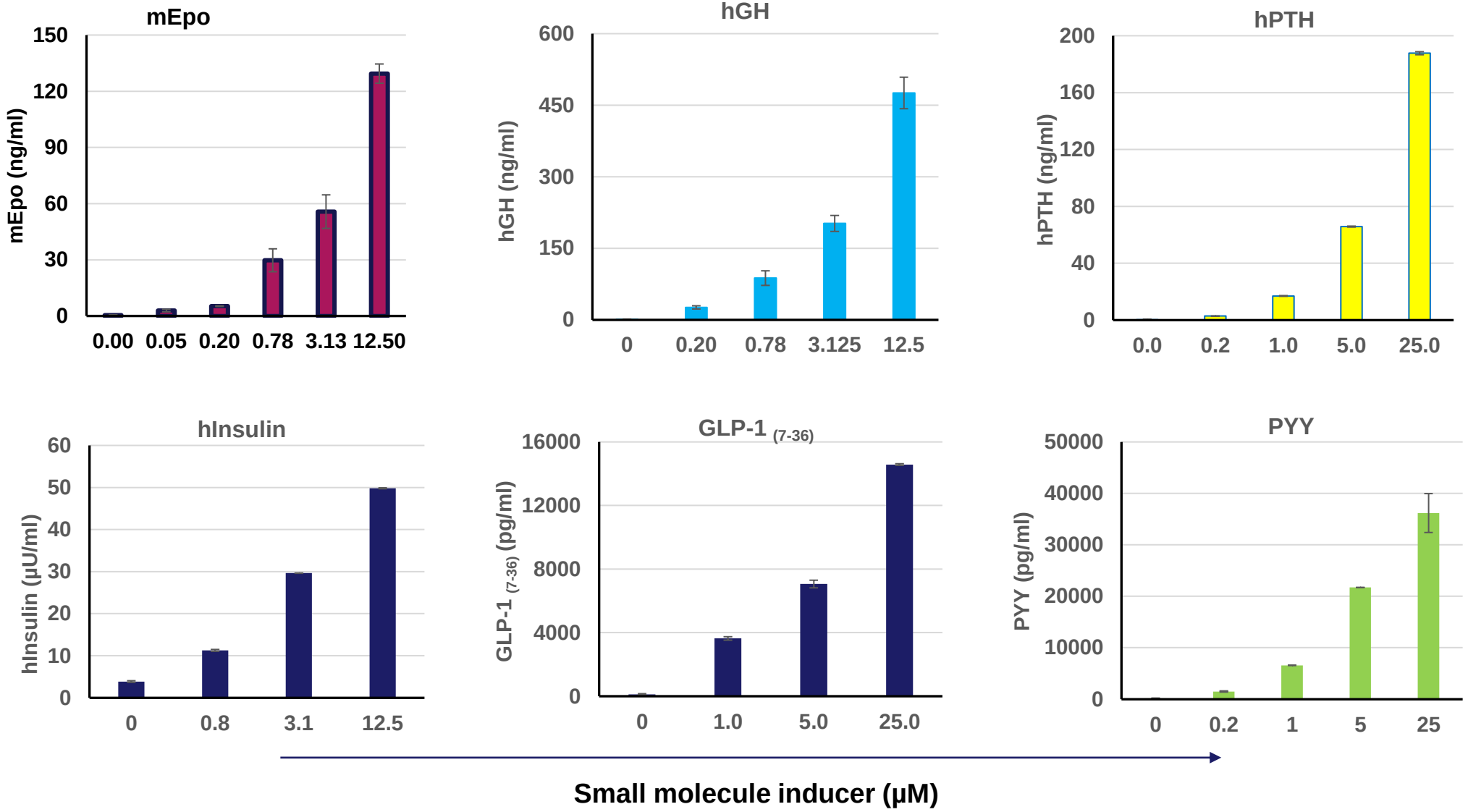
Gene/RNA Editing Nucleases

- Cas9
- CasRx

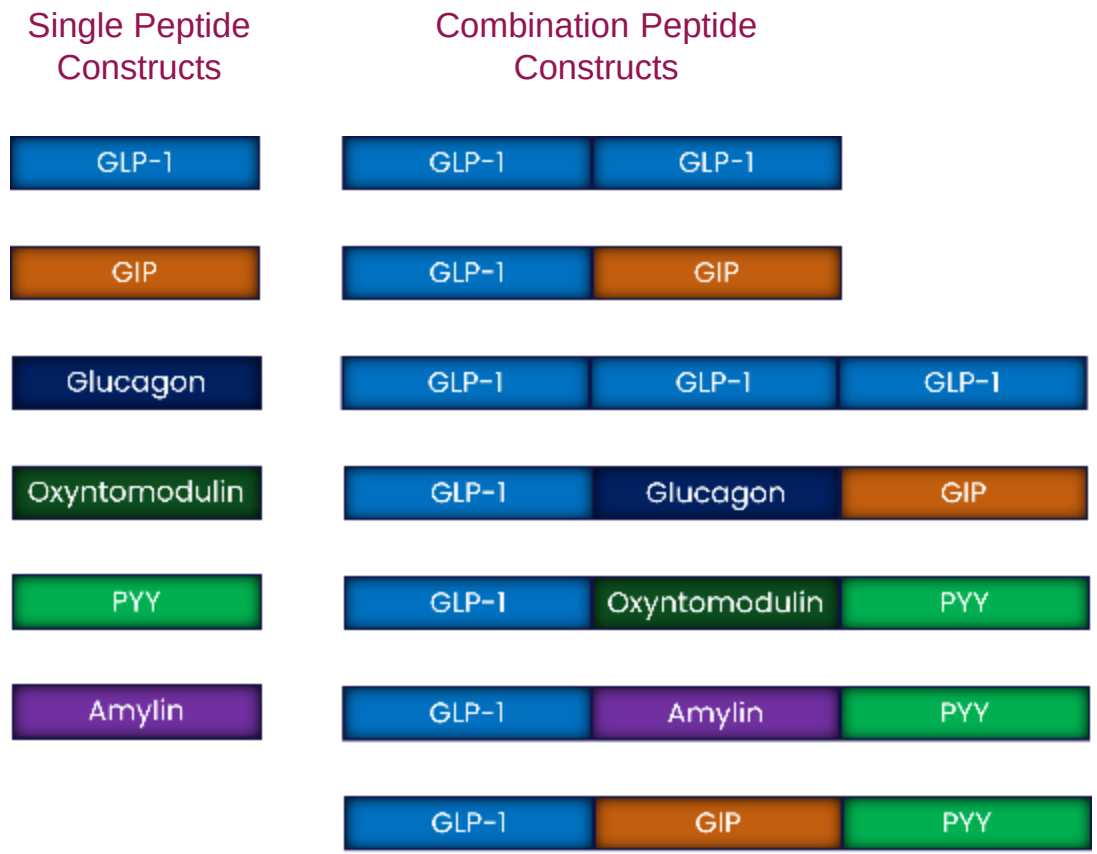
Tight Dose Response Control of Expression of Vectorized Peptides and Hormones



Riboswitch Regulation of Gut Peptides

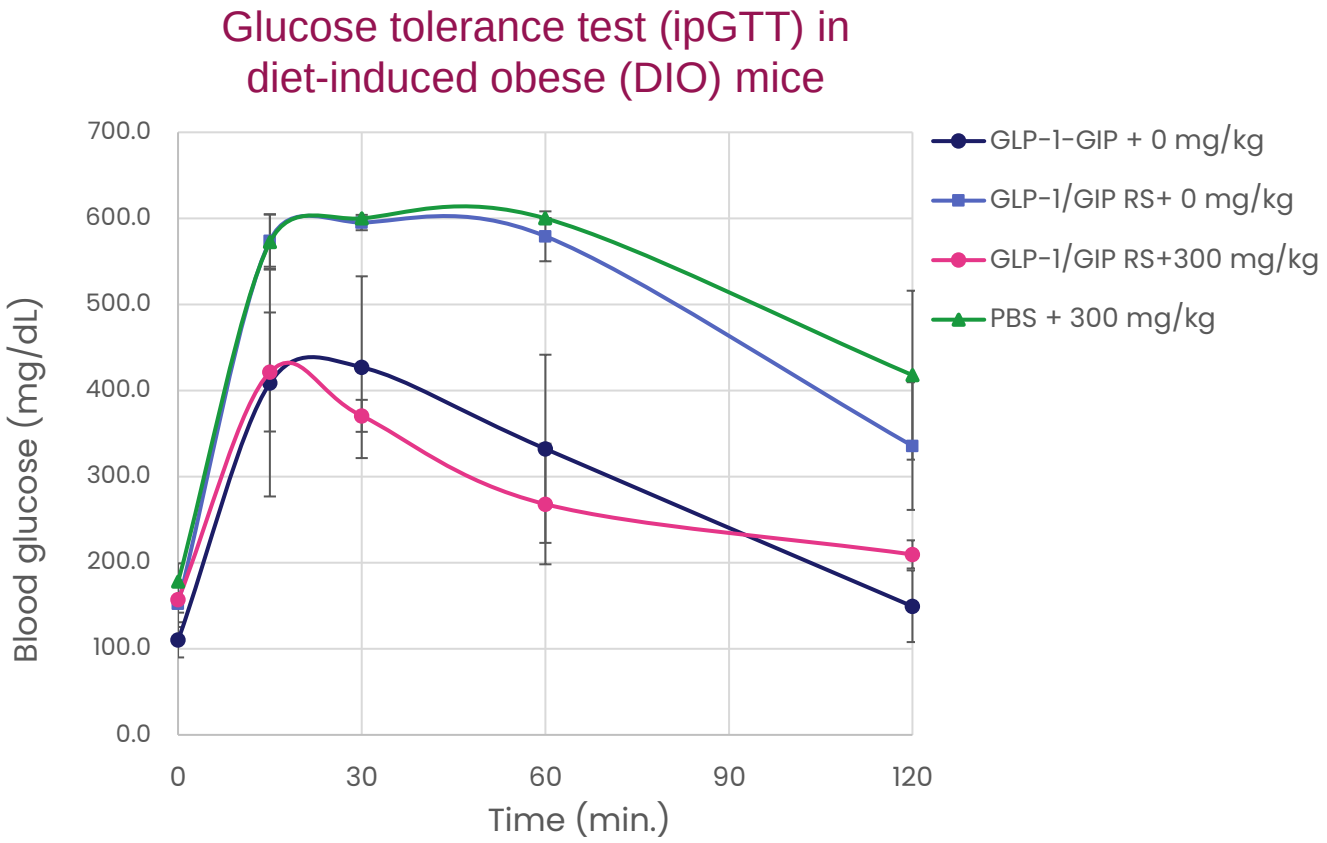
Gene Therapy with natural gut peptides:

- Expressing gut peptides has been challenging
- MeiraGTx has achieved high expression of natural gut peptides, alone or in combination
- The riboswitch platform provides tight and controlled expression of unmodified, wild-type peptides



Example: GLP-1 and GIP in DIO Mice: Glucose Tolerance Test

DIO mice injected with AAV expressing riboswitch-controlled GLP-1 & GIP show improved glucose tolerance (line in magenta), similar to mice with constitutive GLP-1 and GIP expression (dark blue line)



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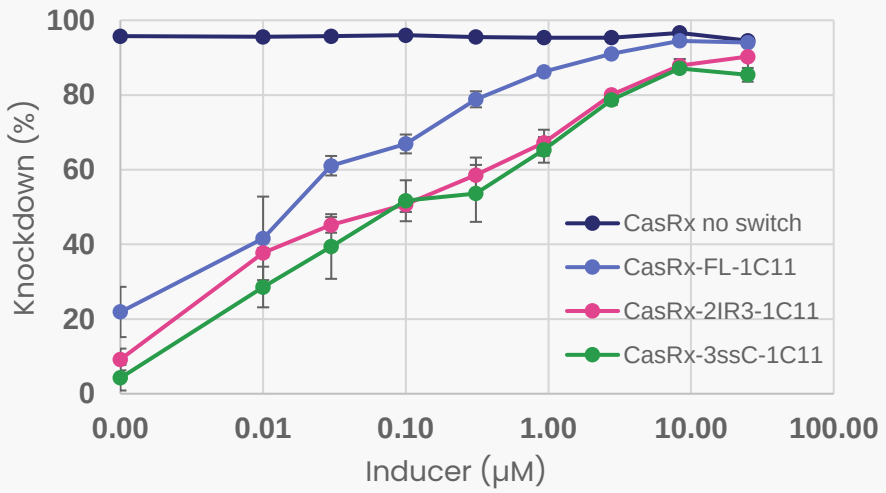
CRISPR-CasRx: Undetectable Levels of Basal Expression Provides Unprecedented Regulation of Nucleases

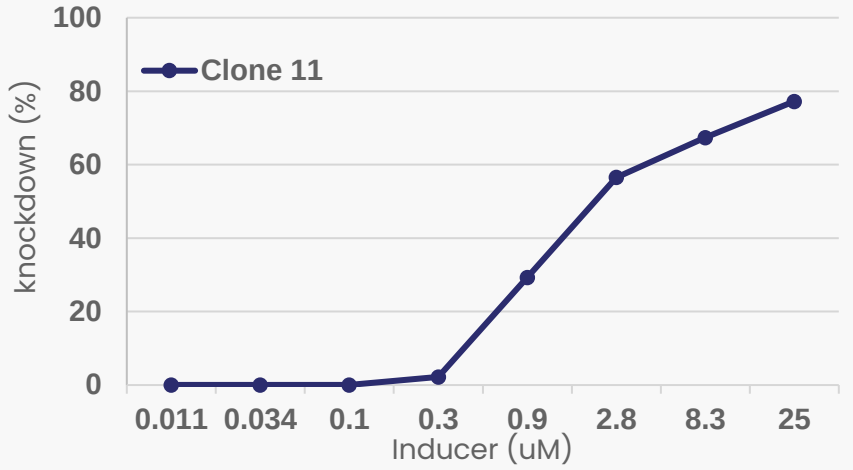
Use of intron sequence modifications in the regulation cassette enables potent activation from undetectable basal level of gene expression

