Corporate Presentation

January 2025

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 January 12, 2025.

MeiraGTx Introduction: Late Stage Clinical Pipeline

MeiraGTx is a late-stage genetic medicines company with 4 clinical programs with potential BLA filings in 2025, 2026 and 2027.

Our strategy centers on local delivery of genetic medicines for large indications with high unmet need.

- **Our current clinical focus is on advancing two pivotal stage programs with potential disease-modifying effects in prevalent, non-inherited indications:**
  - **AAV-AQP1 for radiation induced xerostomia:** Currently enrolling a potentially pivotal study, with potential future label expansions as a pre-treatment to radiation therapy as well as xerostomia caused by PSMA radioligand therapy and Sjogren's disease.
  - **AAV-GAD for Parkinson's Disease:** The only gene or cell therapy for Parkinson's disease to demonstrate statistically significant benefits in UPDRS in a double blind, sham-controlled study as well as disease modifying changes in CNS circuitry in patients no longer responding to dopamine. Phase 3 is initiating in 2025.
- **Two other Inherited Retinal Disease (IRD) programs have potential near term BLA filings in the next 6 months:**
  - **AAV-AIPL1 for LCA4:** Severe inherited retinopathy. 11/11 children blind from birth treated under 3 years old gained visual acuity. MHRA requested discussion of Marketing Authorization under Exceptional Circumstances.
  - **AAV-RPGR for X-linked Retinitis Pigmentosa:** Acquired by Janssen

MeiraGTx Introduction:
Broad Capabilities in Manufacturing and Genetic Medicine Technologies

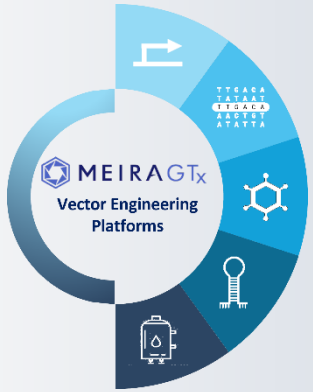
In order to support our pipeline of programs from pre-clinical through Phase 3 and commercialization, the company has built industry-leading broad capabilities in manufacturing and vector engineering:

Manufacturing:

MeiraGTx has become a global leader in end-to-end manufacturing with 5 facilities in London, England and Shannon, Ireland, including: plasmid and GMP viral vector production, fill and finish, and a commercially licensed QC testing facility.

The company's platform process, established by our internal MSAT organization, was developed using >20 different viral vectors and over 50 GMP runs, and today is recognized by over 16 global regulatory agencies.

By internalizing end-to-end manufacturing capabilities, we can rapidly move any product to the clinic with a commercial-ready manufacturing process, potentially saving 3 years or more in clinical development and regulatory timelines as well as significantly reducing Cost of Goods.



Vector Technologies:

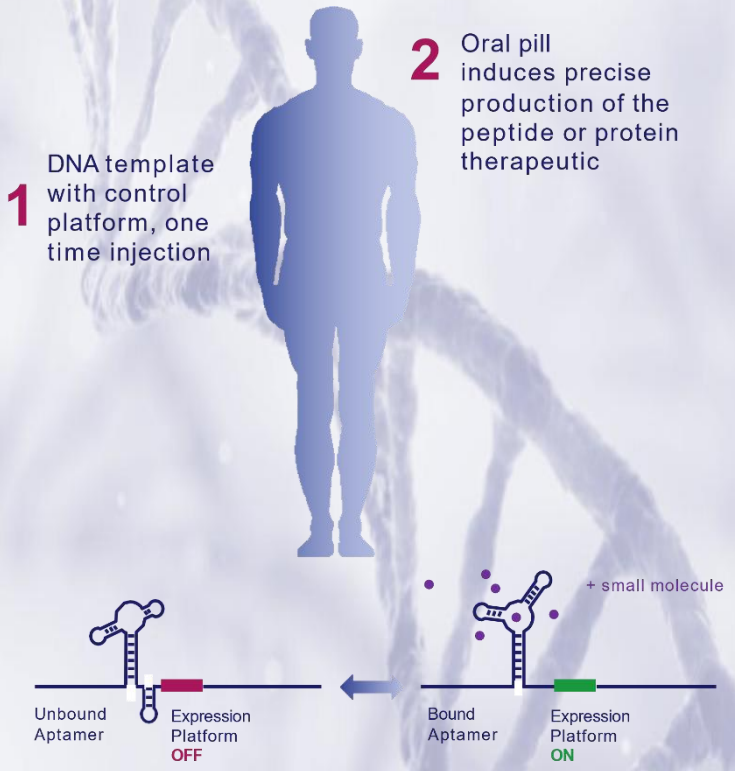
MeiraGTx has developed broad technologies for vector optimization which increase the potency of our vectors by up to 3-4 logs, thus decreasing dose, improving safety, and massively decreasing Cost of Goods.

MeiraGTx Vectorology Technologies include:

- Capsid engineering and screening for multiple tissue types.
- Promoter and enhancer discovery utilizing large high-throughput genomic screens to bespoke engineering, and leveraging proprietary predictive AI models for in-silico promoter design. Our promoter platforms have yielded thousands of promoters ranging from ubiquitous small promoters to highly cell specific promoters, validated across multiple platforms, including in human organoids.
- Proprietary non-coding sequences for increased protein expression independently of the promoter, increasing potency by up to 7x.

MeiraGTx Introduction: Proprietary Riboswitch Gene Control Platform for Precisely Controlled *in-vivo* Delivery of any Therapeutic Protein with Orally Dosed Small Molecules

Riboswitch Technology

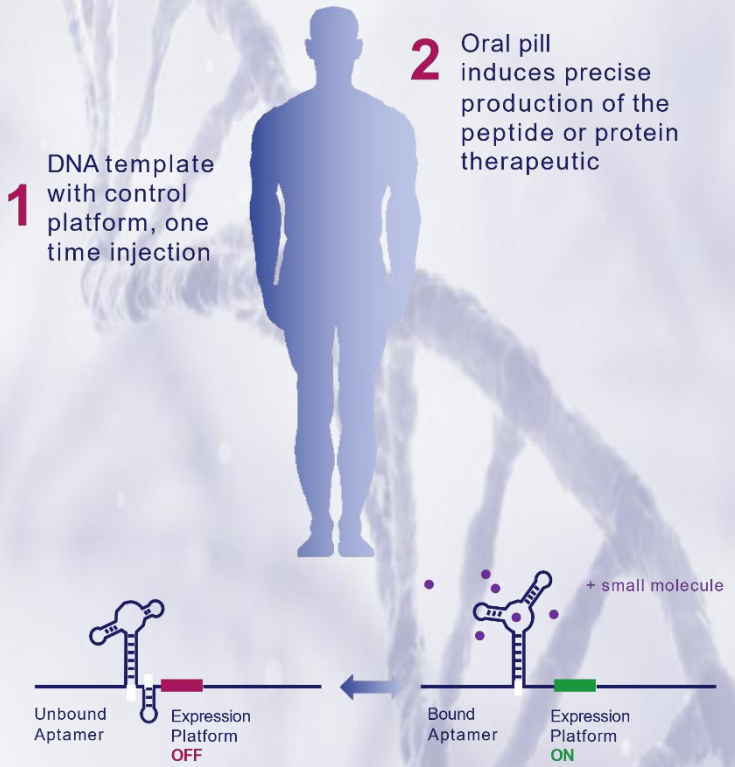


MeiraGTx's proprietary in-vivo delivery technology uses our splicing based riboswitch platform to precisely control mRNA production with novel, orally dosed small molecules, resulting in controlled production of any biologic therapeutic, *in vivo*.

- Our splicing-based riboswitch platform provides a completely innovative approach for delivery of any therapeutic biologic, circumventing the need for ex-vivo production and repeat injections.
- We have demonstrated in-vivo efficacy across multiple targets (vectorized antibodies, peptides, hormones, cell-surface receptors and nucleases) and therapeutic modalities (gene therapy, gene editing, and cell therapy).
- When applied to the in vivo delivery of short-lived agonists, we have demonstrated significantly enhanced efficacy, providing a new paradigm in drug development of agonist molecules in homeostatic systems where rapid response to changing environmental factors is critical to maximize function.

MeiraGTx Introduction: *in vivo* Expression of Native Proteins and Chimeric Antigen Receptors with Riboswitch Solves Many of the Issues Facing Current Cell Therapies and Metabolic Disease Therapies

Riboswitch Technology



MeiraGTx's riboswitch platform provides a new technology for delivering short-lived agonists and a new paradigm in drug development of molecules in homeostatic systems where rapid response to changing environmental factors is critical to maximize function and efficacy.

- Pre-clinically, MeiraGTx is undertaking IND enabling studies in metabolic disease and cell therapy, leveraging our proprietary riboswitch gene regulation platform, which uses the patient's own cells to produce native metabolic peptides when dosed with an oral small molecule.
- **Metabolic Disease:** When applied to different combinations of vectorized native peptides, gut peptides, myokines and adipokines, our *in vivo* delivery platform provides the solution to many of the current issues associated with injectable peptides or oral drugs, with important implications for delivery, manufacturing, patient access, and cost.

  In preclinical models, we have demonstrated remarkable improvements in efficacy and safety upon pulsatile delivery of native short lived gut peptide combinations, and have demonstrated the impact of delivering adipokines and myokines on prevention of fat regain and muscle maintenance.
- **Cell therapy:** MeiraGTx has applied riboswitch technology to control any CAR or cell fate determining factor via an oral small molecule.

  In CAR-T, we have demonstrated improved manufacturing, naïve T-cell phenotype identical to untransduced T-cells, lack of exhaustion markers, durable proliferation, 4x increase in in vitro cytotoxicity and 3x improvement in *in vivo* potency compared to the currently approved CD19 CAR-T as well as other CARs for solid tumors.

Metabolic disease and CAR-T are both examples of biologic targets that agonize, rather than repress receptor signaling, and that function significantly better when delivered in a pulsatile more physiological time frame rather than constitutively active or long-acting.

MeiraGTx: Late Stage Clinical Pipeline and Comprehensive End-to-End Capabilities and Technologies in Genetic Medicine

Focus on *in vivo* delivery of vectorized biologic therapeutics addressing unmet needs in prevalent disorders

Diverse clinical pipeline

4 late-stage clinical programs pivotal/Phase 3

- **Retinitis Pigmentosa: Phase 3 dosing complete**. Recently acquired by JNJ.
- Commercial manufacturing agreement
- **AIPL1 associated retinal dystrophy: potential approval in 2025**

Disease modifying effects in prevalent, non-inherited indications:

- **Radiation Induced Xerostomia: potentially pivotal**
- **Parkinson's Disease: Phase 3 ready**

End-to-end GMP manufacturing

Flexible and Scalable

- **2 GMP facilities**, both commercial scale
- **Plasmid production for GMP**
- **QC facility** with commercial license
- **Fill and Finish,** warehouse and supply chain
- **Specials License**
- Industry leading **proprietary manufacturing platform process**
- **AI-driven optimization** of new vector process based on 8 years data, 20 different vectors and >50 GMP runs

Next generation vector optimization

Potency, safety, dose, COGS

- **Capsids:** Muscle, CNS, eye, liver,
- **Promoters:** ubiquitous, muscle, CNS, eye, liver
- **Proprietary Vectorization Technology:** Peptides and antibodies with 2-10x increased potency from same promoter
- **AI-driven in silico cloning** now drives capsid and promoter optimization
- **Organoid testing for HUMAN function**

Transformative Riboswitch technology

***In vivo* delivery of any biologic therapeutic via oral small molecule**

- **Precise dose Response** of protein expression to oral small molecule dosing
- **Gene, tissue, vector agnostic:** *in vivo* efficacy for antibodies, peptides, hormones and cell therapy demonstrated
- **GLP-1, GLP-1-GIP, GLP1-GIP-Glucagon, Amylin, PYY combinations**
- **CAR-T: for liquid and solid tumors, as well as autoimmune disease**

Expected Near Term Global BLA Filings based on current studies **in 2025 (RPGR, AIPL1), 2026 (AQP1), 2027 (GAD)**

Large markets, unmet patient need, strong data, physician and patient demand, low cost of goods

Deep pre-IND pipeline: ALS, MC4R obesity, Stargardt's, AMD, Glaucoma

Speed: New vector to tech transfer within 2-3 months, reducing to 6 weeks with AI

Regulatory Interactions: deep global experience

Avoid CDMO bottlenecks & quality failures

Saves 3 years in development timeline of any product from IND to BLA–significantly increasing ROI on every product

Significantly reduced Cost of Goods

Improvements in potency > 3 logs

Maximize outcomes for patients: lower dose, improved safety and efficacy

Vast reduction in COGS : 3 log lower dose, 3 log lower cost of goods

Affordable therapies increasing access to effective treatments in common diseases

Metabolic disease: leapfrogs current approaches, with transformative impact on:

- **Efficacy** and **tolerability**
- **Muscle loss** and fat regain
- **Neurodegenerative** disease
- **Manufacturing**, cost and patient access

Next-generation Cell Therapy: transforms efficacy, safety, manufacturing and durability in liquid and solid tumors as well as autoimmune disease

Broad Pipeline of Transformative Genetic Medicines
Clinical programs across multiple TFAs

Product	Indication	Discovery / Preclinical	Phase 1/2	Phase 2	Phase 3
Salivary Gland					
AAV-AQP1	Xerostomia			***RMAT, 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			**RPDD, MHRA Specials License**	
A007, A008	RDH12, BBS10, Stargardt, KCNV2			RPDD	
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.