Dose-dependent knockdown in response to small molecule inducer, MXU-001



- Riboswitch cassettes FL-1C11, 2IR3-1C11 and 3ssC-1C11 contain different intron sequences, which affect splicing activity and, as a result, give rise to different basal expression levels of CasRx
- CasRx-3ssC-1C11 showed the lowest basal activity of CasRx

Efficient knockdown activity is induced from undetectable levels in cells stably expressing CasRx

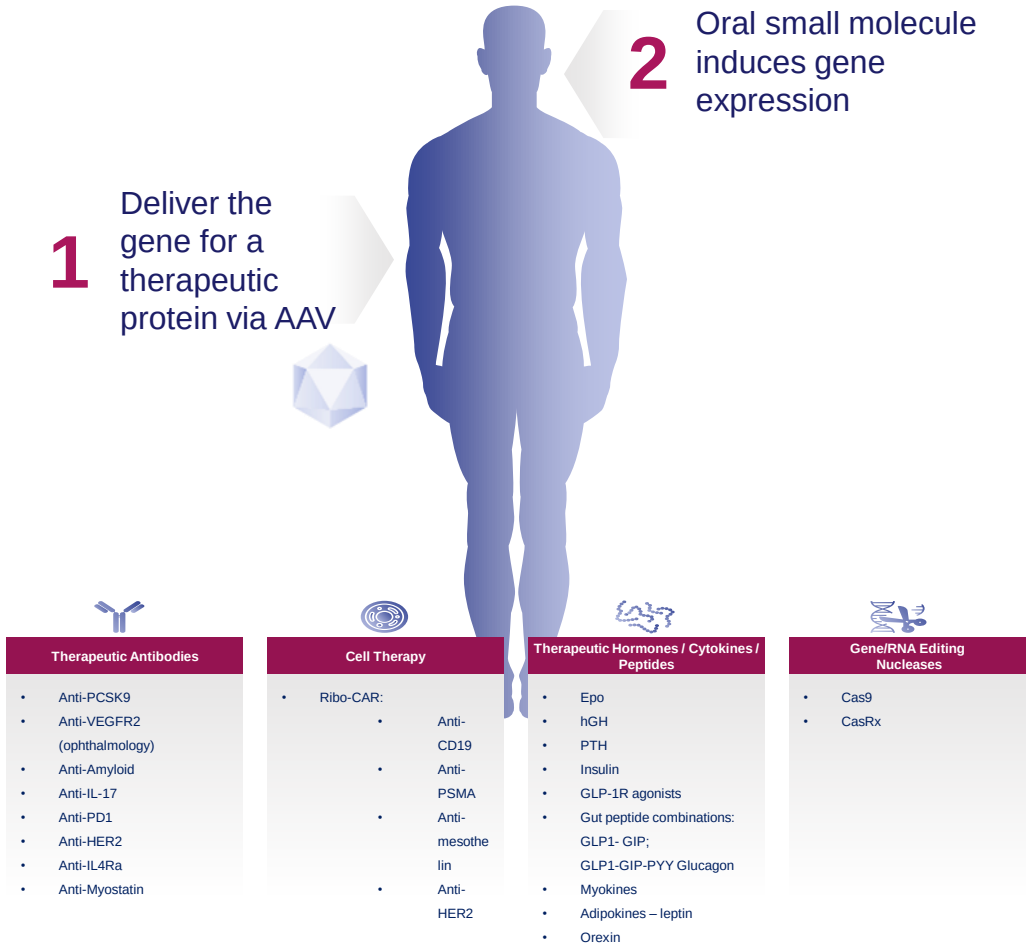


- Zero basal activity of CasRx in cells stably expressing the CasRx-3ssC-1C11 cassette in the absence of inducer

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 expression levels by novel small molecules inducers
- 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

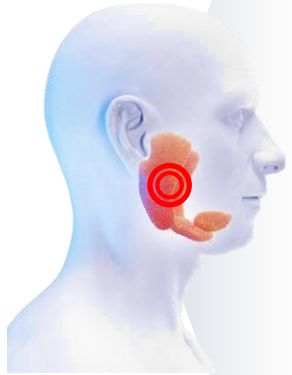


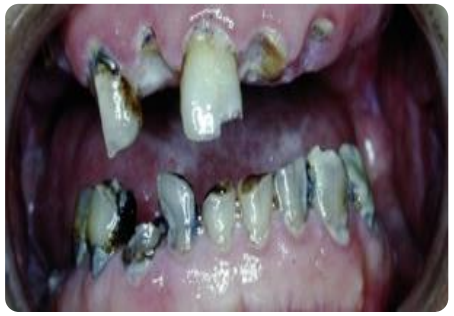
AAV-hAQP1: A First-in-Class Gene Therapy for Treatment of Radiation-Induced Xerostomia (RIX)

Radiation-Induced Hyposalivation and Xerostomia (RIX)

Serious, debilitating complications as a result of reduced saliva production

- RIX is one of the most frequent complications of radiation treatment for head and neck cancer
- 85% of radiation-treated patients experience reduced saliva production, of whom 40% have persistent Grade 2/3 RIX
- Persistent Grade 2/3 RIX is a common, durable and severely debilitating condition
- Patients' experience:
  - Difficulty eating, chewing and swallowing; taste alterations
  - Speech difficulties and abnormalities
  - Difficulty sleeping; difficulty exercising
  - Uncontrollable dental caries with severe tooth decay/periodontal disease
  - Inability to wear dentures
  - Oral pain and throat pain
  - Burning mouth sensation in 40% of patients
  - Harmful changes in oral flora





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)

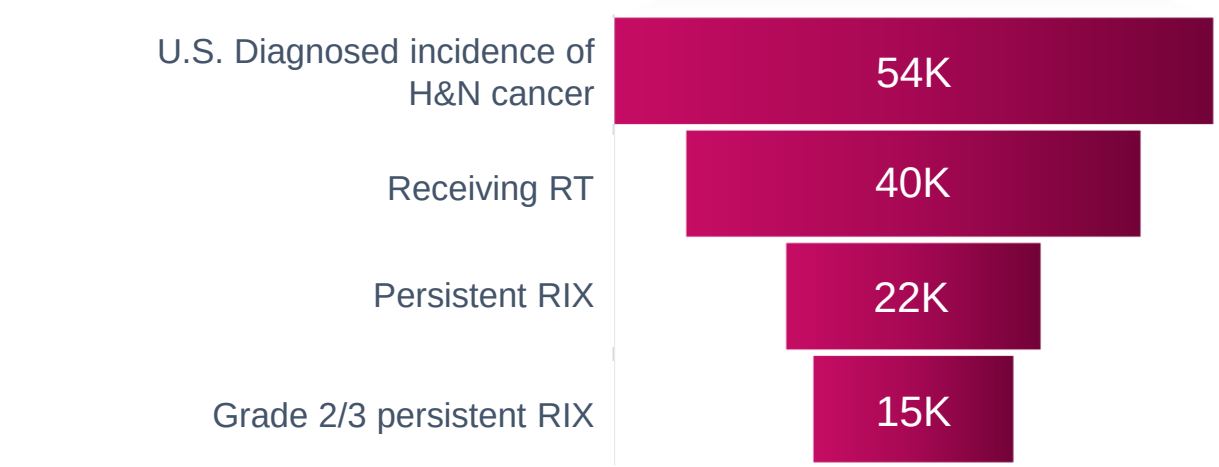
170K

Grade 2/3 RIX patients in the US

Incidence (US)

15K

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

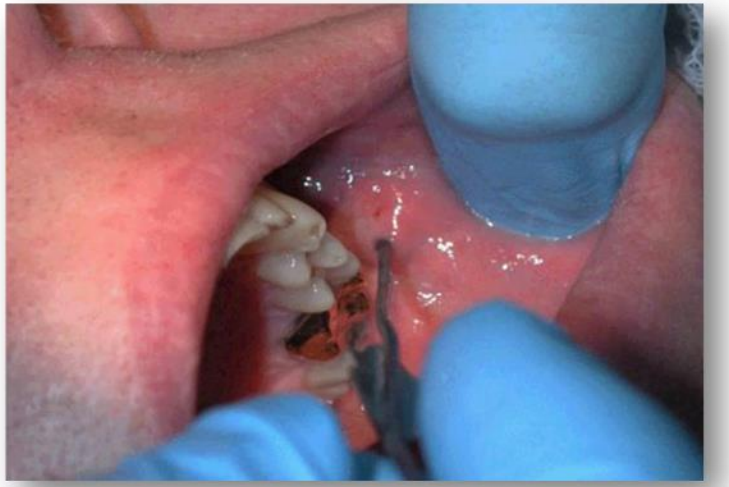


[1] SEER, Cancer.net
[2] Marta GN et al (2014). Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol. 110(1):9-15
[3] Jensen S.B., et al. (2010). A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: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

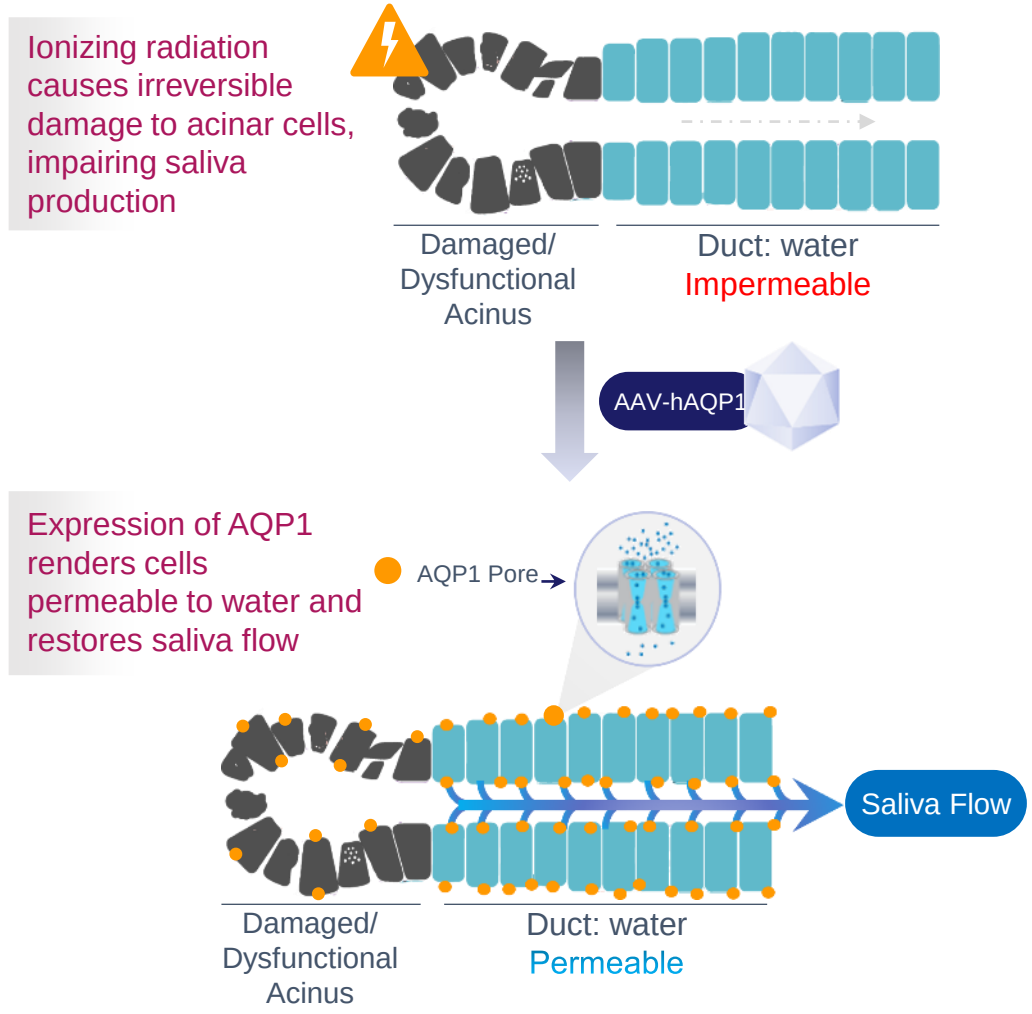
» **One-time therapy** | Well tolerated by patients, with durable efficacy

» **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**



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

Summary: MGT016 AQUAx Phase 1 Study

Study Status: COMPLETED

- Four unilateral treated cohorts (n=12)
- Four bilateral treated cohorts (n=12)
- Study completed, database locked
- Subjects continue to be followed for up to 5 years in the long term follow up study

Data Presented at 12-Month Update:

- Data from all unilateral (n=12) and bilateral cohort subjects (n=12) out to 12 months post treatment
- Data from those long term follow up subjects who have reached 2- and 3-years post treatment

Safety:

- AAV2-hAQP1 treatment appears safe and well tolerated at each dose tested
- No dose limiting toxicity or drug related serious adverse events

Activity:

- Improvements observed in both of the patient reported assessments of xerostomia symptoms, GRCQ and XQ, in both unilateral and bilateral treated cohorts at 12 months post treatment
- Improvements in salivary flow were seen in unilateral as well as bilateral cohorts
- Durability out to 2 years in 4 participants and 3 years in 3 participants

Click here for MeiraGTx's June 2023 Clinical Update Presentation from the Phase 1 AQUAx Trial

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

GRCQ: Strong, Durable Improvements in Severity of Xerostomia was Demonstrated 12 Months After Unilateral Treatment

GRCQ UNILATERAL		Dry Mouth Symptoms? Better (+), Worse (X), or Same (=), How Much Better/Worse?					
Cohort	Participant	Day 90	Day 180	Day 360	Month 18	Year 2	Year 3
1	1-1	+, 5	+, 6	+, 7	N/A	+, 7	+, 7
	1-2	+, 3	+, 3	+, 6	N/A	+, 2	+, 3
	1-3	+, 3	+, 3	=	N/A	+, 4	+, 4
2	2-1	=	=	=	N/A	=	
	2-2	+, 2	+, 4	+, 4	N/A	+, 4	
	2-3	+, 6	+, 6	+, 6	N/A		
3	3-1	+, 4	+, 3	+, 3	+, 3		
	3-2	=	=	=	=		
	3-3	NA	=	+, 5	=		
4	4-1	+, 4	+, 4	+, 4	+, 4		
	4-2	=	=	=			
	4-3	+, 4	+, 4	+, 6			

GRCQ Score for Unilateral Treatment (n=12) All participants to 12 months or more

- 8/12 participants at 12 months reported symptoms of dry mouth as ‘better’ following treatment
- Each of the 8 participants reported a score of 2 or more ie: “an important change”
- At 12 months, 4 participants rated the change in xerostomia symptoms with the highest improvement scores of 6 or 7 denoting “a very important improvement”
- Improvement in xerostomia symptoms can be seen persisting through 2 years in 4 patients and 3 years in 3 patients
- No participant reported any worsening of xerostomia symptoms

N/A: Month 18 data collection was included in a protocol amendment, data was not collected for these patients

GRCQ: Strong Improvements in Severity of Xerostomia At 12 Months Following Bilateral Treatment

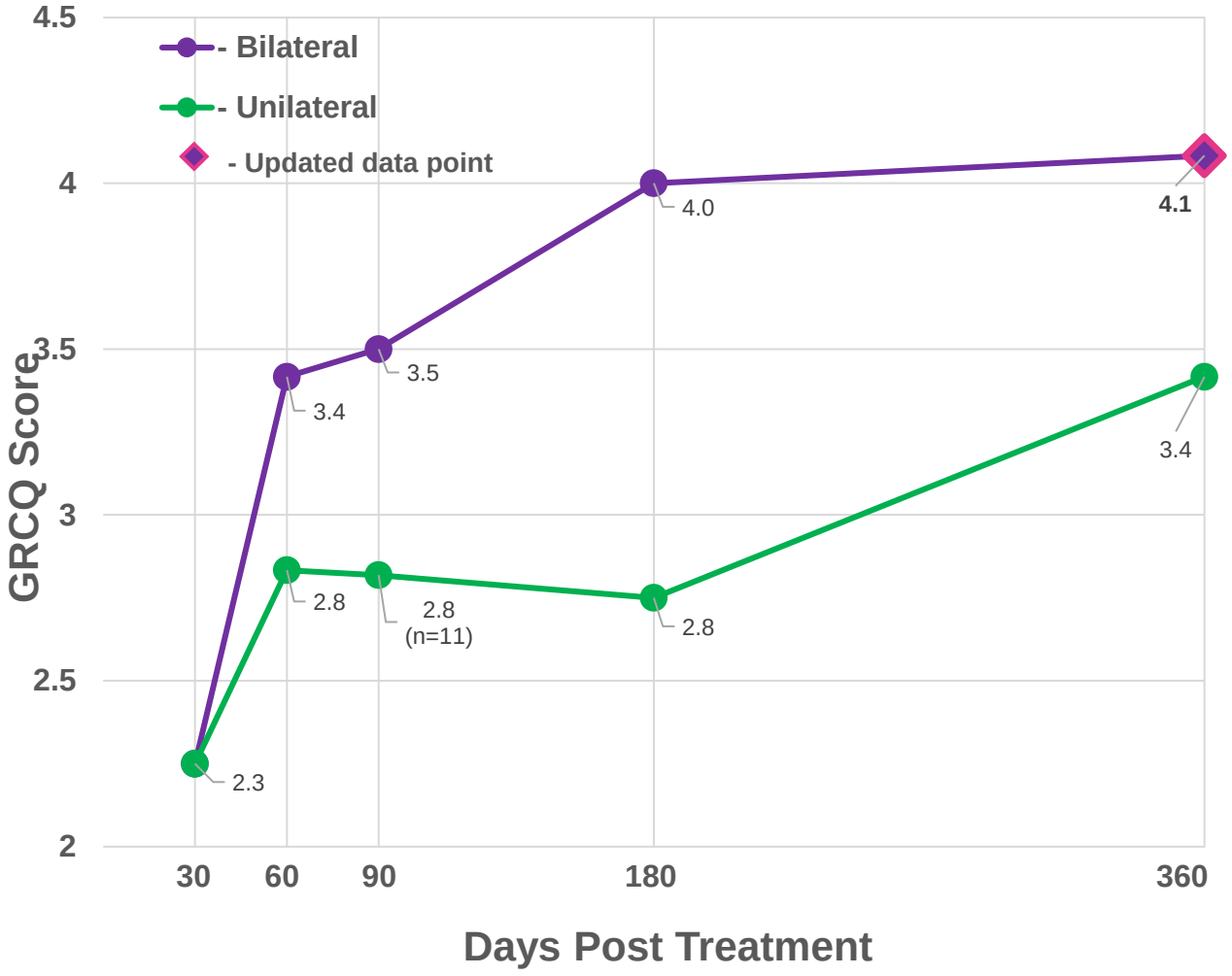
GRCQ BILATERAL		Dry Mouth Symptoms? Better (+), Worse (X), or Same (=), How Much Better/Worse?		
Cohort	Participant	Day 90	Day 180	Month 12
1b	1b-1	+, 4	+, 4	+, 4
	1b-2	+, 4	+, 5	+, 6
	1b-3	+, 5	+, 6	+, 5
2b	2b-1	+, 1	=	=
	2b-2	+, 5	+, 5	+, 5
	2b-3	+, 1	+, 2	=
3b	3b-1	+, 2	=	+, 2
	3b-2	+, 6	+, 7	+, 7
	3b-3	+, 6	+, 6	+, 6
4b	4b-1	+, 4	+, 4	+, 6
	4b-2	+, 4	+, 5	+, 2
	4b-3	=	+, 4	+, 6

GRCQ Score for Bilateral Treatment (n=12) All participants to 12 months

- 10/12 (83%) participants at 12 months reported symptoms of dry mouth as ‘better’ following treatment
- Each of these participants rated changes in xerostomia scores that were important or very important with a score of 2 or more at 12 months
- 5 participants rated the change in xerostomia symptoms with scores of 6 or 7 denoting “a very important improvement”
- No participant reported any worsening of xerostomia symptoms
- For all patients including bilateral and unilateral (n=24), 18/24 or 75% reported dry mouth as ‘better’ with a clinically meaningful score of 2 or more

GRCQ: Overall Improvement Greater in Bilateral compared to Unilateral treatment group; Unprecedented 4-point Improvement at 12 Months

GRCQ improvements for Bilateral and Unilateral and Treated Cohorts



- In the overall cohorts, the average improvement score in GRCQ was greater in bilateral compared to unilateral
- Overall improvements were maintained and increased over time in both unilateral and bilateral cohorts
- A 2-point change in GRCQ compared to placebo is considered significant by KOLs
- Anything 3 points or greater is considered a substantial improvement over standard of care and “transformative” by KOLs
- Unilateral cohort achieved overall improvement of >3 points at 12 months
- Bilateral cohort achieved overall improvement of >3 points at 2 months and an overall improvement of 4 points by 6 months, this 4-point improvement is maintained at 12 months

n=12 unless otherwise indicated

Xerostomia Questionnaire (XQ): Very Strong Improvements (Decrease in Score) Compared to Baseline Observed in Both Unilateral and Bilateral Cohorts

Change From Baseline Unilateral

Cohort	Participant	Day 90	Day 180	Day 360	Month 18	Year 2	Year 3
1	1-1	-14.7	-14.7	-18.7	N/A	-19	-17.7
	1-2	-8.3	-0.3	-17.3	N/A	-7.3	-28.3
	1-3	-6.3	-6.3	-3.3	N/A	-6.3	-4.3
2	2-1	-14.0	-9.0	-8.0	N/A	-1.0	
	2-2	-23.0	-24.0	-21.0	N/A	-17.0	
	2-3	-38.7	-29.7	-34.7	N/A		
3	3-1	-19.3	-20.3	2.7	-14.3		
	3-2	7.7	1.7	-0.3	-7.3		
	3-3	5.3	-1.7	-4.7	-5.7		
4	4-1	-37.7	-34.7	-12.7	-20.7		
	4-2	-3.3	0.7	3.7			
	4-3	-39.0	-41.0	-43.0			

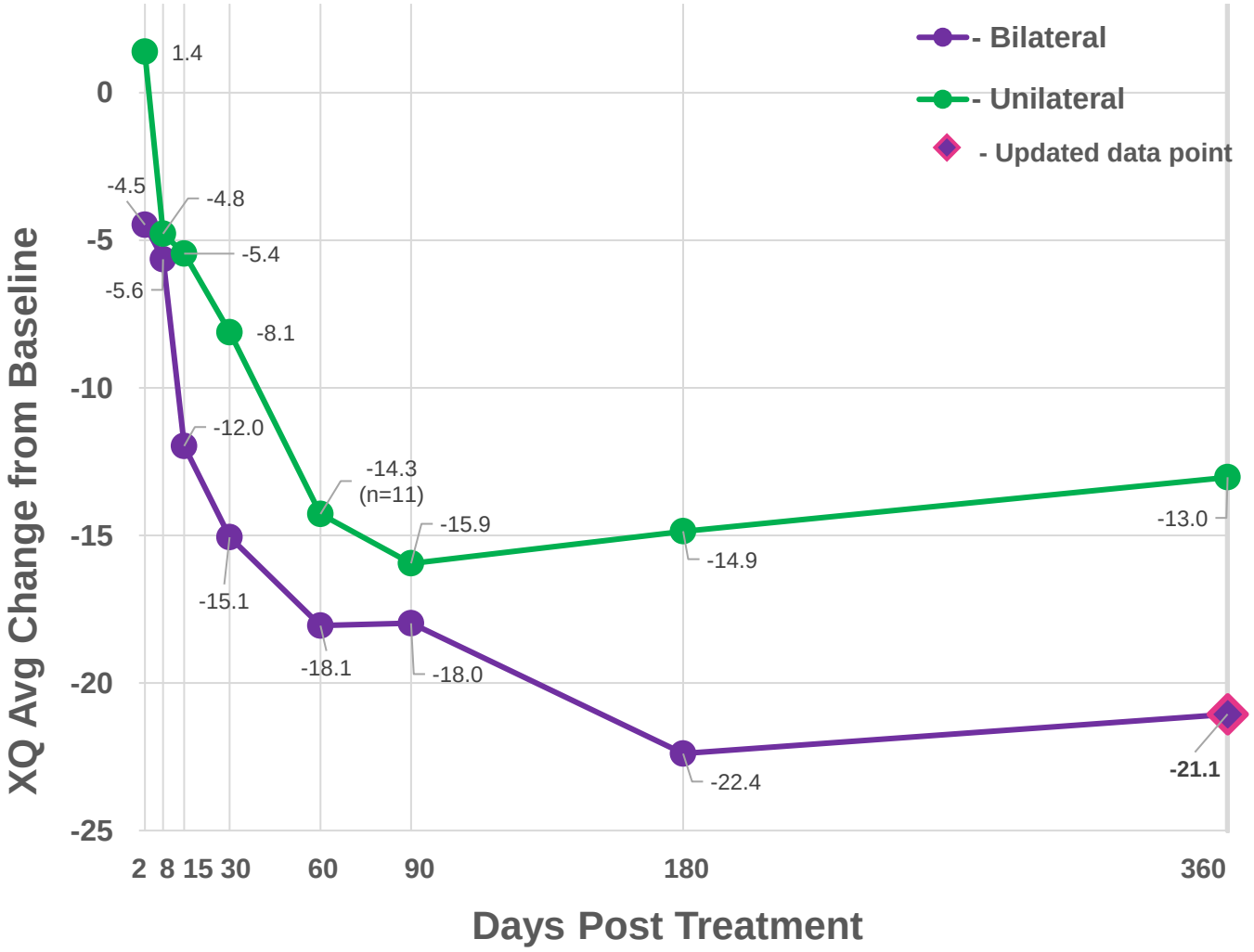
Change From Baseline Bilateral

Cohort	Participant	Day 90	Day 180	Month 12
1b	1b-1	-15.3	-17.3	-16.3
	1b-2	-31.3	-26.3	-41.3
	1b-3	-11.0	-10.0	-10.0
2b	2b-1	-7.3	-11.3	-2.3
	2b-2	-34.7	-33.7	-37.7
	2b-3	-15.7	-23.7	-4.7
3b	3b-1	-4.0	-5.0	-6.0
	3b-2	-26.3	-30.3	-23.3
	3b-3	-29.7	-44.7	-27.7
4b	4b-1	-27.0	-35.0	-31.0
	4b-2	-16.0	-31.0	-30.0
	4b-3	2.7	-0.3	-22.3

- **Unilateral:** 7/12 had score improvements (decrease) ≥8 at 12 months
- **Bilateral:** 9 /12 had score improvements ≥8 at 12 months
- **Overall:** 16 /24 (66%) had an improvement following treatment of ≥8 points
- A decreased score of 10 is considered transformative
- 6/12 or 50% of unilateral at 12 months and 9/12 or 75% of bilateral at 12 months achieved at least a 10-point improvement
- There was good concordance with the individual patients who responded in XQ and GRCQ

N/A: Month 18 data collection was included in a protocol amendment, data was not collected for these patients

XQ: Substantial Clinically Meaningful Improvements From Baseline in XQ in both Unilateral and Bilateral treated Cohorts