Strong Industry Partnerships

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)

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)

MeiraGTx end-to-end internal manufacturing infrastructure, capabilities and production process

- ❑ **Reduced Cost of Goods**: Process, Plasmid, Vector Production and QC
- ❑ **Commercial process at IND**: Saves 2-3 years for an AAV clinical development timeline from IND to commercial, allows faster move to pivotal with expedited time to market. Increases ROI on each Product
- ❑ **Commercial grade manufacturing with scalable and flexible capacity for full internal pipeline and commercial partners**
- ❑ **Unique end-to-end offering of innovative technology, commercial quality and capacity**

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

- **Over the past 8 years, MeiraGTx has established broad end-to-end manufacturing process and viral vector production capabilities**
- Process and facilities are built to be flexible and scalable and are fit for IND through commercial supply.
- Through iterative global CMC regulatory interactions on multiple products, MeiraGTx has acquired extensive global regulatory expertise, enabling the company to cross reference CMC filings and expedite regulatory review.
- Using outside vendors currently results in delays from long lead times for plasmid and vector production, poor quality, failed batches and onerous QC release assay timelines throughout the industry.

- **2 GMP Viral Vector Production Facilities (London, UK and Shannon, Ireland)**
  single use philosophy; flexible and scalable; fit for clinical through commercial
- **Large-scale Plasmid Production for GMP (Shannon)**
  for GMP starting material, large capacity for potential commercial scale supply
- **Commercial QC Facility (Shannon)**
  Commercial and Clinical Licenses (HPRA) 2024 for full clinical and commercial release and stability
- **In-House Fill and Finish, Warehouse, Supply Chain Infrastructure (London and Shannon)** ready for commercial supply
- **Stand Alone MSAT Dedicated Facility (London)**
  >30 employees; Proprietary platform process established over a period of 8 years with best-in-class yield and full-to-empty capsid ratios
- **QC analytics development (London)**
  expertise leveraged for Phase 3 & commercial potency assay development and QC analytic development and transfer to GMP
- **Extensive CMC Regulatory Know How and Experience**
  filed multiple CMC INDs and amendments with the FDA and 15 global agencies
- **Specials License**
  the only gene therapy manufacturing facility with a ‘Specials License’ allowing supply of physician-led studies for rare degenerative disorders outside of company sponsored clinical studies. 2 ‘specials’ are currently underway – one with unprecedented efficacy data in children age 2-4 years old (AIPL1)

Flexible & Scalable GMP Manufacturing for Clinical and Commercial Production

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

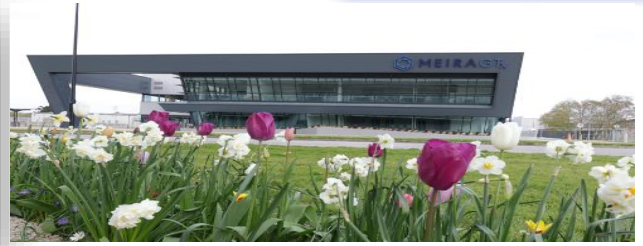
Shannon Facilities

- **cGMP, 150,000 sq ft**
- Up to 12 viral vector suites with 2x 500L bioreactor per suite (each suite with capacity up to 2000L or larger bioreactors)
- Flexible high capacity GMP manufacturing hub for clinical through commercial supply
- Fully scalable automated fill and finish
- Full QC laboratories for global release
- cGMP plasmid manufacturing facility
- Extensive warehouse and Clinical supply storage
- Covered by QA to support clinical through commercial supply

200+ FTEs Dedicated to Best-in-Class AAV Manufacturing

London Facility

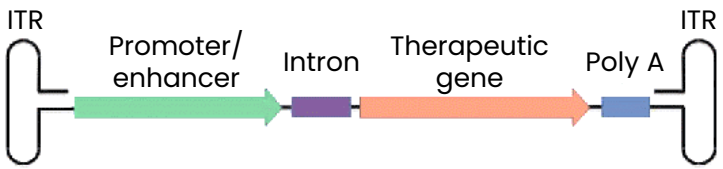
- **cGMP, 29,000 sq ft**
- 2 cell suites; 3 viral vector suites
- Each with independent air handling
- Single use philosophy / fully enclosed technologies
- Designed for minimal downtime and maximum flexibility
- Designed to meet MHRA, EMA and FDA regulatory requirements
- Support laboratories: Quality Control
- Adjacent MSAT (Manufacturing Science and Technology) area/pilot plant for process development and optimization
- MSAT to GMP tech transfer

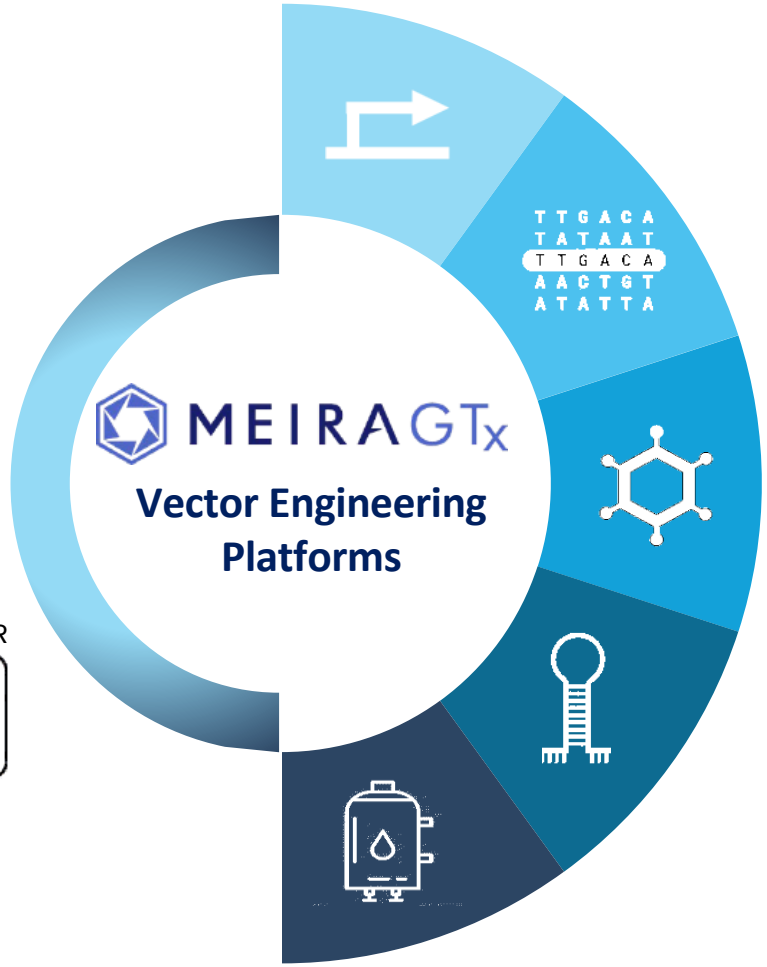


Comprehensive Vector Engineering Toolkit: Potency Optimization and Precise Gene Control

In-House Vector Engineering Platforms

Extensive in-house vectorology capabilities addressing each element of vector genome sequence as well as capid





PROMOTER ENGINEERING & DISCOVERY

Control cell specificity and expression levels driving potency and safety

GENE SEQUENCE OPTIMIZATION

Intron/exon configuration; 3', 5' and Poly A, Kozak sequence, optimization; translation efficiency, mRNA stability, immune regulation

CAPSID SELECTION

Tissue Tropism: Drives differential transduction efficiency and potency

RIBOSWITCH GENE REGULATION

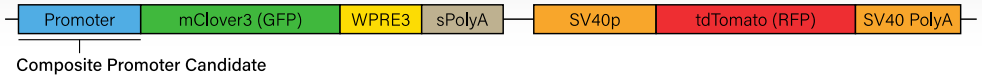
Precise, specific, dose responsive control of genetic medicine levels

MANUFACTURABILITY

Optimal Plasmid design, and vector genome sequence for maximal full legth packaging

MeiraGTx Multi-Platform Promoter/Enhancer Discovery Engine

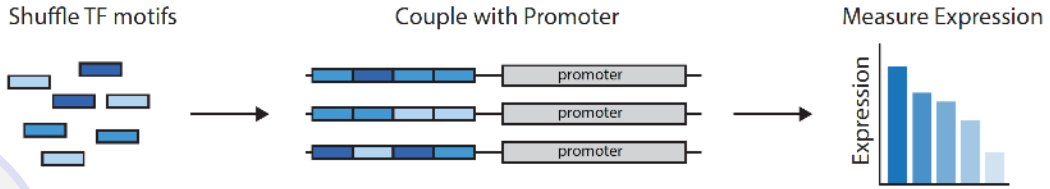
Rationally Designed Screens



- 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

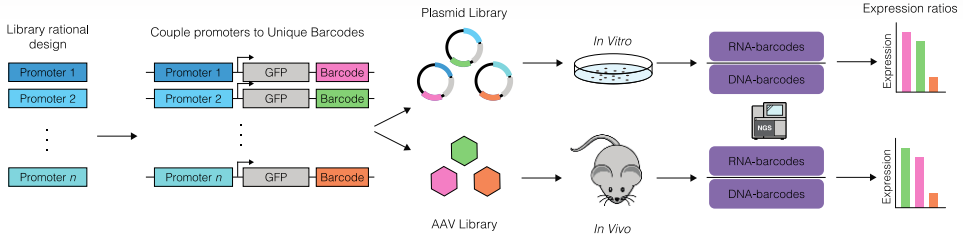
- Generation and screening of synthetic enhancers via cell specific transcription factor binding site (TFBS) shuffling



MEIRAGTx

Promoter Engineering Platforms

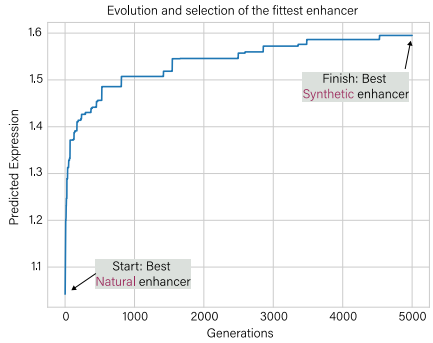
AAV-based or plasmid-based promoter screens using barcodes