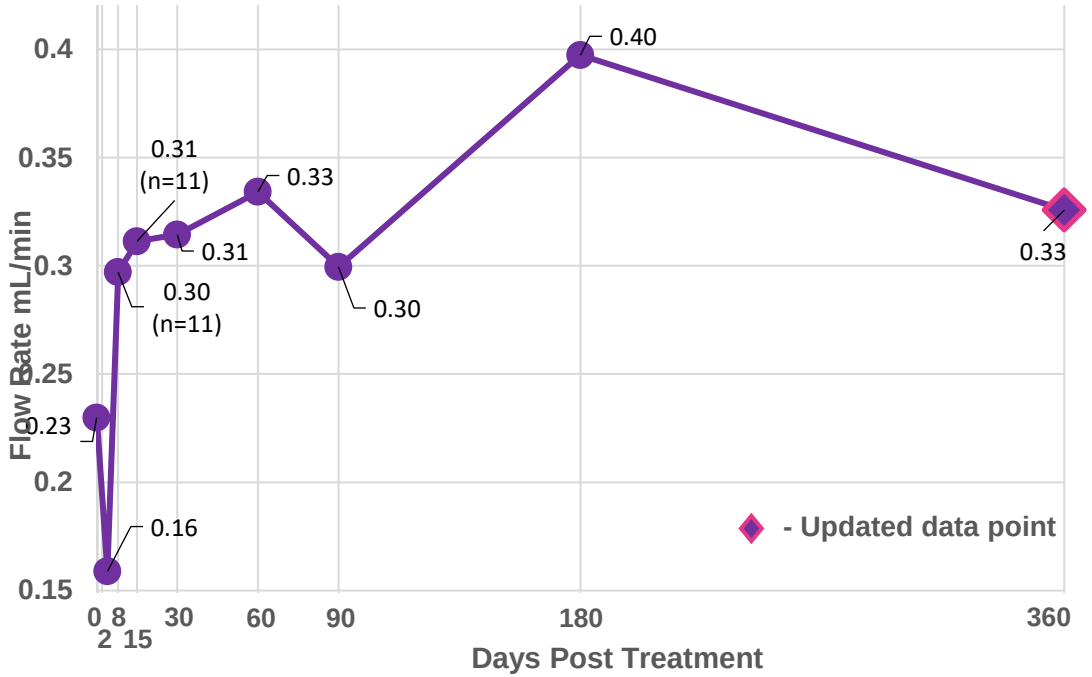


- **Unilateral:** 13-point improvement from baseline at 12 months
- **Bilateral:** 21-point improvement from baseline at 12 months
- Improvement in XQ was observed rapidly post treatment
- In both groups XQ scores improved (declined) >8 points soon after treatment, and >10 points within 2 months after treatment
- **This level of benefit is considered transformative by KOLs**
- As with the GRCQ, the degree of improvement was greater in bilateral compared to unilateral treated cohorts

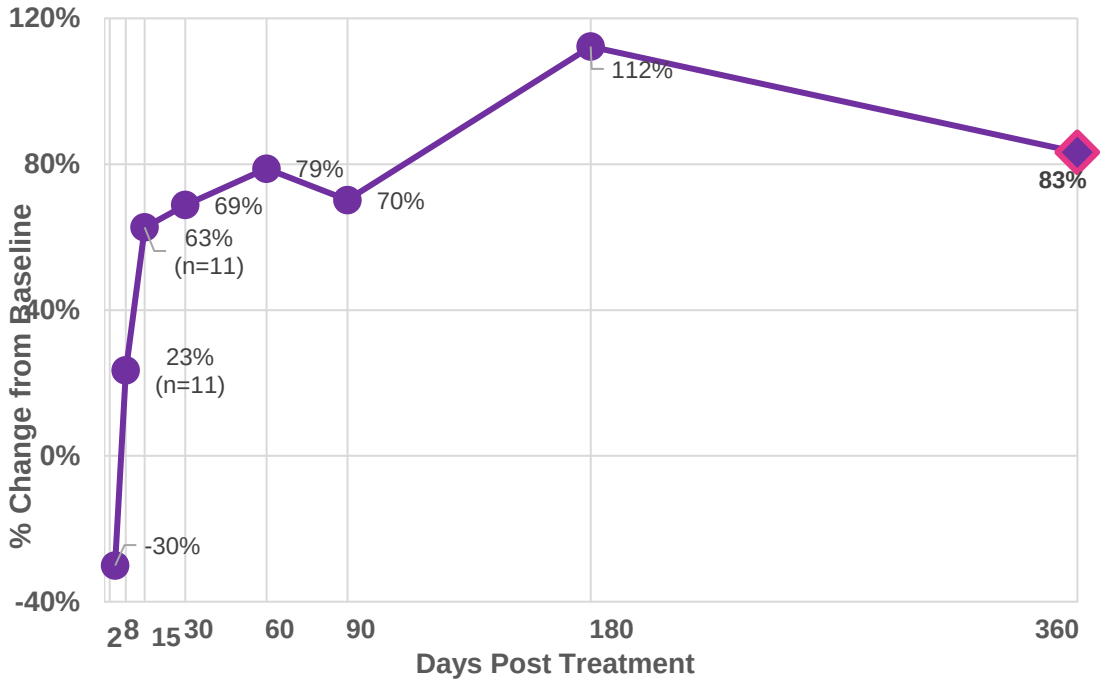
n=12 unless otherwise indicated

Bilateral Cohorts: Meaningful Improvement in Unstimulated Whole Saliva Production Achieved Reaching Normal Levels Following AAV2-hAQP1 Treatment

Whole Salivary Flow Rate (mL/min)



Average % Change from Baseline Flow Rate



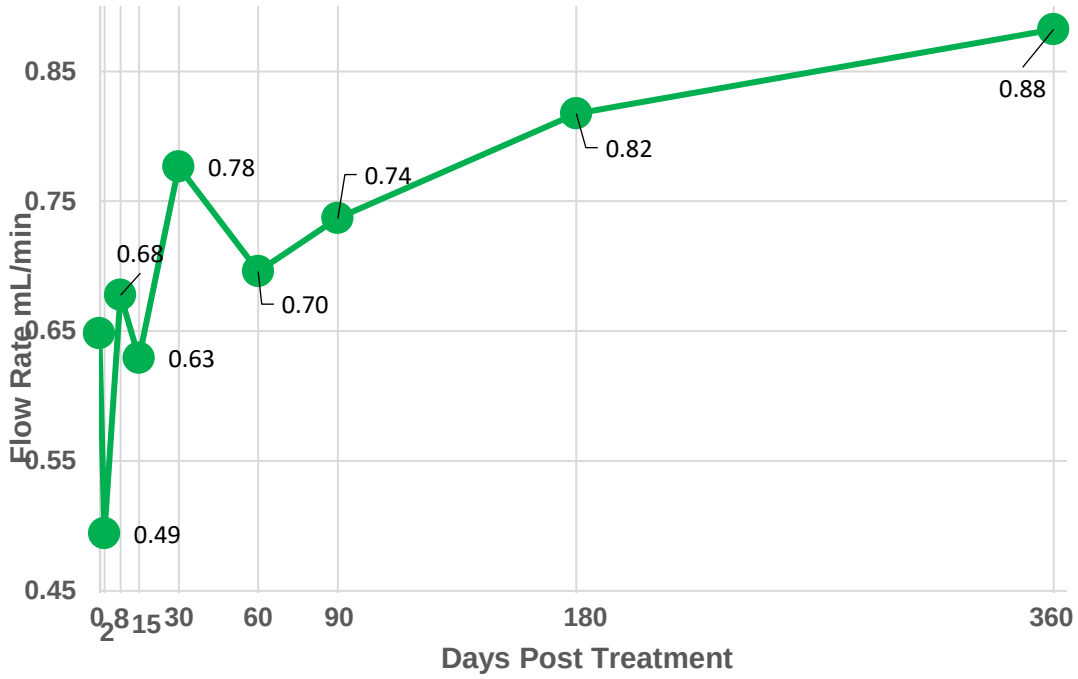
- Meaningful increase in whole salivary flow was seen in bilateral treated patients
- The overall flow rate improved to an average of 0.33 mL/min which is in the normal range for unstimulated whole saliva production
- Normal unstimulated salivary flow rate averages 0.3-0.4 mL/min
- If flow rate of unstimulated saliva is >0.1-0.2mL/min, then salivary hypofunction is diagnosed with associated xerostomia likely

- The average % change from baseline was 83% at 12 months
- This is clinically meaningful as a 50% reduction in whole saliva volume is associated with xerostomia symptoms

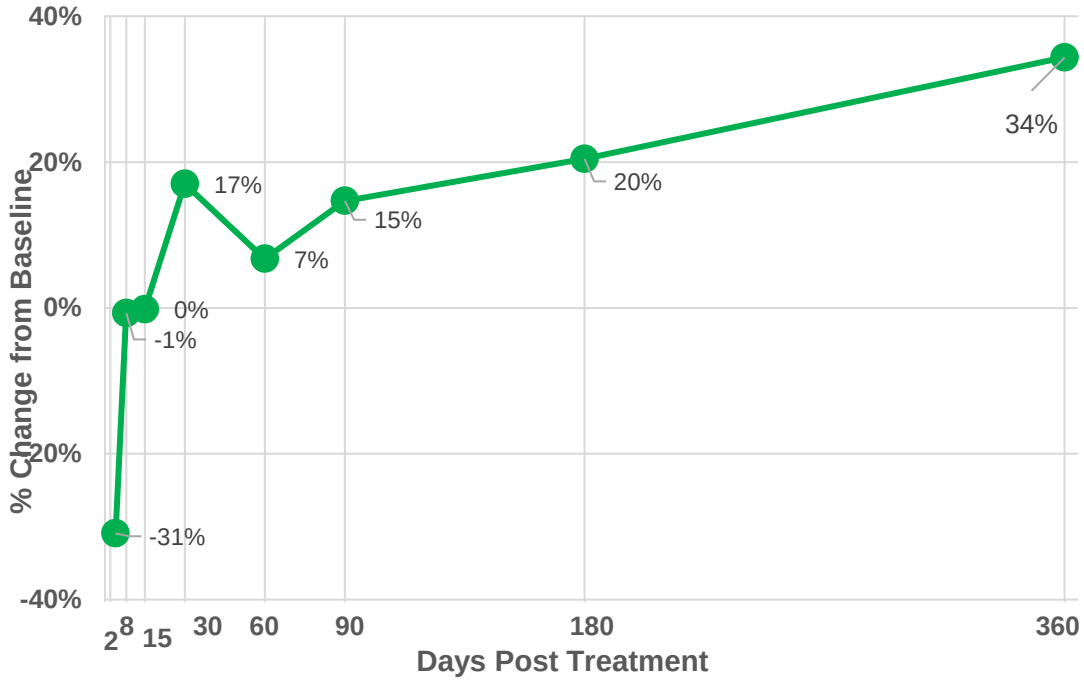
- Based on both absolute whole resting saliva as well as the overall % change from baseline – the improvement in unstimulated salivary flow in the bilateral appear to be of clinically meaningful size that could result in improvement in xerostomia symptoms

Unilateral Treated Subjects Also Showed Improvement in Absolute Whole Saliva Measures (Stimulated)

Absolute Salivary Flow Rate (mL/min)



Average % Change from Baseline Flow Rate



- Increase in whole salivary flow was seen in unilateral treated patients
- Whole saliva was collected using gum stimulation, however this was directly following citric acid stimulation for extended periods with manipulations to attempt collection from individual glands

- Normal stimulated salivary flow rate averages 1.5–2.0 mL/min
- A diagnosis of hyposalivation is made with flow rate ≤0.5–0.7 mL/min

Improvements in Both Xerostomia Severity Scores and Saliva Production Demonstrated Following AAV2-hAQP1 Treatment

Summary of Clinical Data:

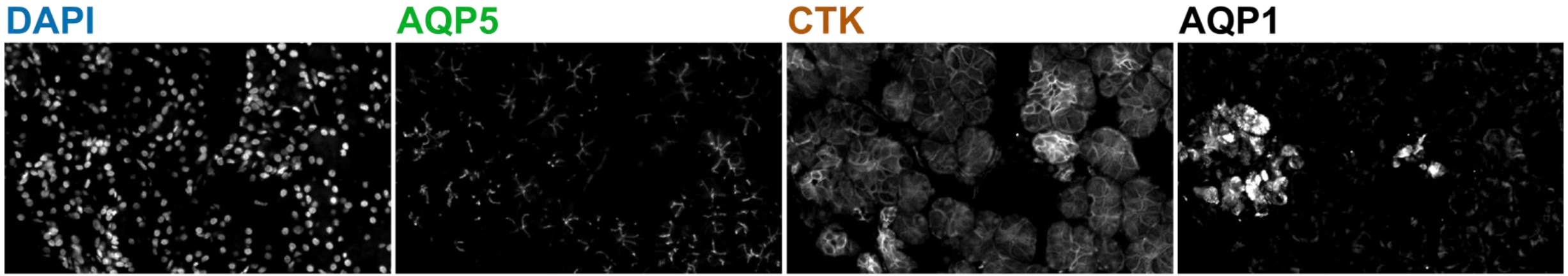
- Meaningful improvements in xerostomia symptoms were reported across both unilateral and bilateral treated cohorts
- As assessed by the GRCQ in unilateral and bilateral treated patients, 18/24 (75%) reported a clinically meaningful score of 2 or more
- Using the XQ severity scale, 16/24 (66%) had an improvement of ≥8 points and 15/24 (63%) had an improvement of 10 or more points
- Increases in whole saliva flow rates observed post-treatment, providing objective evidence supporting biological activity
- Unstimulated whole saliva flow increased meaningfully in the bilaterally treated cohorts with improvement to normal levels being achieved 6 months post treatment
- Greater improvements were observed in bilaterally treated patients across every assessment compared to unilateral
- Early long-term follow-up data suggest durability of improvement 3 or more years post-treatment
- Biopsy data shows transduction of cells of parotid glands treated AAV-hAQP1, expression of hAQP1 protein, and persistence to at least 24 months post treatment

Study MGT001: AAV2-hAQP1 Persists in Parotid Gland for at Least 24 Months After Treatment

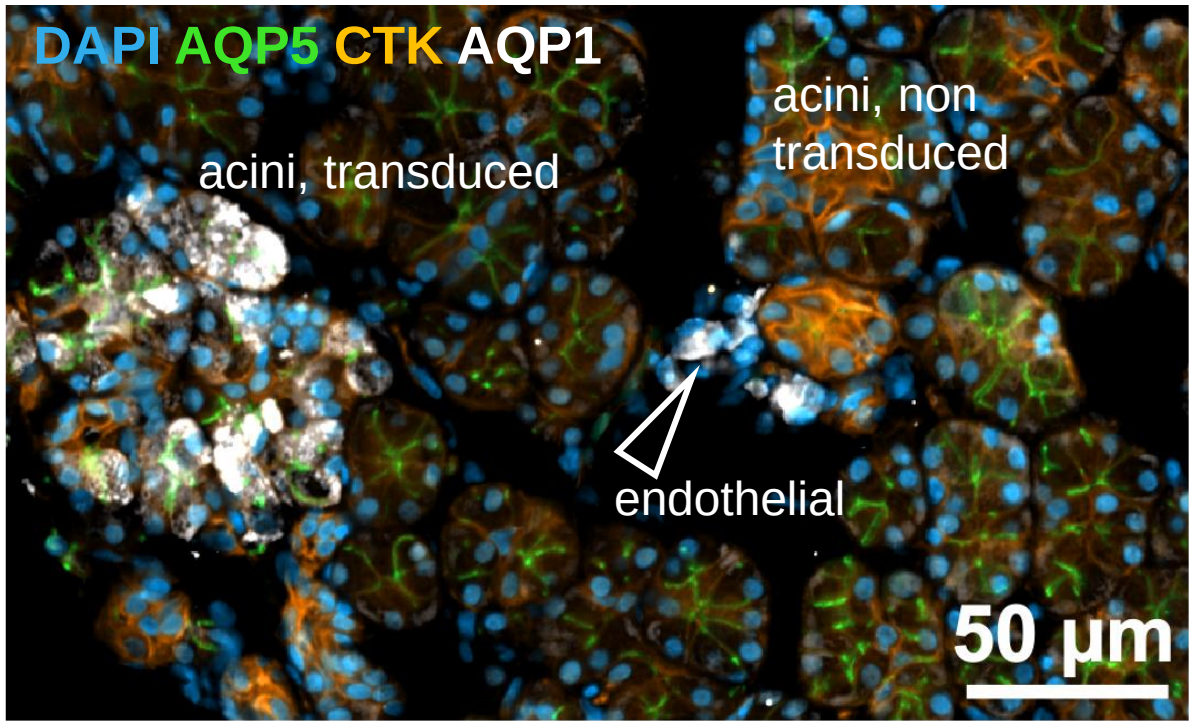
Participant	Cohort	Dose per gland	Dose Concentration	Visit of Biopsy	Copy #/ng DNA	Copy #/Cell
AAV001	1	1E10	1.43E10	18 Months	160	0.96
AAV005	1	1E10	5.00E9	24 Months	122	0.73
AAV002	2	3E10	1.76E11	18 Months	236	1.4
AAV019*	3	1E11	1.11E11	24 Months	5393	32
AAV020	4	3E11	1.50E11	30 Months	ND	ND
AAV021*	4	3E11	1.15E11	12 Months	87390	524
AAV031	5	6E11	3.16E11	12 Months	7313	43

- Biopsies were obtained in 7/15 participants enrolled in MGT001
- 6/7 biopsies showed AAV2-hAQP1 genomes ≥12 months post-treatment
- There is a trend of increasing copy number of transduced vector genomes with increasing viral vector dose

Study MGT001: AAV2-hAQP1 Persists in Parotid Gland for at Least 24 Months After Treatment



- The image in this slide comes from a core needle biopsy from participant AAV019 in the NIH Phase 1 study
- AQP1 protein expression is observed in parotid gland cells at 24 months post-treatment
- Acinar cells in this section express AQP1 (shown in white) whereas they normally express only AQP5 – here shown in green
- Levels of AQP1 protein in transduced acinar cells appear similar to the endogenous levels seen in non-parotid endothelial cells



AQUAx 2: Phase 2 Study Design and Efficacy Endpoints

Phase 2 randomized, double-blind, placebo-controlled study is now open

Study Design

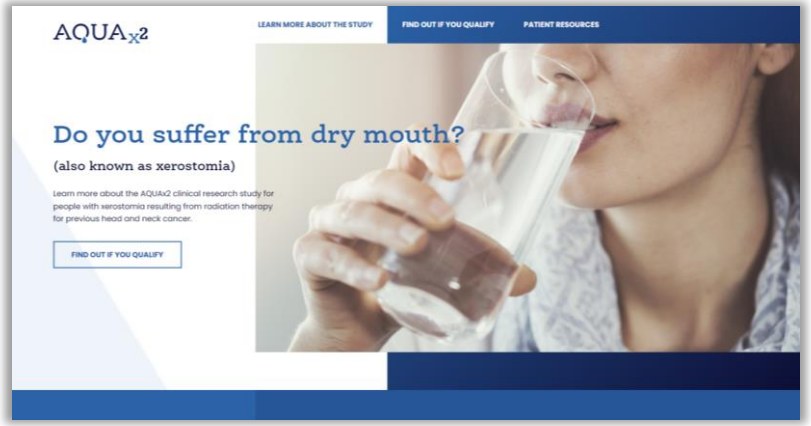
- Randomized, double-blind, placebo-controlled
- 120 participants: Two active doses of AAV2-hAQP1 vs Placebo 1:1:1
- Active Doses: 0.4E12 and 1.2E12 (n=40 for each arm)
- A third higher dose of 3.6E12 may be added to the blinded design at a future date
- MHRA approval to open the trial has been obtained and UK site startup is underway

Primary Efficacy Endpoints

- Change from Baseline to 12 Months in Symptom-specific Xerostomia Questionnaire (XQ)

Key Secondary Endpoints

- Change from Baseline to 12 Months in Whole Saliva Flow Rate
- Safety and tolerability of AAV2-hAQP1 treatment
- GRCQ is also being assessed as a secondary endpoint



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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 ongoing

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

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

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

Combination Therapy

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

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

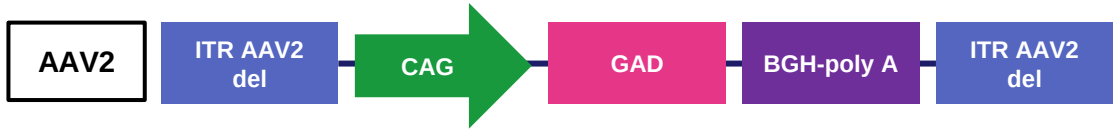
Approach

- 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

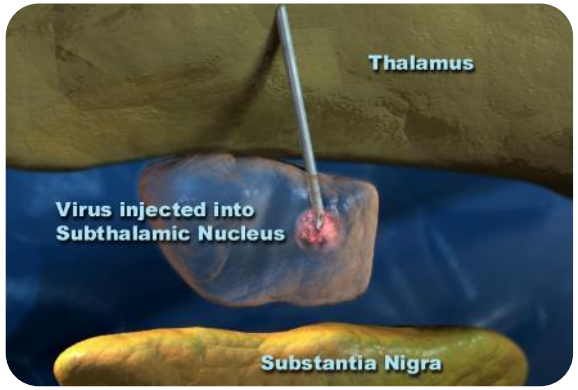
Localized delivery of AAV-GAD directly into the STN | local delivery of very small dose avoids safety risks associated with high dose/broad exposure of AAV in CNS and provides site-specific changes in neurotransmitter activity.

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



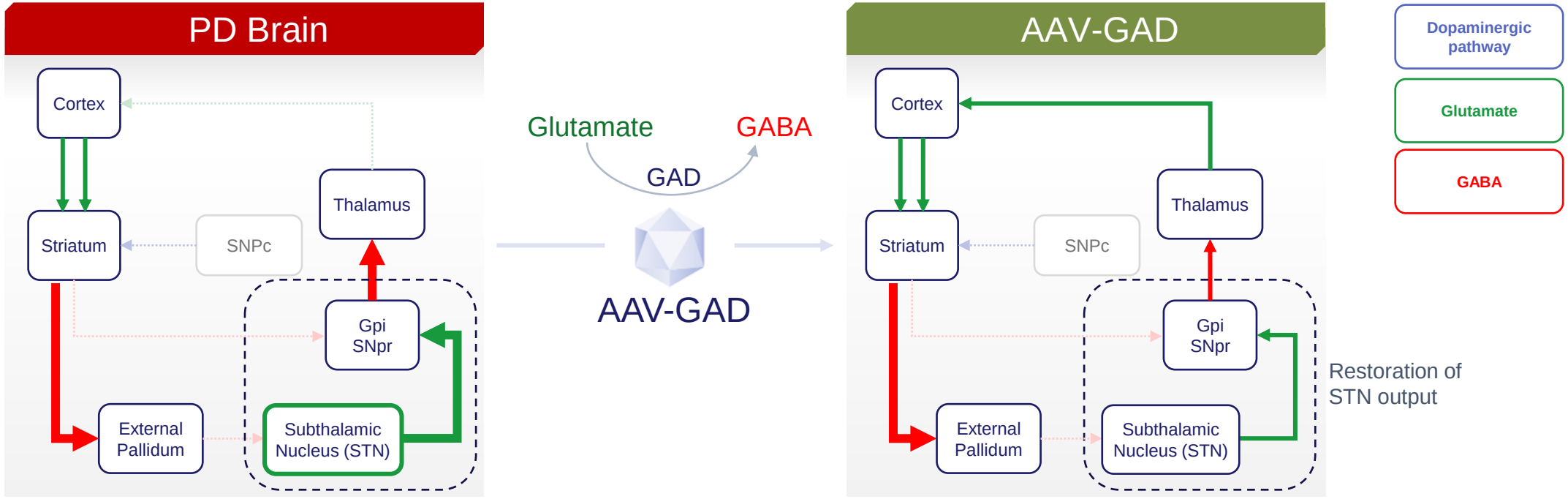
The Glutamic Acid Decarboxylase (GAD) gene is delivered locally to the STN to increase production of GABA only at the specific site that is required for alleviating PD related motor symptoms



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:

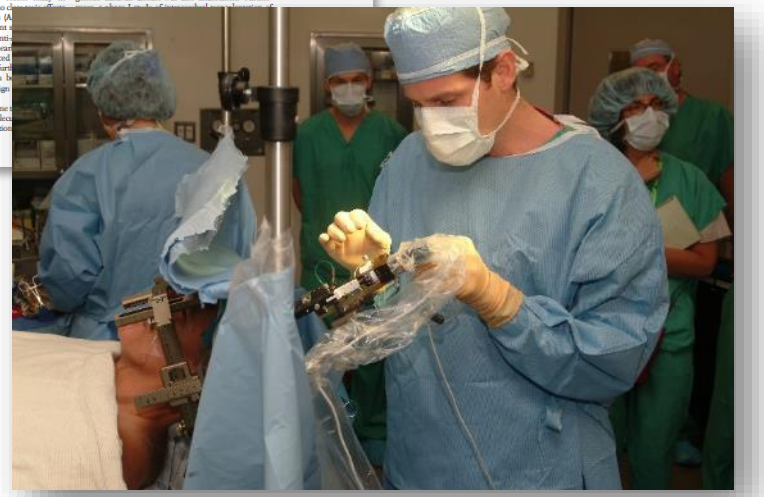
- AAV-GAD was safe and well tolerated, with no adverse events related to the gene therapy
- No abnormalities were noted on postsurgical MRIs up to 1 year
- No evidence of adverse events in the perioperative period and for at least 1 year after treatment (most patients followed up for >2 years)
- No evidence 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: change in off-medication UPDRS Part 3 score at 6 months between treated and sham

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

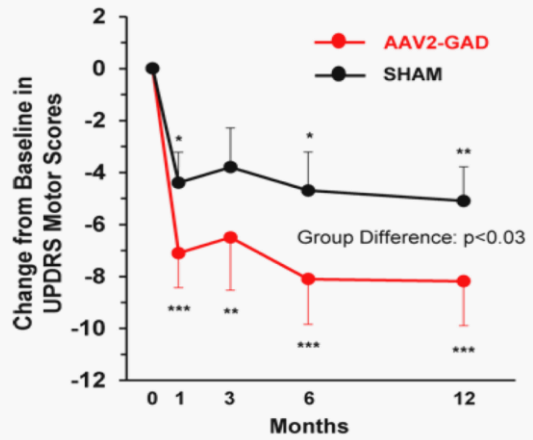
Efficacy findings (summary):

- Study met primary endpoint: UPDRS motor score improvement significantly greater than sham over 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)
- FDG-PET imaging showed significant changes in brain motor networks of AAV-GAD subjects **(GADRP)** not observed in the sham group while sham subjects exhibited a sham PET pattern not observed in the AAV-GAD 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

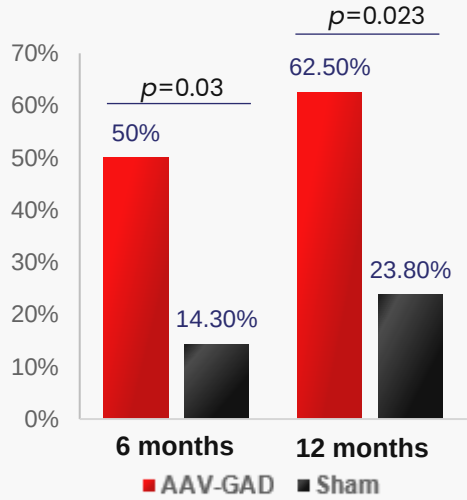
Significant improvements in UPDRS motor scores



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

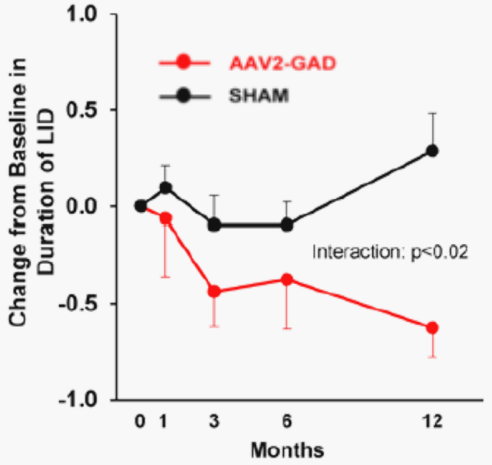
- Met primary outcome measure: improvement in UPDRS 3 motor scores vs. sham at 6 months
- Improvements in the AAV-GAD group were observed at all time points

Significantly greater responder rate (≥9 points UPDRS)



- A 9.0 point improvement in UPDRS motor score corresponds with a 25% improvement from average baseline score
- Significantly greater responder rate was observed in the AAV2-GAD group (50%, 8/16) vs. sham group (14%, 3/21) at 6 months and 12 months (10/16 vs. 5/21 patients).
- 7/8 subjects in the AAV2-GAD group who were classified as responders at 6 months, remained responders at 12 months (in contrast with only 1 of 3 subjects in the sham group).