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

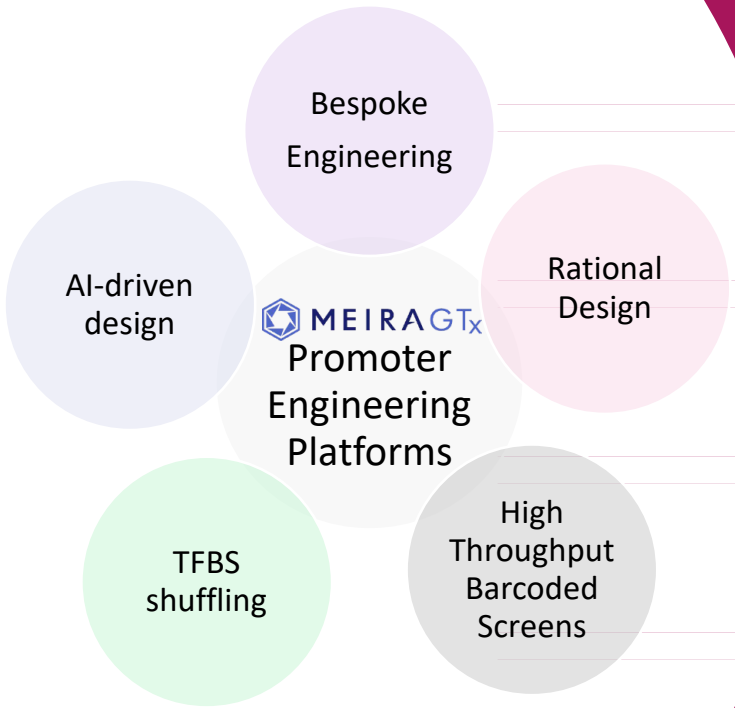
AI-driven Promoter Design and Evolution

- 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

- Large promoters/enhancer screens for highly potent and/or cell specific novel promoter/enhancer sequences
- Millions of experimental data points are fed into "CLARA", MeiraGTx's proprietary Convolutional Neural Network (CNN) model for *in-silico* prediction of promoter activity
- Top Performing promoters are characterized and validated across multiple translationally-relevant models, including human organoids



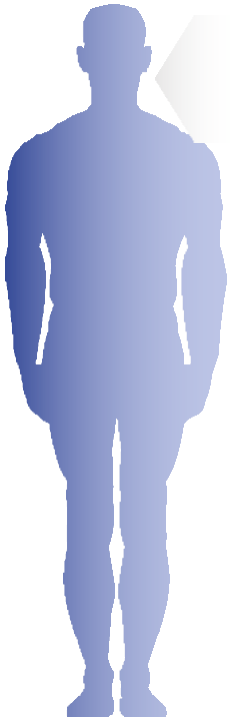
Ubiquitous Promoters	>100 promoters up to 15-fold stronger than CAG/CMV; >200,000 ultra short promoters screened
Ocular Promoters	for multiple cell types in the eye e.g., the strongest known human pan-cone promoter
Muscle Promoters	Stronger vs. promoters used in the clinic: e.g., synthetic promoter 17x 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

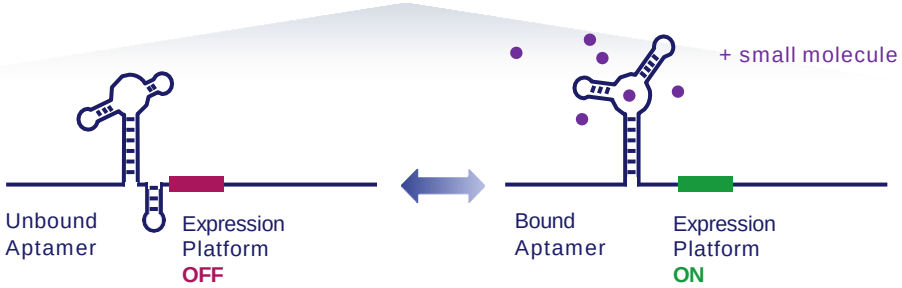
Riboswitch Platform: Precise *in vivo* production of Therapeutic Proteins and Peptides using Oral Small Molecule Inducers

Use cDNA Template For any Protein Sequence to Deliver That Protein, *in vivo*, with Very Precise Control Based on Oral Small Molecule Dosing

1 DNA template with control platform, one time injection

2 Oral pill induces precise production of the peptide or protein therapeutic

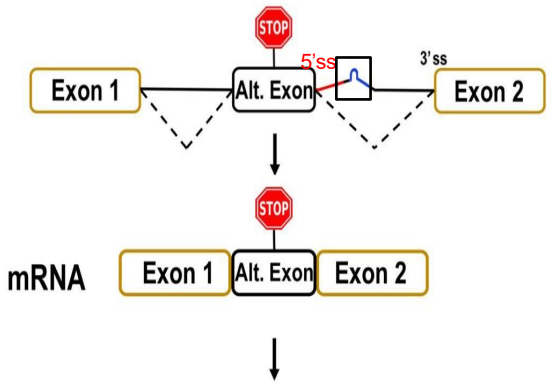




mRNA formation is controlled by alternative splicing cassette via aptamer : small molecule ligand binding

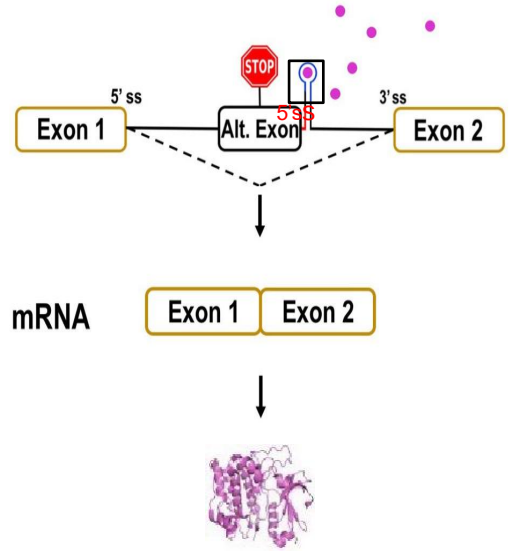
1 small molecule binding leads to the irreversible formation of 1 stable mRNA

No Small molecule (OFF state)



no protein

+ Small molecule (ON state)



protein expressed

Broad Applicability of Riboswitch Gene Control Technology

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’, cell fate determination

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 Vaccines with built-in capacity for Oral Small Molecule Driven Persistance

MEIRAGTx

Late-Stage Clinical Programs:

- AAV-AQP1 for treatment of Xerostomia (Phase 2 potentially pivotal)
- AAV-GAD for treatment of Parkinson's Disease (Phase 3 ready)
- AAV-AIPL1: Near Term Path to Marketing Authorization Under Exceptional Circumstances

Overview: AAV-AQP1 for Treatment of Xerostomia Large Patient Population with no Treatment Options

Patient Need: Radiation-Induced Xerostomia

- Large Patient population with severe, unmet need
- No competition
- Readily accessible patients and engaged KOLs
- Low cost of goods and payor support for pricing

Prevalence (US)

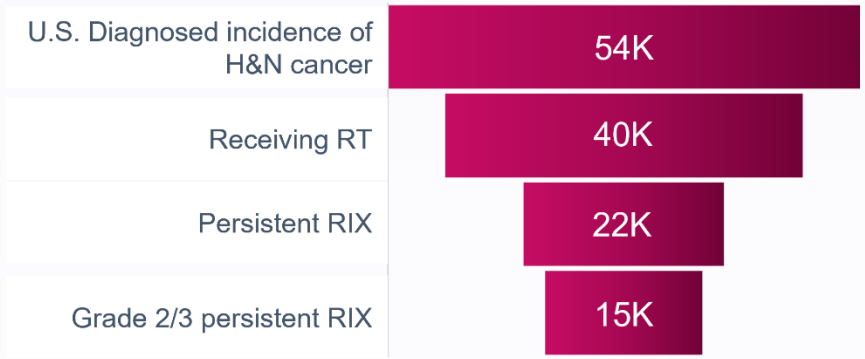
170K

Grade 2/3 RIX patients in the US

Incidence (US)

15K

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



Clinical Data:

- Strong Phase 1 data presented AAOM April 2024
- Effect across all endpoints considered ‘unprecedented’ and ‘transformative’ by KOLs
- Potentially pivotal Phase 2 enrolling (with commercial CMC)

“Pipeline in a Product”:

- Radiation-induced Xerostomia
- Radioligand therapies (xerostomia is a dose limiting AE for PSMA radioligands)
- Prevention of radiation-induced Xerostomia
- Sjogren’s syndrome

RMAT designation from FDA December 2024
Potentially pivotal Phase 2 study currently enrolling
Potential global filings in 2026

AAV-GAD for Parkinson's Disease - Phase 3 Ready: Late Stage Potentially Disease Modifying Clinical Program in Neurodegenerative Disease

Parkinson's disease:

10M
Parkinson's patients worldwide

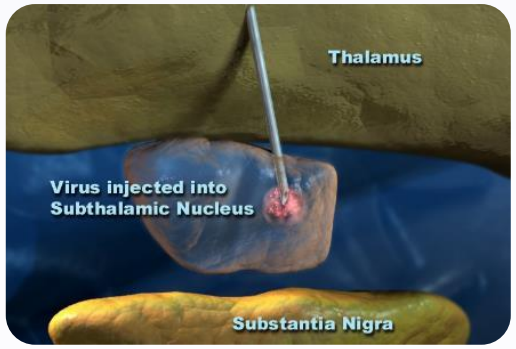
$52B
Estimated economic burden of PD in the US

Large Patient population in need of effective, safe treatment

- Single low dose to STN - the target of DBS
- Well known routine intervention at most neurosurgery centers globally
- No general anesthesia
- Short time in operating room
- No in-dwelling hardware associated safety concerns and off target side effects
- Strong efficacy vs. sham control
- Small dose - very low COGS

MOA and Delivery

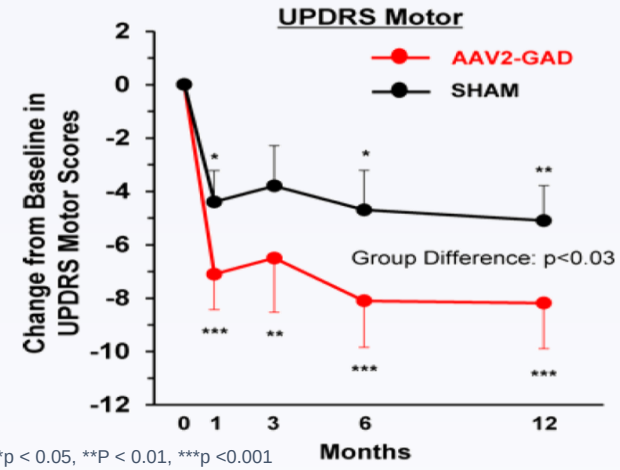
The Glutamic Acid Decarboxylase (GAD) gene is delivered locally to the STN to increase production of GABA only at the specific site that is required for alleviating PD related motor symptoms



Phase 3 Ready

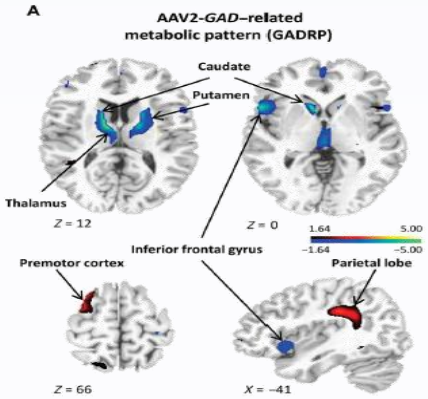
Disease Modifying in patients no longer responding to Dopamine

Significant improvements in UPDRS motor scores vs Sham



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

FDG-PET shows treatment responsive rewiring of the ganglion to motor cortex



Overview: AAV-AIPL1 targeting LCA4 - Near Term Path to Marketing Authorization under Exceptional Circumstances

AAV-AIPL1 Treatment Under MeiraGTx Manufacturing Specials License in UK:

LCA4 is an ultra rare and severe inherited retinal disease (IRD) resulting from mutations in the aryl hydrocarbon receptor interacting protein-like 1 gene (*AIPL1*) which encodes a retinal photoreceptor-specific protein expressed in cones and rods.