Reduction in duration of levodopa-induced dyskinesia



- Significant improvement in drug-induced dyskinesia at 12 months relative to baseline in the AAV2-GAD group (vs. no change in the sham group)

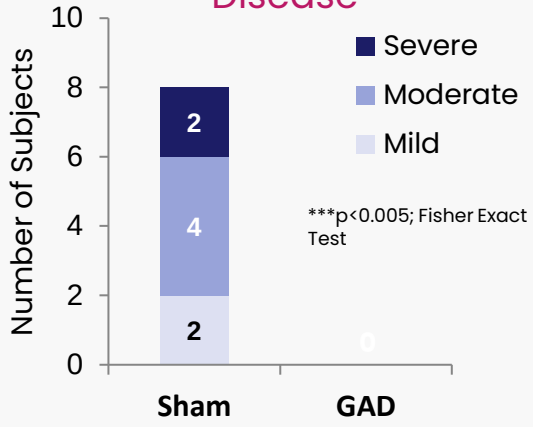
- *LeWitt PA. AAV2-GAD gene therapy for advanced Parkinson's Disease: a double-blind, sham-surgery controlled, randomized trial. Lancet Neurology. 2011; 10(4):309-19.*
- *Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133*

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

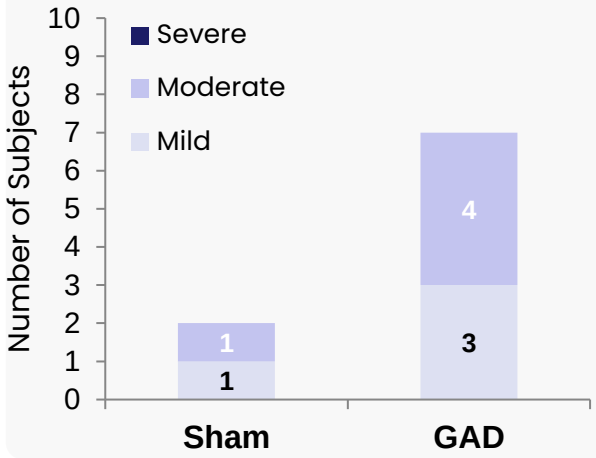
Adverse Events Over 12 Months (20% or Greater Frequency)

No GAD-treated Subjects Experienced Worsening Parkinson's

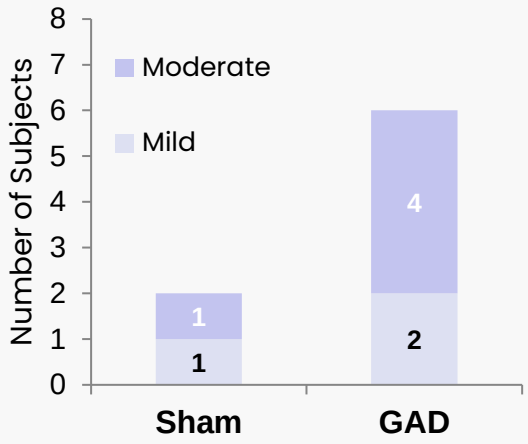
Worsening of Parkinson's Disease



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

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FDG-PET (Fluorodeoxyglucose positron emission tomography):

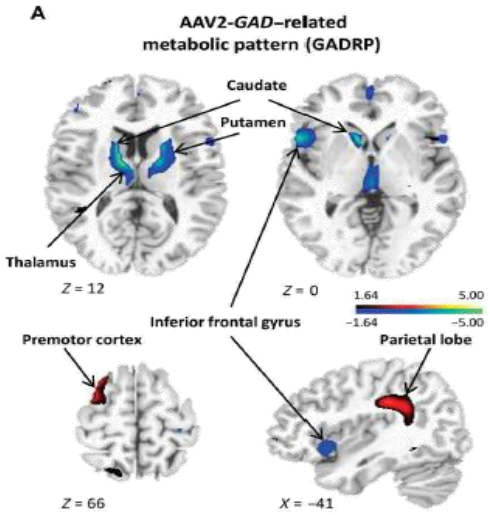
- Neurons metabolize glucose proportionate to their level of activity
- FDG-PET measures regional metabolism of radioactive glucose to determine changes in activity

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 marker 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) developed from **unbiased mathematical algorithm**
- GADRP correlates with clinical meaningfulness: Statistically significant correlation between improvement in UPDRS motor ratings and GADRP ($p < 0.009$)
- This treatment-induced brain circuit, comprised of **relevant motor regions** (comprised of brain regions essential for normal motor function) 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 ($p < 0.009$)
- ShamRP also identified

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

Ko et al. Network modulation following sham surgery in Parkinson’s disease. J Clin Invest 2014 124:3656-3666

Higher Dose Phase 1/2 Safety Study Enrollment Complete

Randomized, double-blind, sham-controlled 6-month study and a long-term follow-up safety study has completed dosing:

- **MGT-GAD-025 -** One of two doses of AAV-GAD vs. sham surgery, 5:5:4 randomization (n=14)
- 6 sites in the US
- Primary endpoint: Safety
- Efficacy assessments: MDS-UPDRS including Part 3 (motor examination) in the “off” and “on” states, glutamic acid decarboxylase-related pattern (GADRP), and MDS-Unified Dyskinesia Rating Scale
- **MGT-GAD-026 - Long-term follow-up study:** 5 years post-treatment. Participants randomized to the control arm in the Phase 1/2 study may receive AAV-GAD treatment in the long-term follow-up study.

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 complete with material manufactured at MeiraGTx using an optimized commercial process. Randomized sham-controlled study with 2 doses.
- Global regulatory interactions around pivotal design ongoing – with potential global pivotal study in late 2024

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Ocular Gene Therapy

MeiraGTx Leadership in Ocular Gene Therapy

Combining broad in-house capabilities in ocular gene therapy and manufacturing enables accelerated development of class-leading products with optimal expression levels, efficacy and safety.

Preclinical Ocular Technology Toolkit

- Vector optimization
- Proprietary ocular promoters and enhancers: small size - enabling strong targeted gene expression
- Vector sequence elements: improving stability, durability and reducing immune response
- Ocular capsids: intravitreal, subretinal, back and front of the eye – to be tailored for each indication
- Inteins and dual genome approaches
- Human retinal organoid expertise
- Potency assay development broad experience up to BLA
- Smart suprachoroidal injector

Clinical and Regulatory Expertise & Infrastructure

- Clinical experience – from Phase 1 through phase 3: >30 global clinical sites
- 225 eyes treated in MeiraGTx studies
- Extensive global regulatory agency interactions
- Expertise in wide range of retinal disease, global natural history studies
- Expertise in disease appropriate endpoint design - agreed with global regulatory agencies
- Optimized steroid regimen
- Optimized validated surgical technique and training (phase 3 success)

End-to-End Manufacturing

- 2 cGMP viral vector production facilities
- Large-scale plasmid production facility
- Commercial QC facility
- In-house Fill & Finish, warehouse, supply chain Infrastructure
- MSAT dedicated facility
- Extensive global CMC regulatory know how and experience
- Material used at IND is generally fit for pivotal and then commercial supply
- Saves multiple years in clinical development with significantly reduced regulatory risk

Extensive Clinical and Regulatory Expertise in Ocular Gene Therapy

❑ Extensive Clinical Experience in Opthalmology - IRDs

- Phase 1 through phase 3 clinical experience
- 4 Phase 1/2 studies successfully completed at UK and US sites
- Global Phase 3: enrollment and dosing >95 subjects, >30 sites in N. America and Europe
- Total of 225 eyes treated in MeiraGTx IRD studies

❑ Optimized Surgical Technique

- Unique optimized subretinal surgery technique resulting in safe exposure across the full extent of preserved central retina between the arcades.
- Validated training methodology driving consistency across >30 sites and surgeons (phase 3 success)

❑ Optimized Steroid Regimen

- Multiple iterations of steroid prophylaxis across 5 clinical studies in 4 IRD programs resulting in optimized steroid regimen in pivotal study
- Significant reduction in inflammatory events (ARVO and Phase 3 observations)

❑ Natural History Studies

- Large prospective natural history study for each clinical indication, with 2-5 years of longitudinal data on each patient

❑ Global Regulatory Experience: CMC, Clinical and Pharm Tox

CLINICAL:

- Expertise in wide range of retinal diseases and in disease appropriate endpoint design
- Global regulatory discussions and alignment on appropriate endpoints for approval

CMC, Pharm Tox.

- Extensive experience with global regulatory agency interactions: 6 INDs, multiple Type C meetings, and two Phase 3 CMC amendments
- Commercial ready manufacturing process and infrastructure at IND
- Potency assay development and modification in line with FDA requirements for multiple IRD INDs

❑ Specials License

- 1 ‘specials’ treatment available at 2 sites in the UK: AIPL1
- BBS10 available 2024
- The only AAV manufacturing facility with a specials license to our knowledge

Extensive Preclinical Toolkit for Ocular Gene Therapy Development

MEIRAGTx
PRECLINICAL

1 HUMAN RETINAL ORGANOID PLATFORM

- 3D human cellular models provide increased relevance & architecture for ocular indications
- Screening and validation in relevant human cell subtypes
- Potency assay development across multiple programs

2 IN-VIVO MODELS

- A range of relevant animal disease models (rodents, lagomorphs and non-human primates)
- IND-enabling data package generation (POC and toxicology) for monogenic and acquired disorders

3 PROPRIETARY OCULAR PROMOTERS

- Proprietary library of ocular cell-specific promoters of varying sizes and strengths
- Validated in relevant models, such as human retinal organoids

4 OCULAR CAPSIDS – TAILORED FOR EACH INDICATION

- Clinical experience with multiple subretinal capsids
- Directed Evolution NHP screen for back and front of the eye tissue tropic capsids ongoing

5 NEXT GENERATION VECTORS FOR LARGE GENES

- Dual vector technology employing superfast inteins for protein trans-splicing as well as DNA recombination to deliver large genes (e.g.ABCA4 for Stargardt)

6 SMART SUPRACHOROIDAL INJECTOR

- Proprietary Meira-owned smart suprachoroidal injector with improved delivery

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

Enrollment Complete

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

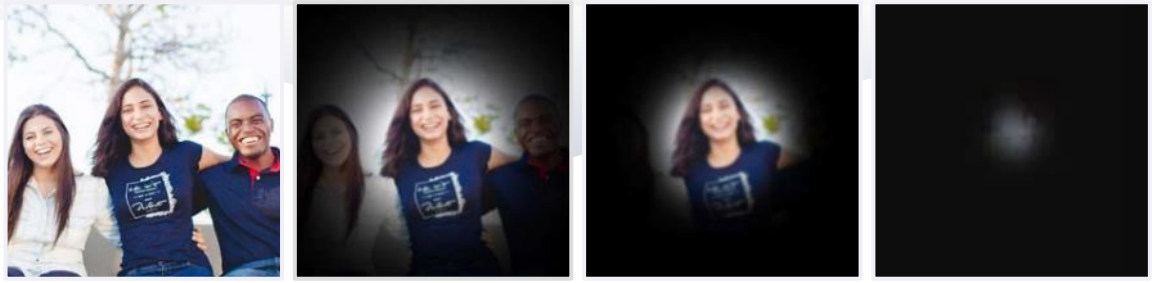
Disease progression

- 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: Phase 3

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 enrollment complete

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

Amyotrophic Lateral Sclerosis (ALS)

Program Overview

- ALS is a severe neurodegenerative disease affecting motor neurons with mean survival of 2-5 years.
- Only 5-10% of ALS cases are inherited, familial ALS (fALS), whereas the rest are sporadic (sALS).
- MeiraGTx is developing a first-in-class gene therapy to potentially address **both** forms of ALS.