Children with LCA4 are blind from birth and by the age of 4 years old, retinal degeneration is complete and irreversible.

MeiraGTx has developed AAV-AIPL1 to deliver the intact *AIPL1* gene to the retina of children with LCA4. This product, manufactured at MeiraGTx's London facility under a Specials License from the MHRA, is available for treatment of children with LCA4.

- MeiraGTx's AAV-AIPL1 has been made available at 2 UK hospitals and used to treat 11 children aged 1 to 3 years old
- 100% of these children, who were blind from birth, now have visual acuity with benefits seen from 1 month following treatment
- The company has presented the data produced under the Specials License to the MHRA
- Based on the strength of the data from the 11 children, MeiraGTx received an Innovation Passport in June 2024
- **Following additional conversations with the MHRA, MeiraGTx has been invited to discuss application for 'Marketing Authorization Under Exceptional Circumstance' in the coming weeks based on the current data. This is in contrast to 'conditional approval' which may require substantive additional clinical data.**
- **Granted Rare Pediatric Disease Designation (RPDD) from FDA in 2024**

MEIRAGTx

AAV-AQP1: a Pipeline in a Product for Xerostomia

RIX, Sjogren's, Prostate cancer Radiotherapeutics, and Xerostomia Prevention

Phase 1 clinical data

RMAT Designation granted from FDA

“Pipeline in a Product” with Multiple Prevalent Indications of High Unmet Need

1 Radiation-Induced Xerostomia

- Currently enrolling in a pivotal Phase 2 study
- **There are >170,000 patients with grade 2/3 xerostomia in the US, of which >80% are inadequately controlled by SoC medications**

Opportunities for Label Expansion

2 Prevention of Radiation-Induced Xerostomia

- Preclinical data suggest that treatment with AAV-AQP1 **prior** to radiation therapy may reduce the risk of radiation-induced xerostomia
- **Each year, >50,000 patients receive radiation therapy for head & neck cancer in the US**

3 Sjögren's-Related Xerostomia

- Sjogren’s syndrome is a prevalent autoimmune condition that disrupts tear- and saliva-producing glands
- No effective treatments for managing Sjogren’s related xerostomia
- **There are >550,000 Sjogren’s patients with grade 2/3 xerostomia in the US**

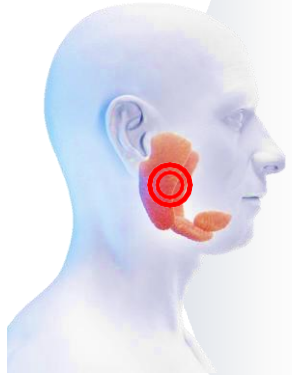
4 Xerostomia Associated with Radioligand Therapy

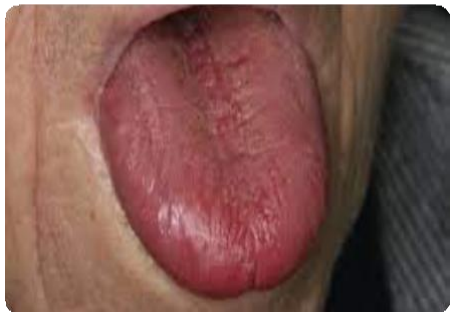
- Xerostomia is the most common AE of PSMA radioligand therapy, and in some studies was a dose-limiting toxicity
- PSMA radioligand therapy is a rapidly growing market, with peak sales of Pluvitco (NVS) estimated at $4Bn
- **AAV-AQP1 has the potential to treat (or prevent, if dosed pre-treatment) xerostomia in this growing patient population**

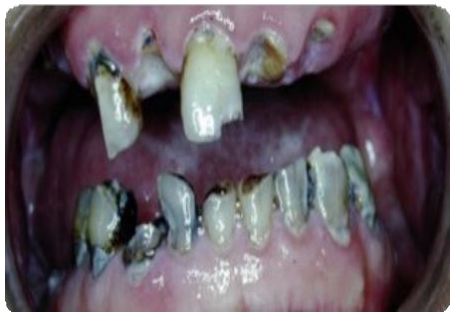
Radiation-Induced Hyposalivation and Xerostomia (RIX)

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







Large Patient Population with Significant Unmet Need

Large patient population with no effective treatments:

- There are >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
- The dose is low and delivery non-invasive and safe
- The cost of goods is low and pricing in this population leads to strong margin

Opportunities for label expansion:

- **Sjögren's syndrome:** large opportunity in a prevalent indication with no effective therapies
- **PSMA radioligand therapy:** Recent approval of radiolabled therapies for prostate cancer leading to large increase in radiation induced Xerostomia

Prevalence (US)

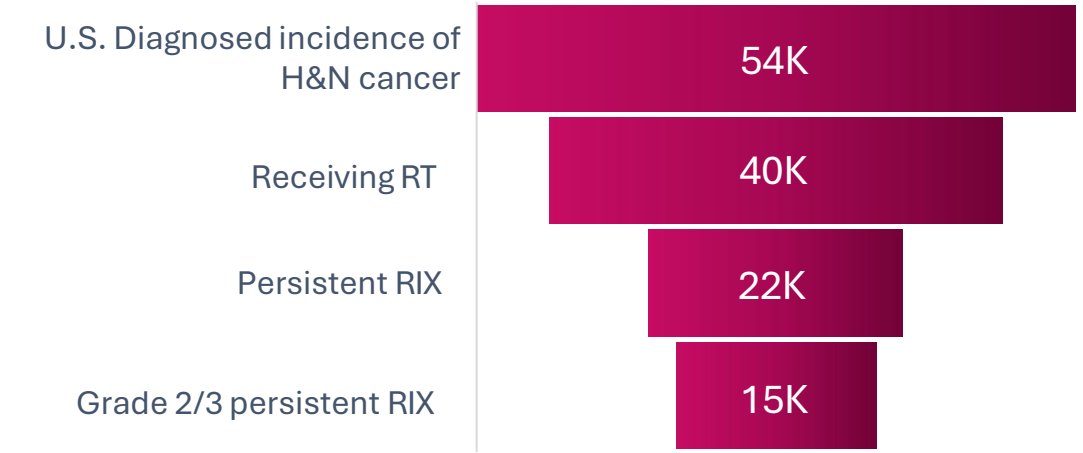
170K

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

AQUAx: Phase 1 Clinical Study Design

- Open-label, multi-center, dose-escalation study (4 sites, US/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 invited to enroll in a long-term follow-up study for a total of 5 years

Primary Endpoint

- Safety

Secondary Endpoints

- Patient reported measures of xerostomia symptoms
  - Xerostomia Questionnaire (XQ)
  - MD Anderson Symptom Inventory – Head and Neck
  - Global Rate of Change Questionnaire (GRCQ)
- Unstimulated whole saliva flow rate

Cohort	Dose
Unilateral Treatment	
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 Treatment	
1b	3×10^{10} vg/gland
2b	1×10^{11} vg/gland
3b	3×10^{11} vg/gland
4b	1×10^{12} vg/gland

AQUAx Phase 1 Clinical Study: Safety

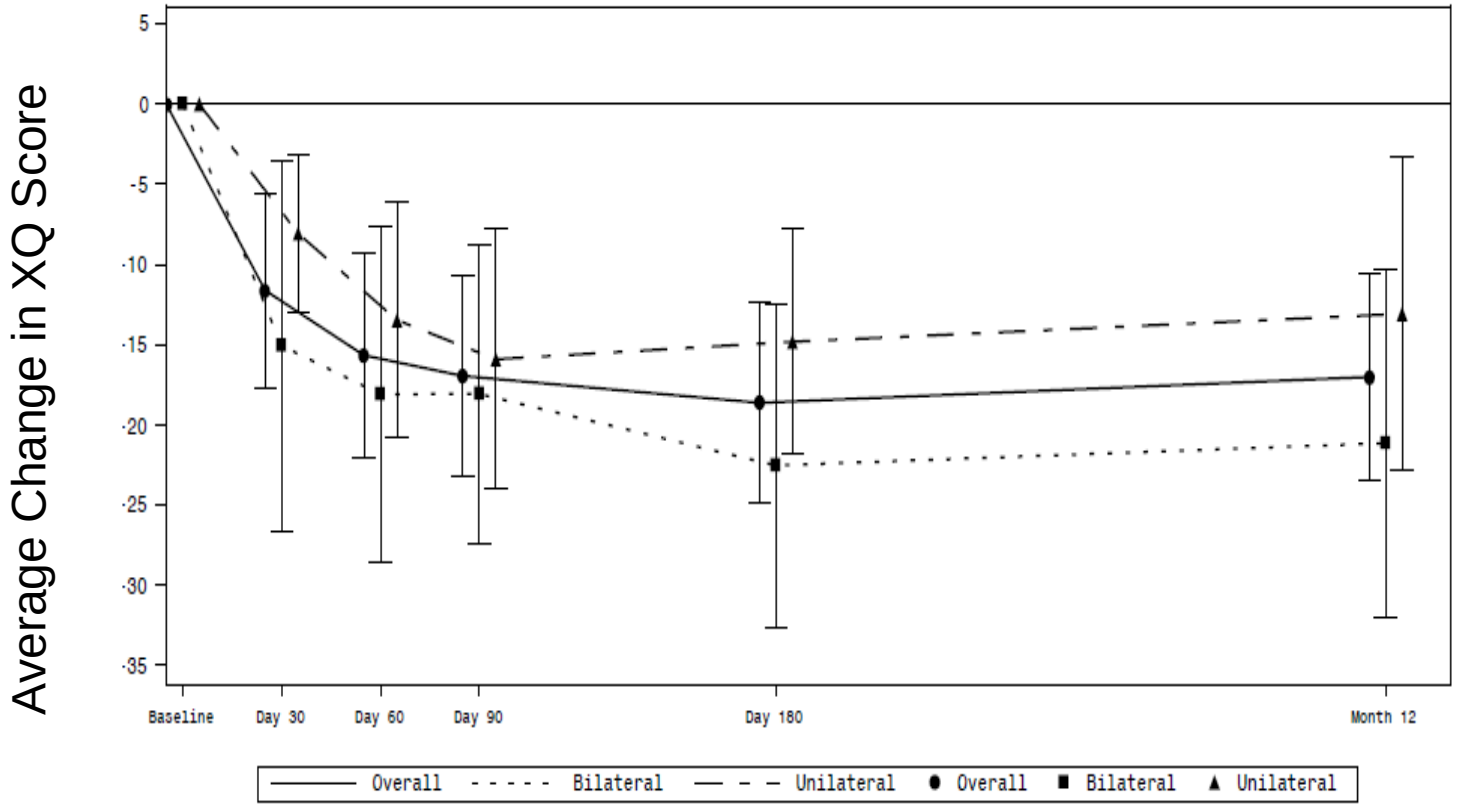
- **AAV2-hAQP1 was safe and well-tolerated at all doses tested**
- No treatment-related serious adverse events
  - 2 SAEs: obstructive airways disorder and coronary artery disease
  - Assessed by the investigator as not treatment-related
- No dose-limiting toxicities
- No participant discontinued from the study
- 6 mild, treatment-related, treatment-emergent adverse events (TEAEs)
  - All resolved without sequelae

Treatment-Related Treatment-Emergent Adverse Events in the AQUAx study

System Organ Class Preferred Term	All Participant N=24 N (%)
Participants with ≥1 treatment-related TEAE	6 (25.0)
Gastrointestinal disorders **Oral disorder** **Salivary gland pain**	2 (8.3) 1 (4.2) 1 (4.2)
General disorder and administration site conditions **Chills** **Fatigue** **Injection site pain**	2 (8.3) 1 (4.2) 1 (4.2) 1 (4.2)
Eye disorders **Eye disorder**	1 (4.2) 1 (4.2)
Investigations **Amylase increased**	1 (4.2) 1 (4.2)
Nervous system disorders **Dysgeusia**	1 (4.2) 1 (4.2)

AQUAx: Xerostomia Questionnaire[1]

- 8 symptom-specific questions which the participant answers using a scale from 0 (not present) to 10 (worst possible)
- Responses to individual questions are summed to provide the Total Score (0-80), an overall measure of disease burden
- An improvement (decrease) of **8 points or more** in XQ Total Score is considered clinically meaningful[2]



Average XQ score improved by 17 points (39.5%) at Month 12, with bilaterally treated participants reporting greater improvement than those treated unilaterally

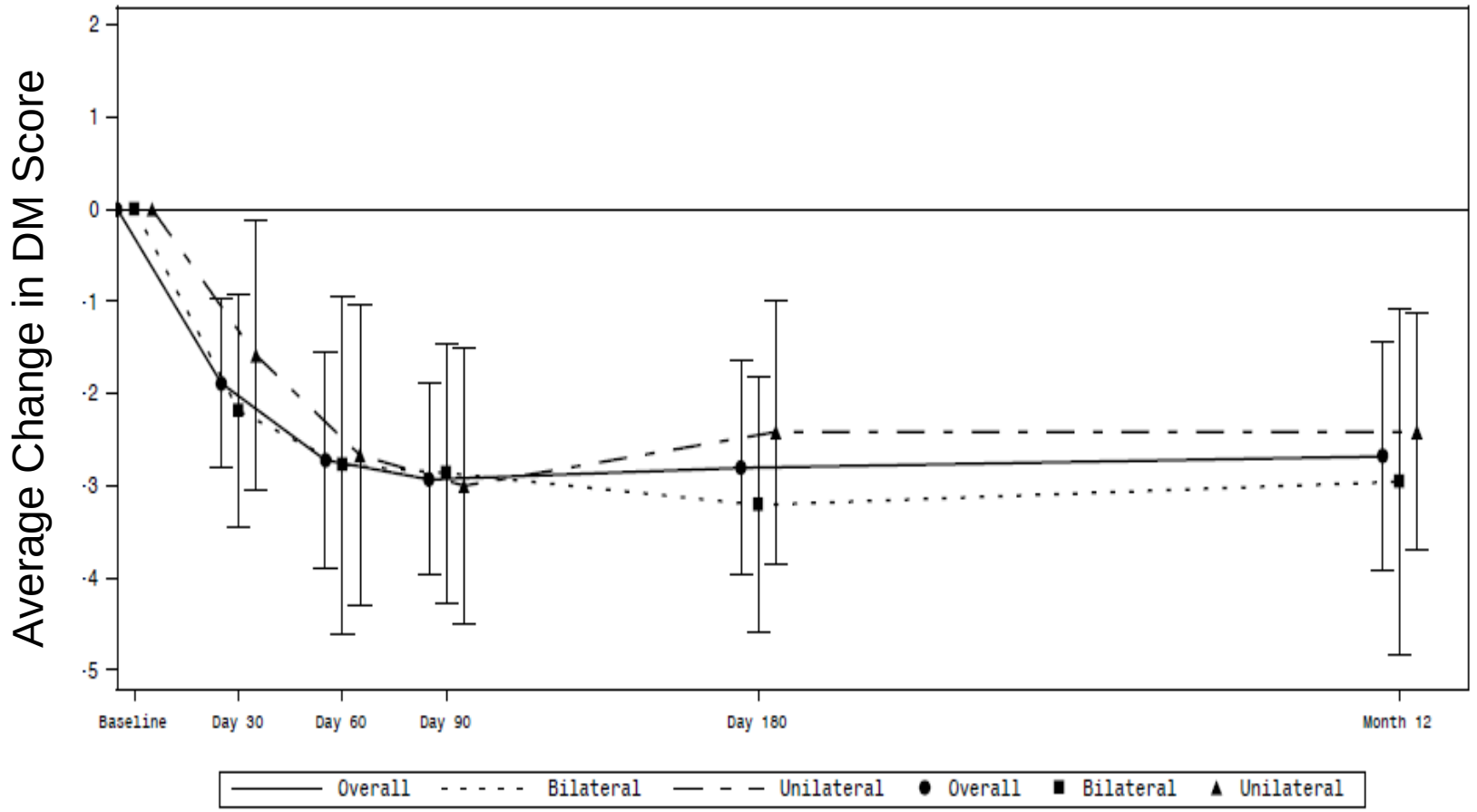
16/24 (67%) participants reported an improvement of ≥8 points in the XQ Total Score at Month 12

[1] Eisbruch A et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001 Jul 1;50(3):695-704

[2] Jabbari S et al. Matched Case–Control Study of Quality of Life and Xerostomia after Intensity-Modulated Radiotherapy or Standard Radiotherapy for Head-and-Neck Cancer: Initial Report. Int. J. Radiat. Oncol. Biol. Phys. 2005;63:725–731

AQUAx: MD Anderson Symptom Inventory Dry Mouth Question

- Question #10 from MD Anderson Symptom Inventory – Head and Neck[1]
- During the last 24 hours, please rate “Your **dry mouth** at its WORST”
- Scale from 0 (not present) to 10 (as bad as you can imagine)

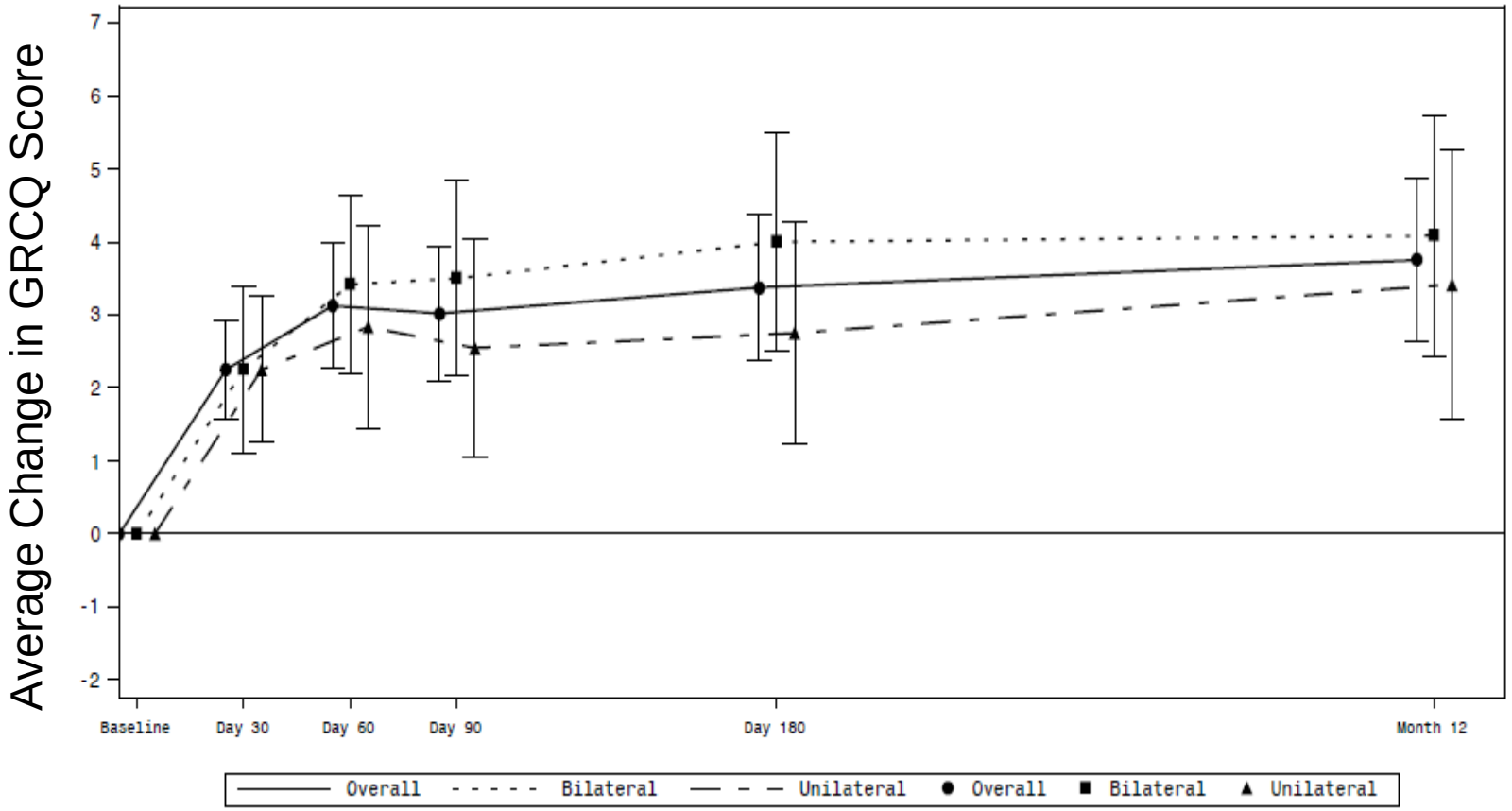


Average Dry Mouth score improved by 2.7 points (42.2%) at Month 12, with bilaterally treated participants reporting greater improvement than those treated unilaterally

[1]Rosenthal DI et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head Neck. 2007 Oct;29(10):923-31

AQUAx: McMaster Global Rate of Change Questionnaire Score

- Participants are asked, “Overall, has there been any change in your Dry Mouth since you received study treatment?”
- Potential answers are “Better”, “About the Same”, or “Worse”
- If they answer "Better" or "Worse", the participant is then asked to rate the degree of change on a 1-7 scale, with changes of 2+ being “important”

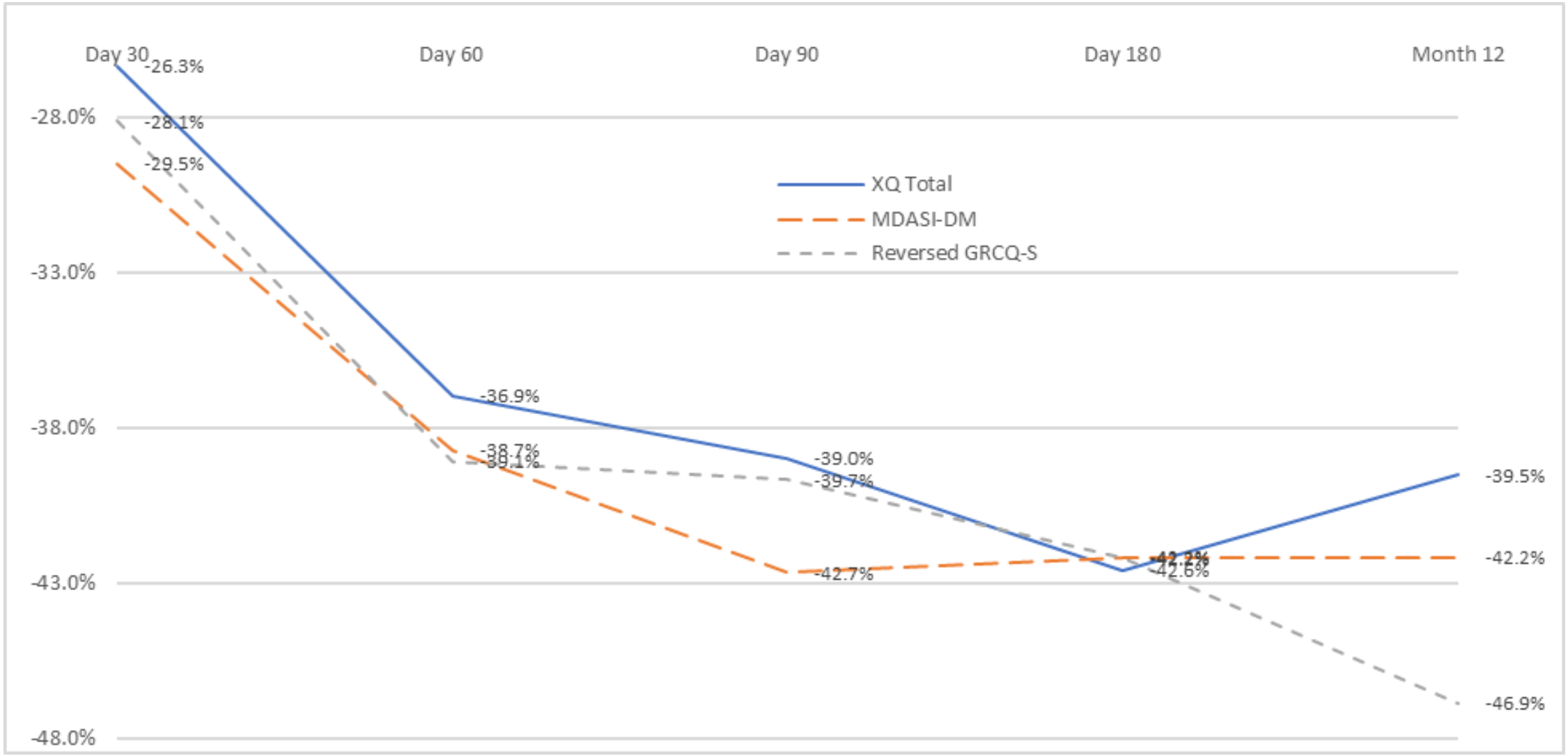


At Month 12, the average GRCQ Score was 3.8, with bilaterally-treated participants reporting higher scores than those treated unilaterally