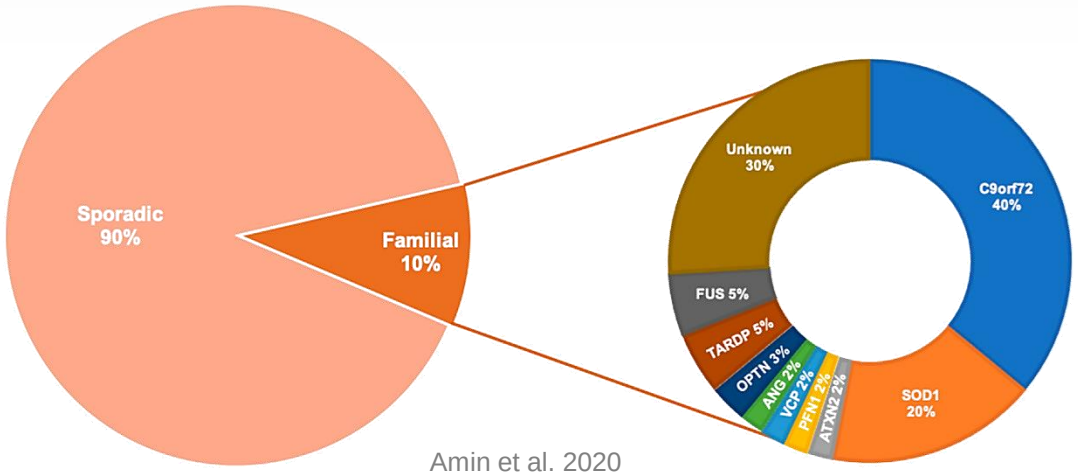
Therapeutic Target: AAV-hUPF1

» Targets underlying cellular defects associated with different forms of ALS

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

TPD43 Proteinopathy is a Cellular Hallmark of ALS

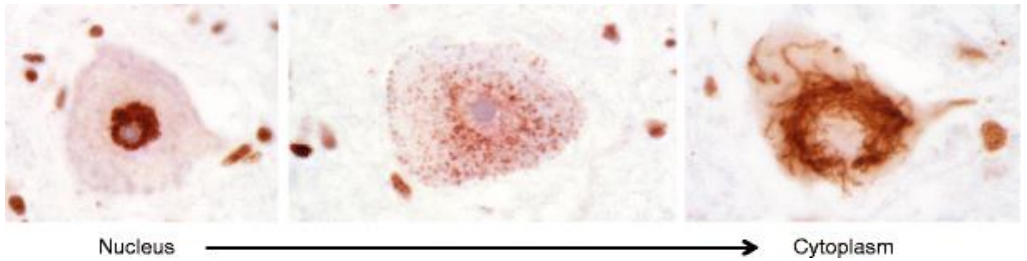
Only 5-10% of ALS is genetically driven



Amin et al. 2020

- Only 10% of ALS cases are inherited, familial ALS (fALS); remaining 90% of cases are sporadic (sALS)
- More than 20 genes were found to be associated with fALS

TDP43 cellular mislocalization and aggregation is present in 97% of ALS cases



Feneberg et al. 2018

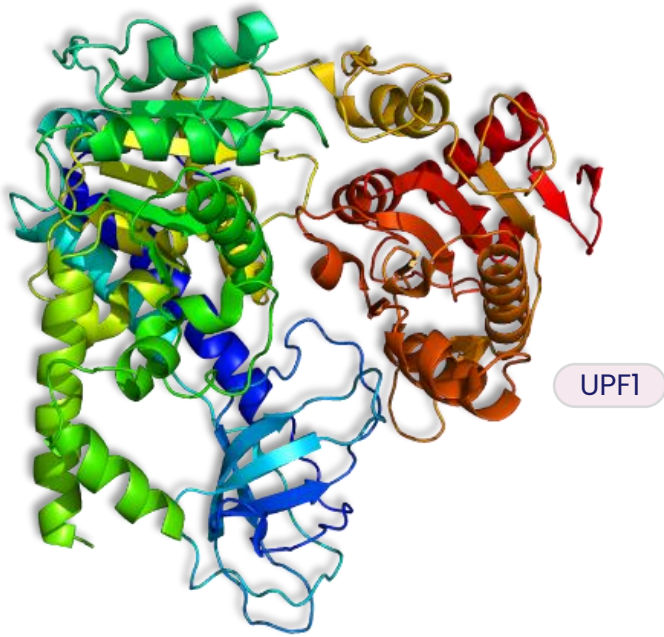
- TDP43 mis-localization and aggregation is a cellular hallmark of ALS (*except for SOD1-driven ALS*)
- TDP43 cytoplasmic granules are also observed in ~50% of frontotemporal dementia (FTD) patients

UPF1 is a Key Player in RNA Metabolism and Homeostasis Pathways Dysregulated in ALS

UPF1 plays a central role in RNA metabolism & quality control; mechanisms dysregulated in ALS:

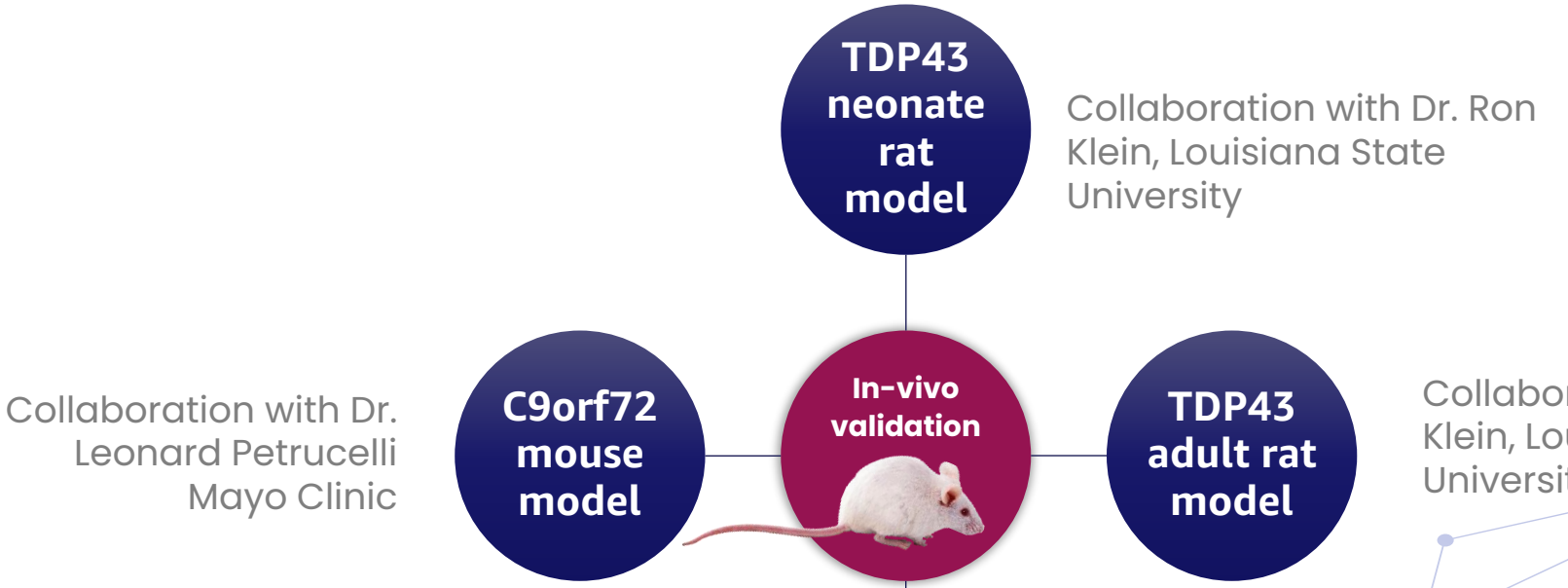
- UPF1 is a core component of the Nonsense-Mediated Decay (NMD) pathway
- UPF1 has multiple roles beyond NMD, including targeting misfolded proteins to the ‘aggresome’ for clearance
- Dysregulation of RNA metabolism is known to contribute to ALS pathogenesis:
  - Mutations such as C9orf72, TDP43 and FUS, have been found to disrupt RNA processing
  - Aberrant RNA species & impaired clearance may disrupt cellular homeostasis and contribute to pathological protein aggregates, such as TDP43 - a cellular hallmark of ALS.

AAV-UPF1 potentially targets cellular defects underlying ALS, providing a way to address both familial and sporadic forms of the disease (>95% of patients)



UPF1 Validation in Multiple *in-vivo* Models of ALS

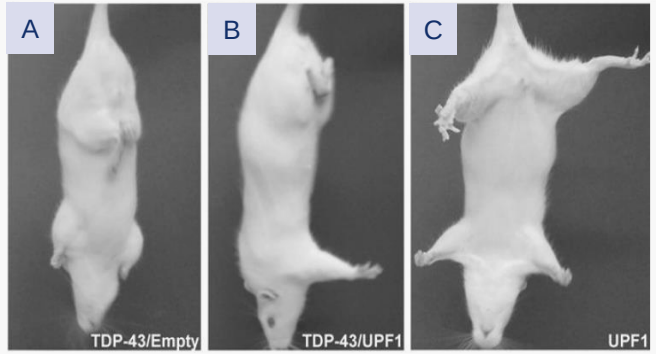
Collaborations with leading ALS researchers to validate UPF1 in multiple in-vivo models of ALS provide **strong evidence** for the **therapeutic potential of UPF1**

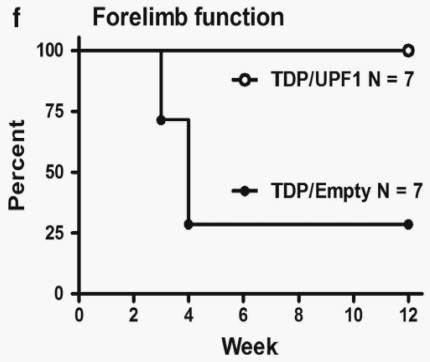


In-vivo validation: Functional Evidence for Therapeutic Potential

In-vivo model 1: TDP43 neonate rat model

AAV-UPF1 in **neonate rescues escape reflex** impairments induced by TDP43

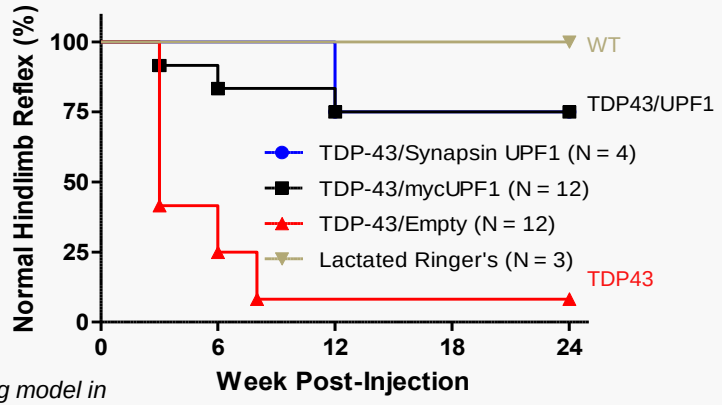




Jackson et al. Gene Ther. 2015

In-vivo model 2: TDP43 adult rat model

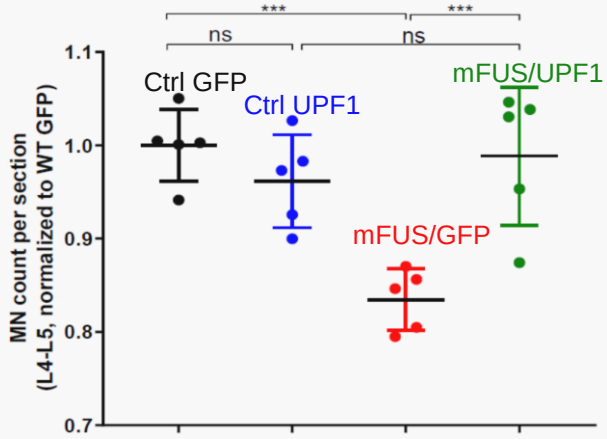
AAV-UPF1 in **adult rat rescues escape reflex** impairments induced by TDP43



Unpublished using model in
Jackson et al. Mol. Ther. 2015

In-vivo model 3: conditional FUS mouse model

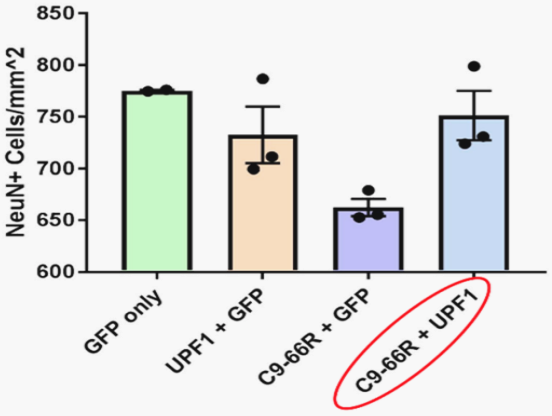
AAV-UPF1 in FUS mouse model **protects against motor neuron loss** & improves hindlimb grip strength



Unpublished using model in
Korobeynikov et al.Nat.Med. 2022

In-vivo model 4: mouse C9orf72 model

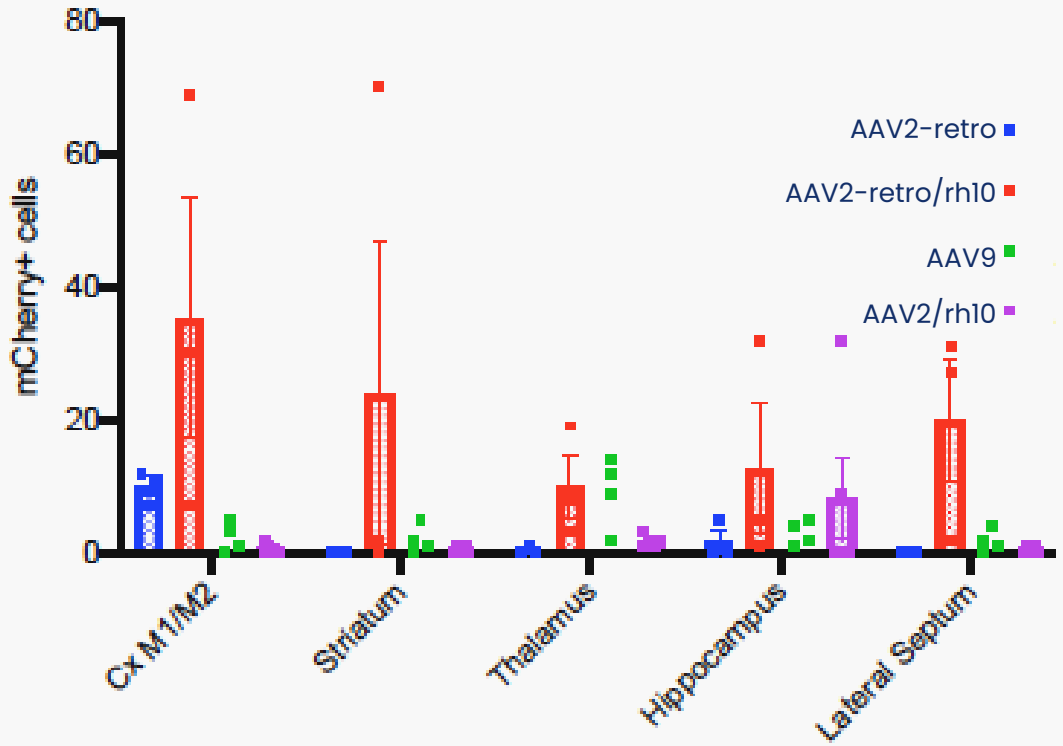
AAV-UPF1 in (G4C2)66 mouse model **protects against neuron loss** & improves locomotor activity