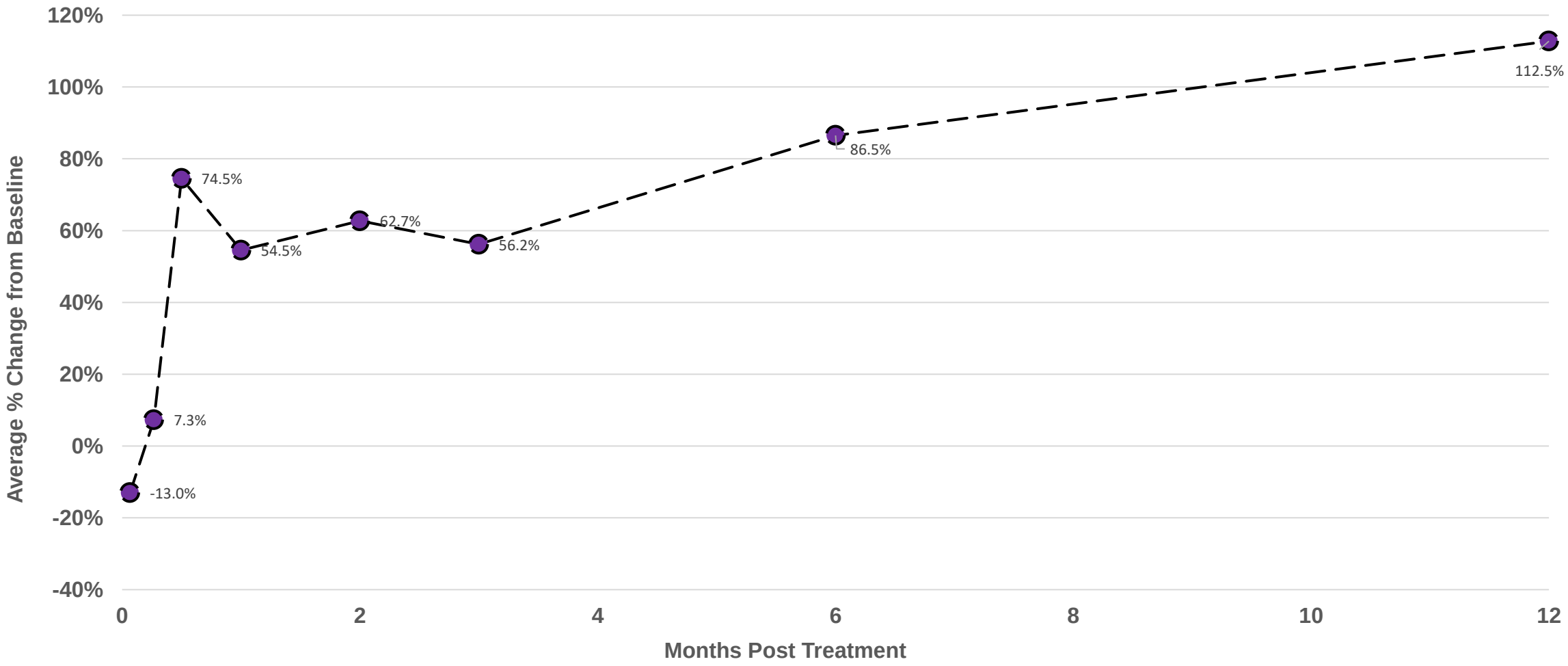
19/24 (79%) participants reported “important” improvements in xerostomia symptoms at Month 12

Use of the **“Global Ratings of Change Questionnaire (GRCQ)”**, authored by Gordon Guyatt was made under license from McMaster University, Hamilton, Canada

AQUAx: Consistent Improvements across Patient Reported Outcome Measures



AQUAx: Unstimulated Whole Saliva Flow Rate Average Percent Change from Baseline



At Month 12, the Unstimulated Whole Saliva Flow Rate increased from baseline by 112.5%

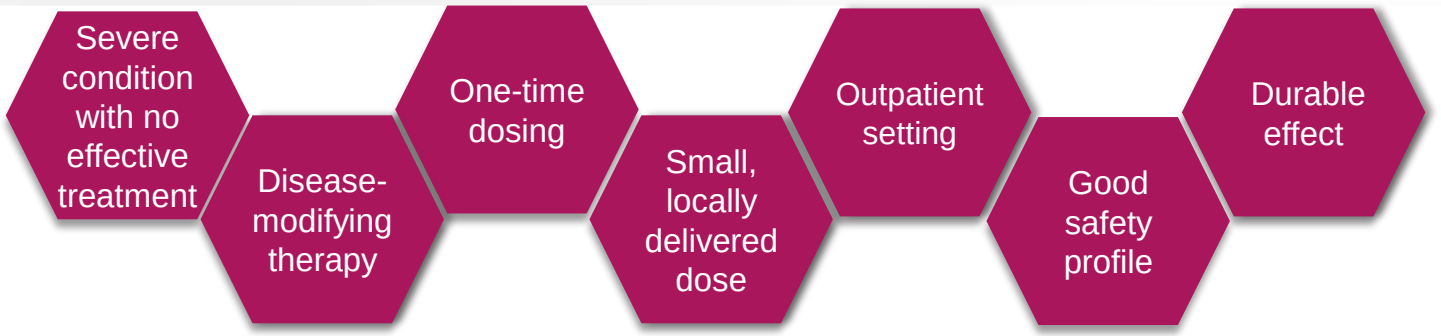
AQUAx - Summary of Findings

- No treatment-related serious adverse events or dose-limiting toxicities were reported, and all participants completed the study
- The 3 different PRO instruments showed statistically significant improvements by Day 30 that were maintained through Month 12
  - At Month 12, the average Total XQ Score improved by 17 points (39.5%) from baseline and 16 of 24 participants reported an improvement of ≥8 points
  - At Month 12, the MDASI-HN-DM score improved by 2.7 points (42.2%) from baseline
  - At Month 12, the average improvement in GRCQ Score was 3.8
  - Across the PROs, bilaterally-treated participants reported greater improvement than those treated unilaterally
- At Month 12, the Unstimulated Whole Saliva Flow Rate increased from baseline by 112.5%

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 delivered through an outpatient cannulation procedure that ENTs and dentists trained in oral medicine are familiar with
- Expected to provide durable long-term benefit in this large population of severely affected patients with no other effective current treatment options
- 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
- Patients are >2 years post successful treatment for head and neck cancer and are therefore in the healthcare system and see physicians at least once per year
- 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
- Compelling Phase 1 dose escalation data presented June 2023 on 24 patients with scale of improvements unprecedented in this disease – Granted RMAT designation from FDA
- Phase 2 study ongoing – which has the potential to be pivotal if data replicates the improvements seen in the Phase 1 does escalation

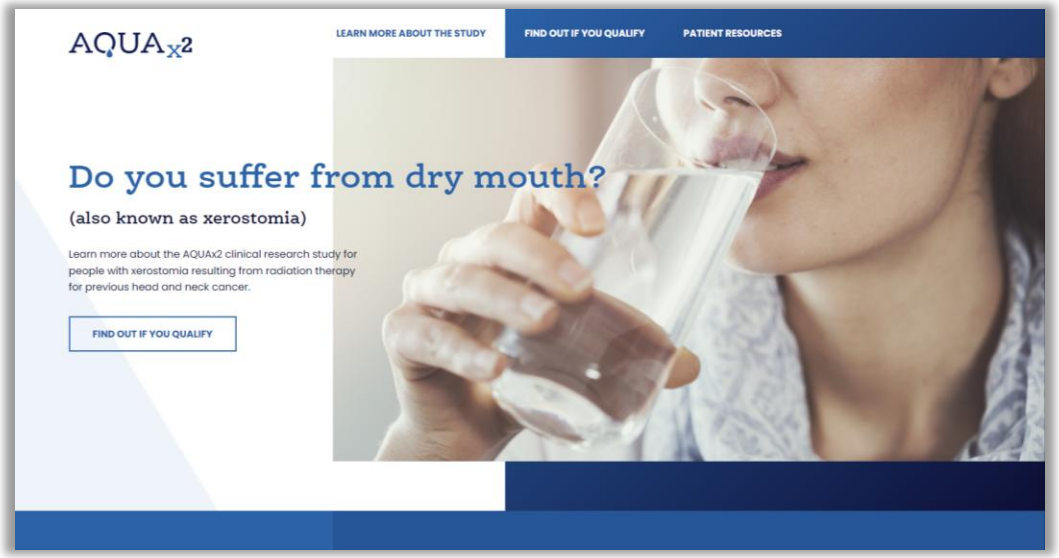


AQUAx2: Phase 2 Study Design and Endpoints

The Phase 2 randomized, double-blind, placebo-controlled study is actively enrolling

Study Design

- Randomized, double-blind, placebo-controlled
- 120 participants: Two active doses of AAV2-hAQP1 vs Placebo, 1:1:1 randomization



Primary Efficacy Endpoint

- Change from Baseline to Month 12 in Xerostomia Questionnaire (XQ) Total Score

Key Secondary Endpoints

- Change from Baseline to Month 12 in Unstimulated Whole Saliva Flow Rate
- Safety and tolerability of AAV2-hAQP1

Given the favorable safety and tolerability profile of AAV2-hAQP1 in the AQUAx study, we plan to amend the protocol to add a higher dose arm

AAV-GAD: A First-in-Class Genetic Medicine for Treatment of Parkinson's Disease

Snapshot: AAV-GAD for Parkinson's Disease - a Late Stage, Potentially Disease Modifying Clinical Program

Parkinson's disease:

10M
Parkinson's patients worldwide

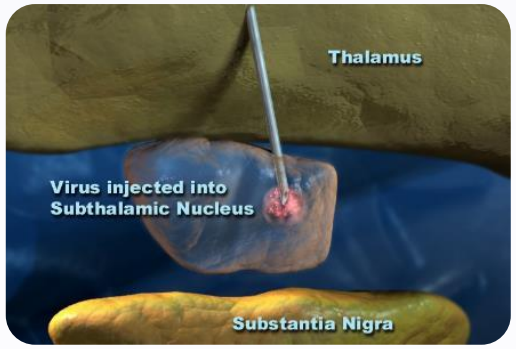
$52B
Estimated economic burden of PD in the US

Large Patient population in need of effective, safe treatment

- PD is the second most common neurodegenerative disease after Alzheimer's
- AAV-GAD is delivered via a one-time infusion through a minimally invasive procedure which does not require general anesthesia
- Safety and meaningful efficacy demonstrated in Phase 1 & Phase 2 studies against sham control
- Small dose and in-house manufacturing: low COGS

MOA and Delivery

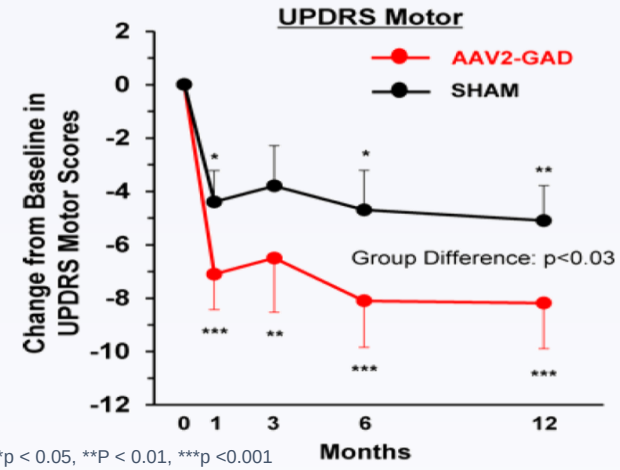
AAV-GAD is designed to reprogram dysfunctional brain circuits through local production of GABA, a neurotransmitter that can help restore more normal activity to these critical cells in any form of PD



Phase 3 Ready

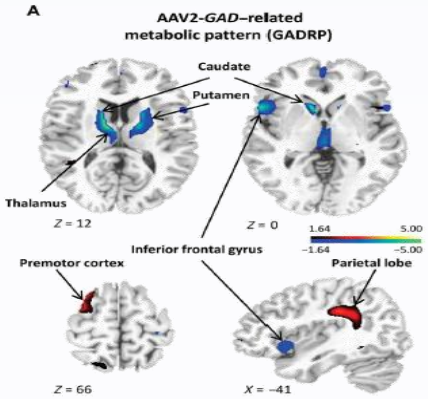
Disease Modifying in patients no longer responding to Dopamine

Significant improvements in UPDRS motor scores vs Sham



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

FDG-PET shows treatment responsive rewiring of the brain network regulating movement

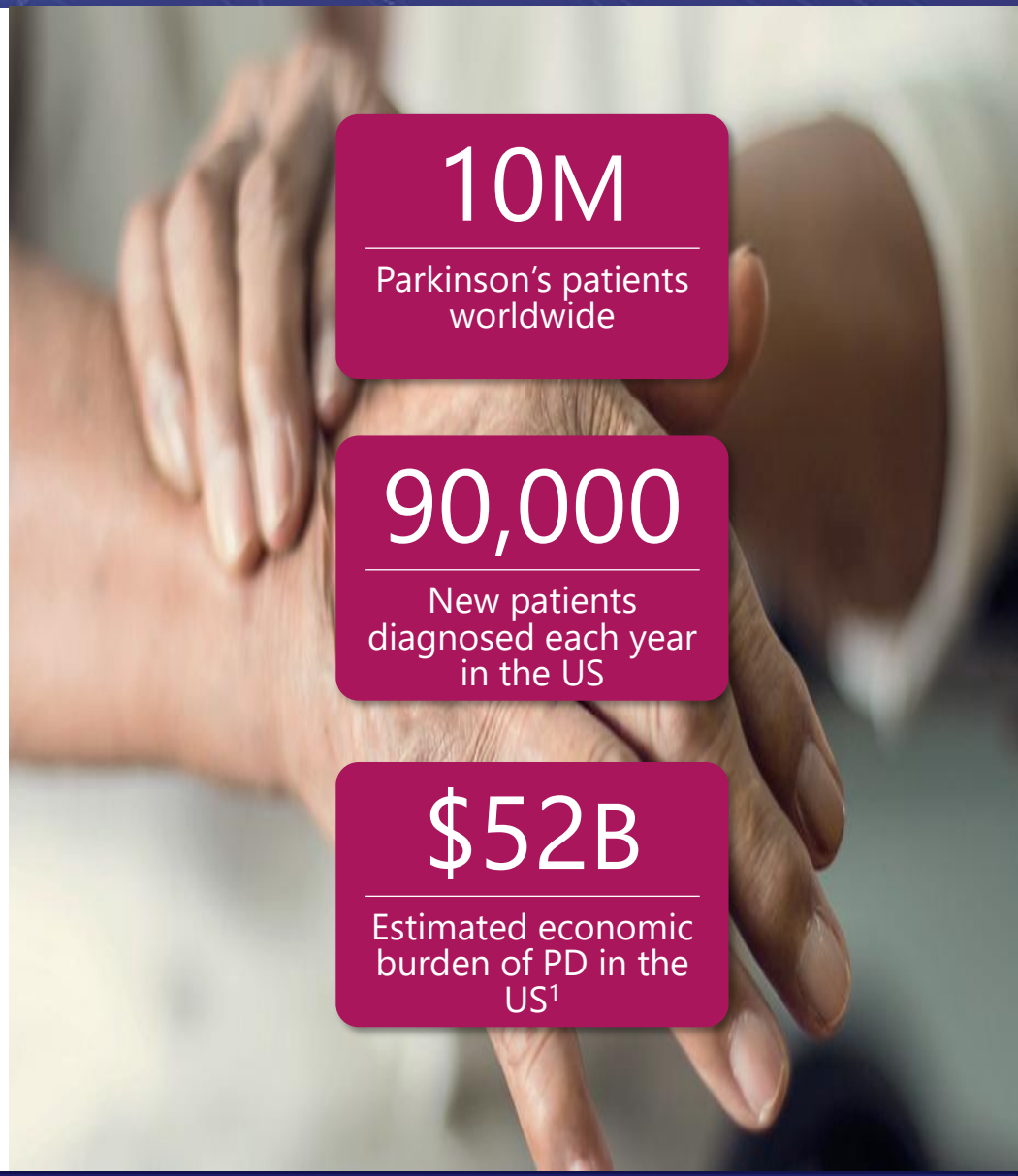


Parkinson's Disease

Disease Overview

- Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's, with nearly one million people in the U.S. currently living with Parkinson's disease and approximately 90,000 new patients diagnosed annually in the U.S.
- There are more than 10 million people worldwide currently living with PD.
- Most individuals with PD initially respond to dopamine replacement therapy, yet for a large percentage of patients, over time, this type of treatment is no longer sufficiently helpful while adverse effects of medication can also occur, leading to a considerable reduction in quality of life and the ability to function effectively.
- The cause of Parkinson's disease is unknown for a majority of patients, while a smaller percentage have a genetic cause, but in all cases, there is dysfunction of the key circuits that control movement –

AAV-GAD is designed to reprogram these dysfunctional brain circuits through the local production of GABA, a chemical neurotransmitter that can help restore more normal activity to these critical cells in any form of PD.



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

Current Standard of Care Leaves Significant Unmet Need

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
- SAEs reported in 56% of patients in a large, randomized U.S. study[1]
- ~15% of patients receiving STN-DBS experience significantly deteriorating speech one year after treatment[2]
- Many eligible patients either refuse, or prefer an alternative to, a permanent device implant
- Limited utilization due to above issues exacerbated for many by limited access to repeat visits for device programming and replacement at expert centers

MEIRAGTx | AAV-GAD

- ✓ One-time therapy
- ✓ The only gene therapy to meet primary efficacy endpoint in a Phase 2, randomized, double-blind, sham-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
- ✓ One time treatment
- ✓ 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

1- Follet KA. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010; 3;362(22):2077-91.
2- Tripoliti E. Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. Neurology. 2011; 76 (1) 80-86.

AAV-GAD Gene Therapy for Parkinson's Disease

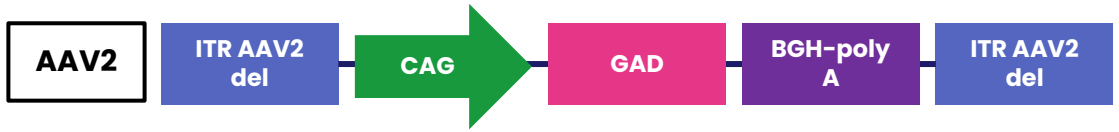
Approach

- AAV-GAD delivers a functional copy of the Glutamic Acid Decarboxylase (GAD) gene locally into the subthalamic nucleus (STN)
- GAD converts glutamate (excitatory neurotransmitter) to GABA (inhibitory neurotransmitter) to alleviate PD-associated dysfunction of the STN and other regions responsible for movement

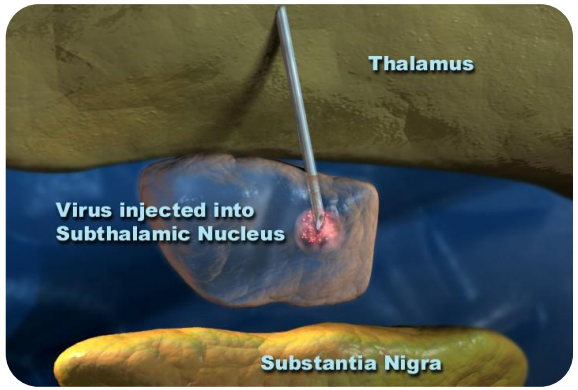
Localized delivery of AAV-GAD directly into the STN | local delivery of very small dose avoids safety risks associated with high dose/broad exposure of AAV in CNS and provides site-specific changes in neurotransmitter activity.

Standard and brief surgical procedure | no need for general anesthesia, well-known surgical route for administration, many highly trained surgeons in this technique, target volume is small (1-2mm) which increases delivery consistency between patients and limits amount of AAV needed per patient.

One-time therapy | does not require frequent follow-ups - significantly lowering treatment burden and improving patient access



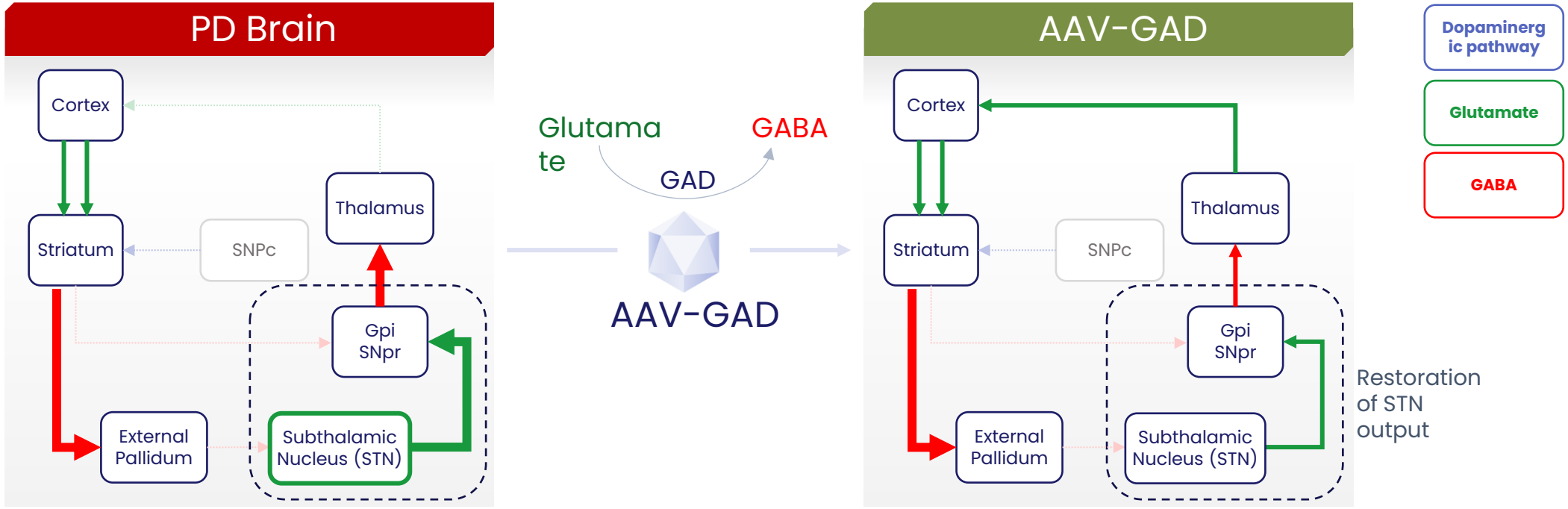
The Glutamic Acid Decarboxylase (GAD) gene is delivered locally to the STN which normalizes GABA levels within the STN and at STN targets to create circuits which circumvent dopamine to alleviate PD related motor symptoms