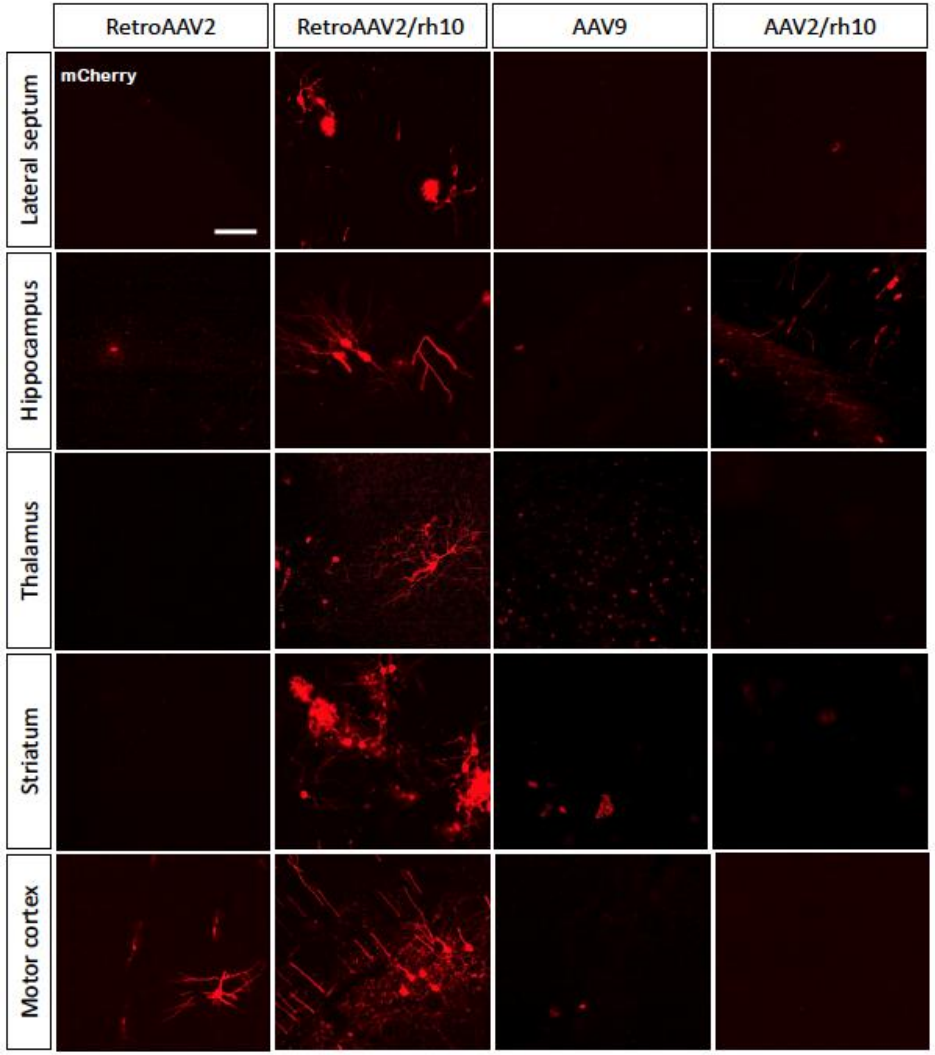
Unpublished using model in
Chew et al. Science 2015

Novel AAV Capsid for Broad CNS Transduction

Novel Capsid: AAV2-retro & variants

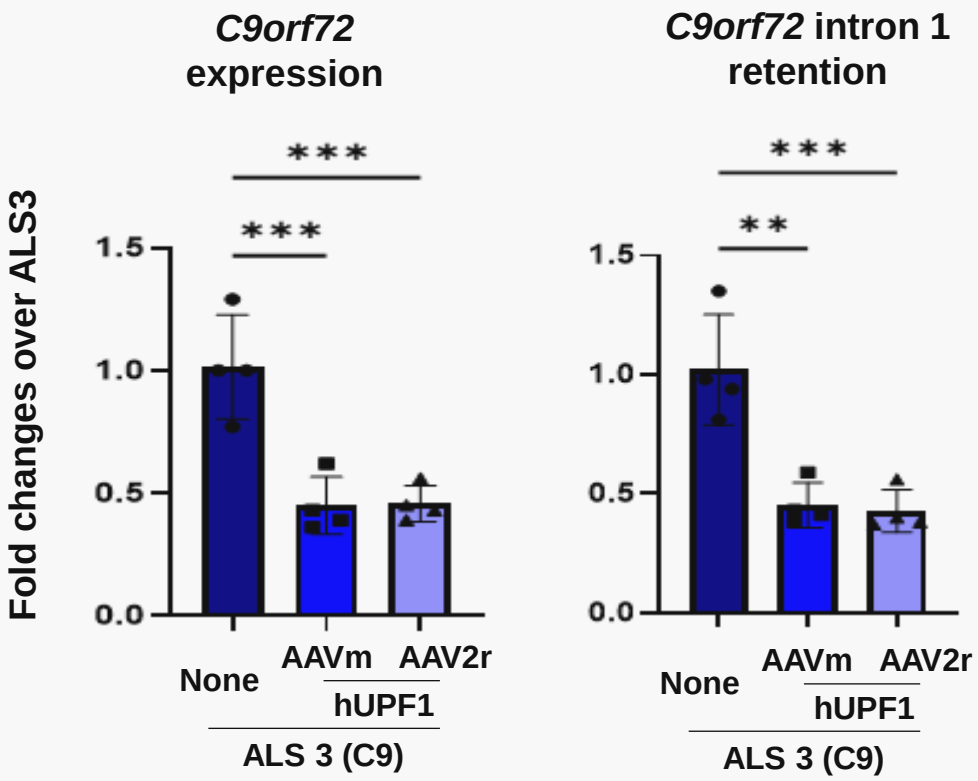


- AAV2-retro variants transduced both upper and lower motor neurons by ICM injection in mice
- In NHPs, transduction in spinal motor neurons was demonstrated at levels sufficient to drive in-vivo rescue in mice

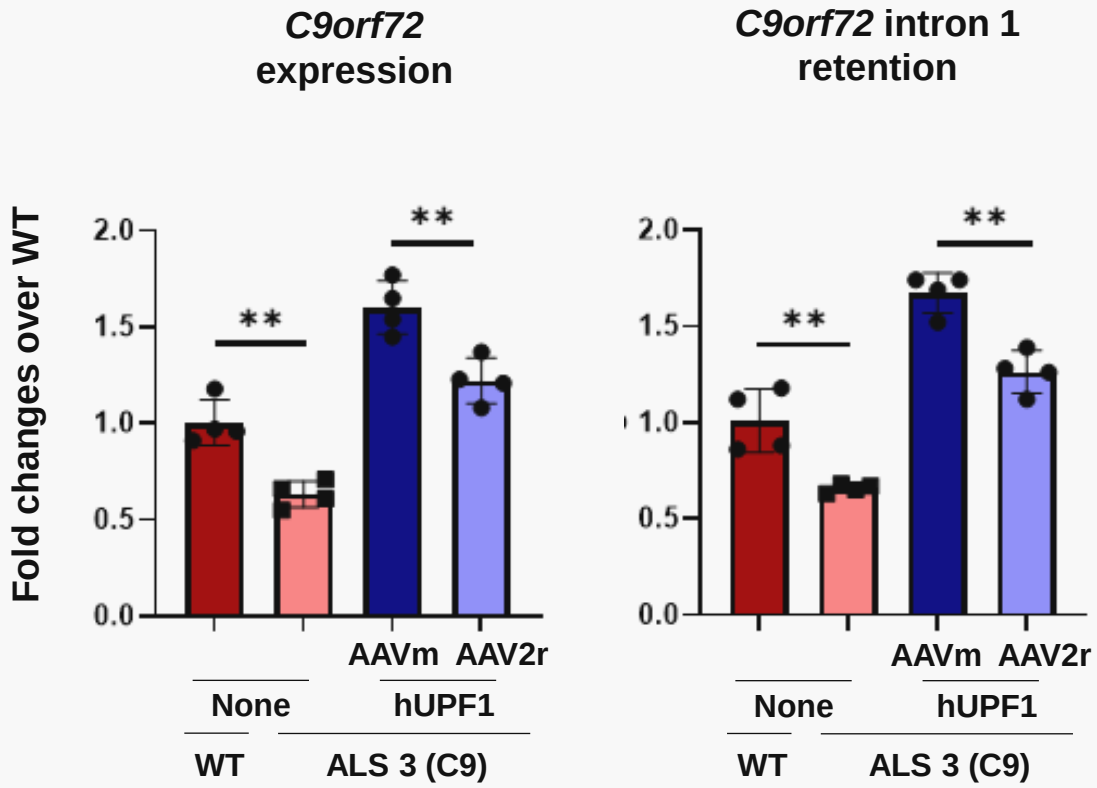


Efficacy of AAV-hUPF1 in C9 ALS Patient-Derived Neurons

Clinical AAV-hUPF1 candidates demonstrate **reproducible target engagement in C9** ALS patient-derived neurons



- Exp. 1 : 2 weeks after AAV transduction

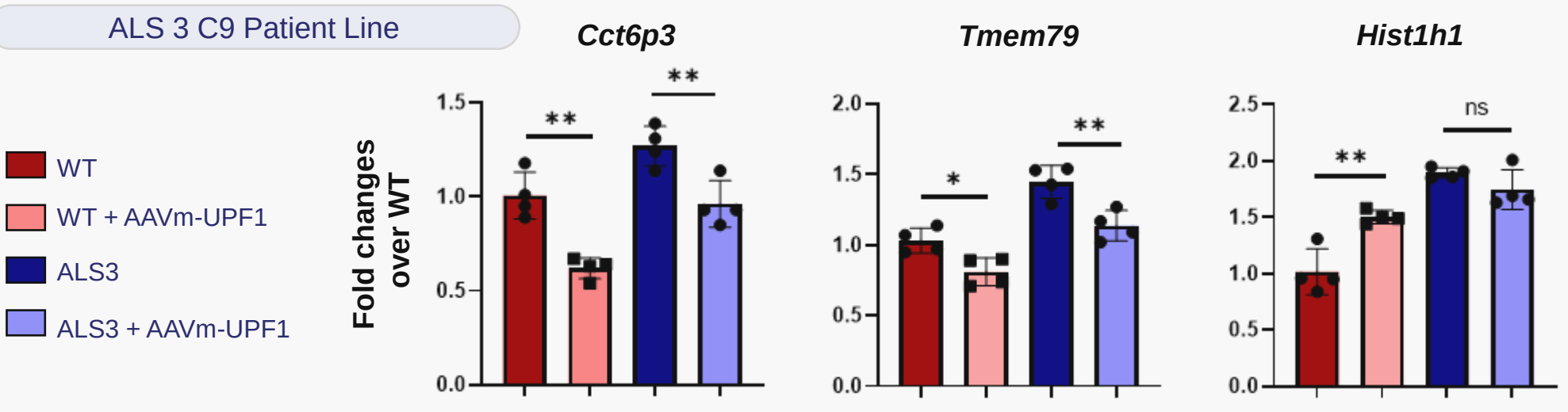


- Exp. 2 : 1.5 weeks after AAV transduction

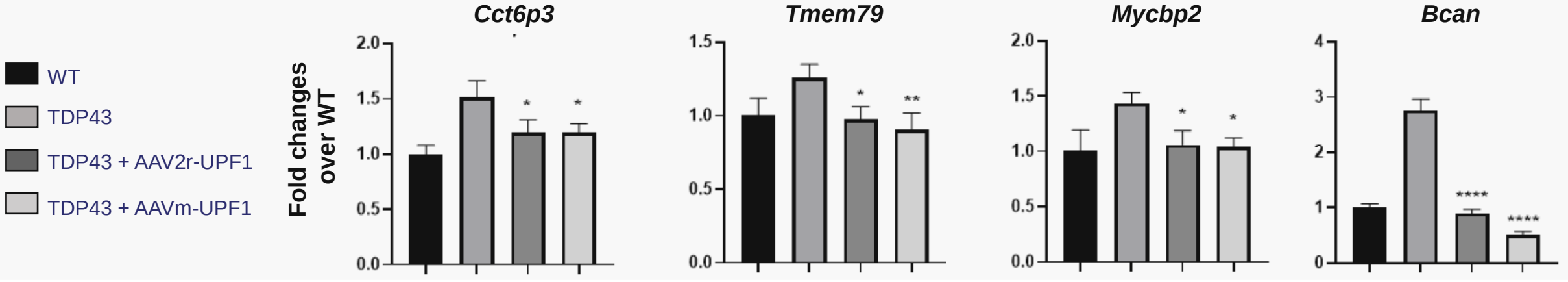
AAV-hUPF1 Rescued in Multiple ALS Patient-Derived Lines

AAV-hUPF1 **efficacy** in ALS patient–derived lines of **different genetic context**: C9 & TDP43

ALS 3 C9 Patient Line



TDP43 (A382T) Patient Line



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AAV-UPF1 Program **HIGHLIGHTS**

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

- 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 models of ALS have demonstrated the ability of AAV-UPF1 to reduce neuronal death and ameliorate ALS symptoms related to limb strength and mobility
- A proprietary capsid, AAV2-retro, demonstrates favorable transduction of upper and lower motor neurons

Status:

- **Vector optimization** – reduced size for enhanced packaging efficiency, and improved potency over original academic construct
- Initiation of IND-enabling studies planned for 2024


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