Status:

- **Positive clinical data from three controlled studies:**
  - Phase 1: unilateral, dose escalation study
  - Phase 2: bilateral, sham controlled study
  - Sham controlled bridging study using GMP material manufactured with commercial ready process in-house at Meira
- **Phase 3 ready – commercial ready drug product released mid year**

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

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 :

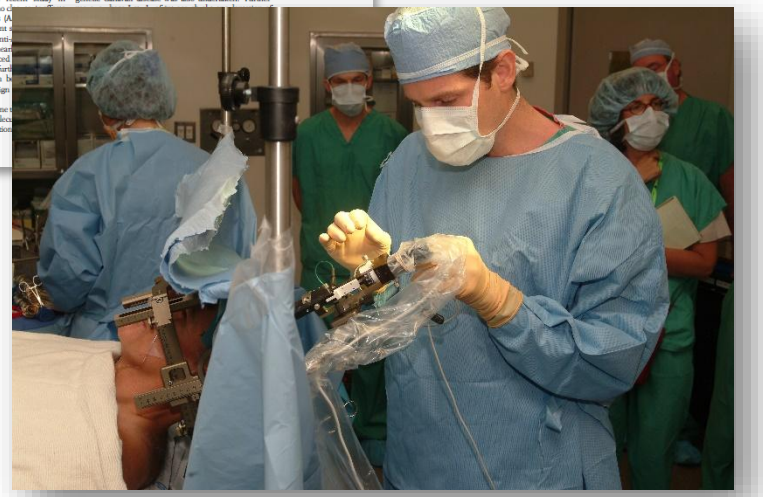
- AAV-GAD was safe and well tolerated, with no adverse events related to the gene therapy
- No abnormalities were noted on postsurgical MRIs up to 1 year
- No evidence of adverse events in the perioperative period and for at least 1 year after treatment (most patients followed up for >2 years)
- No evidence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

Efficacy findings (summary):

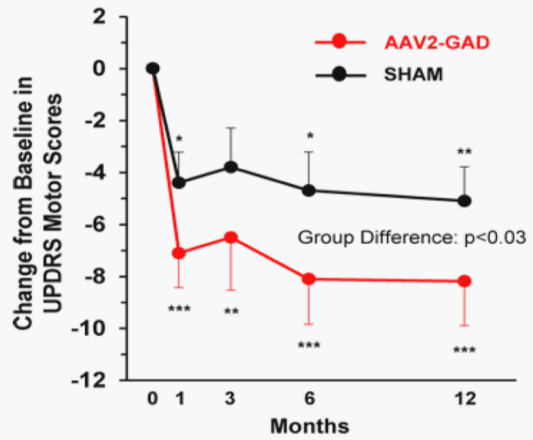
- Study met primary endpoint: UPDRS motor score improvement significantly greater than sham over 6 months; Improvements persisted at 12 months
- Significantly greater responder rate at 6 months in AAV-GAD treated group (50%) compared with sham (14.3%) also persisted at 12 months.
- Improvements in secondary 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

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

- *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

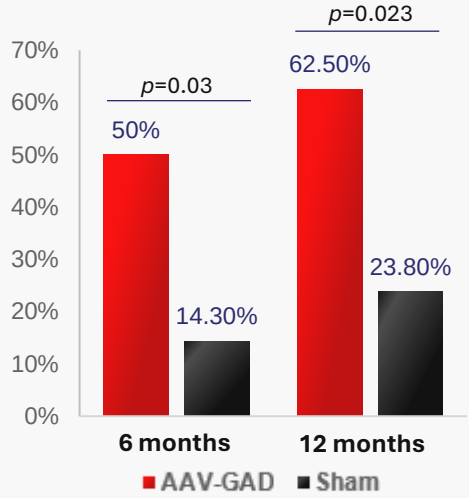
Significant improvements in UPDRS motor scores



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

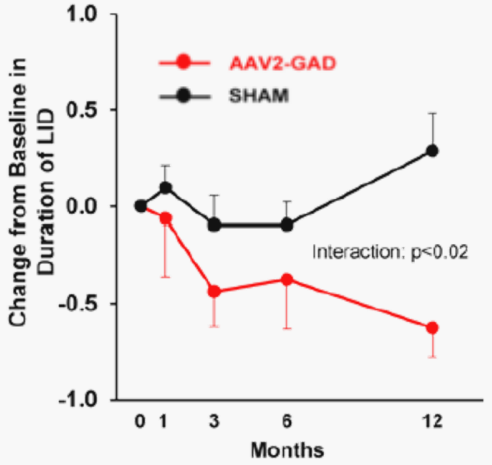
- Met primary outcome measure: improvement in UPDRS 3 motor scores vs. sham at 6 months
- Improvements in the AAV-GAD group were observed at all time points

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 duration of drug-induced dyskinesia over 12 months in the AAV2-GAD group compared with sham

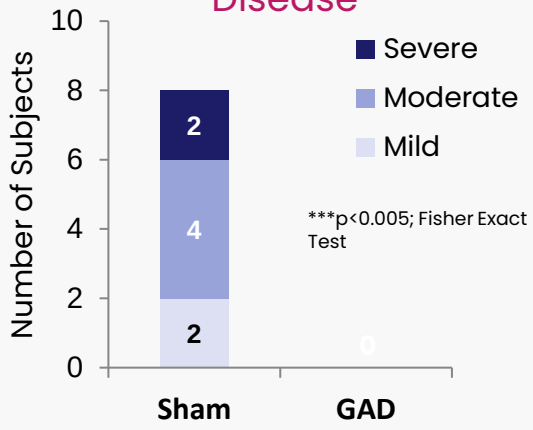
- *LeWitt PA. AAV2-GAD gene therapy for advanced Parkinson's Disease: a double-blind, sham-surgery controlled, randomized trial. Lancet Neurology. 2011; 10(4):309-19.*
- *Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133*

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

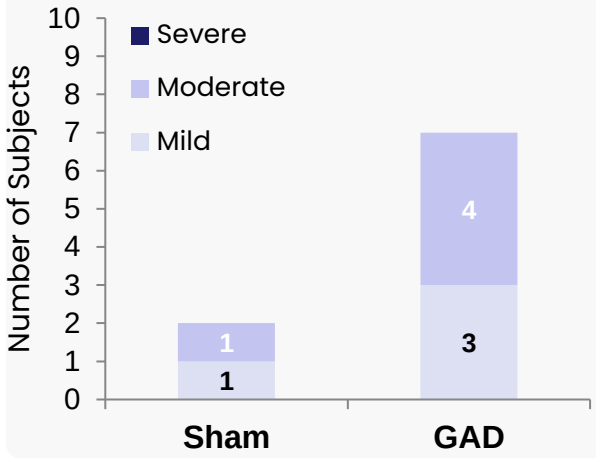
Adverse Events Over 12 Months (20% or Greater Frequency)

No GAD-treated Subjects Experienced Worsening Parkinson's Disease as an adverse event

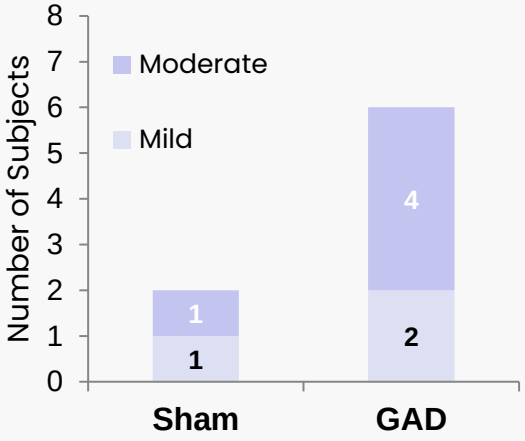
Worsening of Parkinson's Disease



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: GAD Related Pattern (GADRP)

AAV-GAD Related Changes in Basal Ganglia Circuitry Correlate with Improved Motor Symptoms

FDG-PET (Fluorodeoxyglucose positron emission tomography):

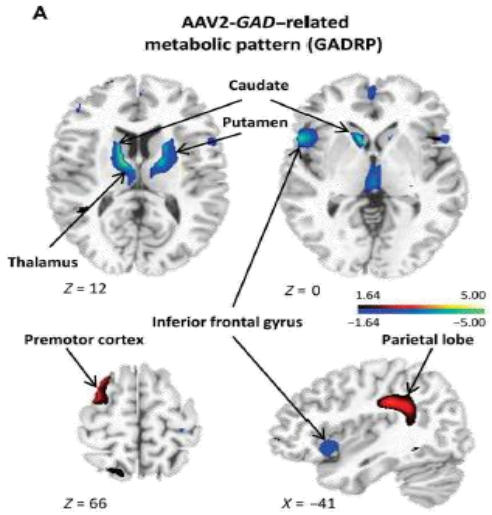
- Neurons metabolize glucose proportionate to their level of activity
- FDG-PET measures regional metabolism of radioactive glucose to determine changes in activity

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 correlated 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), provides a window into some of the biological circuits changes induced by AAV-GAD in these study subjects
- AAV-GAD is the first gene therapy for PD to have an objective imaging biomarker identified from a randomized trial that correlated 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

Disease Modification with AAV-GAD

Preclinical data demonstrated nigral neuroprotection with AAV-GAD

- Pre-treatment with AAV-GAD in the STN reduced toxicity and nigral degeneration with resulting improved motor function in 6OHDA rodents (Luo, et al Science 298:425-429, 2002)

Potential to Combine AAV-GAD with Other Nigral Neuroprotective Gene Therapies

- Nigra is 0.5-1mm below STN in the same trajectory as AAV-GAD STN infusion
- Can readily combine STN AAV-GAD with nigral gene therapy to slow further dopaminergic degeneration in a single procedure

AAV-GAD Reverses Pathological Brain Networks in PD

- Assortativity is the tendency of network connections to link nodes with similar properties
- High assortativity links nodes of similar properties and is associated with unstable, inefficient information flow through networks; Low assortativity is associated with more diversity and resulting greater robustness and network efficiency
- Network assortativity is higher in PD compared with healthy controls and assortativity increases with worsening PD disease severity and in more severe genetic forms of PD
- Dopaminergic pharmacotherapy increases assortativity despite improving symptoms
- **AAV-GAD, reorganizing brain functional connectivity through the unique GAD related pattern (GADRP), reduced brain network assortativity consistent with a normalization of brain network complexity and improved information flow compared with shams where increased assortativity was consistent with untreated PD (Vo et al, Cerebral Cortex 33:917-932, 2023)**

Positive Data from a Randomized, Sham-controlled Clinical Bridging Study: AAV-GAD Was Safe and Well Tolerated with Significant & Clinically Meaningful Improvements Demonstrated for Key Efficacy Endpoints at 26 Weeks

A 6-month, three-arm, randomized, double-blind, sham-controlled study using material manufactured in-house at MeiraGTx with an infusion system owned and produced by MeiraGTx

Study Overview:

- 14 subjects were randomized to one of three groups receiving bilateral STN AAV-GAD infusions: low dose group (3.5×10^{10} vg per STN, n=5), high dose group (10.5×10^{10} vg per STN, n=5) and sham control (n=4).
- AAV-GAD Drug Product was manufactured at MeiraGTx using its commercial platform process at its wholly-owned facilities.
- Primary objective: evaluate the safety and tolerability of AAV-GAD
    - Exploratory efficacy endpoints included mean change from baseline to Week 26 in MDS-UPDRS Part 3 (motor examination) scores in the “off” state and the Parkinson’s Disease Questionnaire *(*PDQ-39) score, a key patient-reported quality of life measure in Parkinson’s disease.
- Inclusion criteria: participants with idiopathic Parkinson's disease, a history of levodopa responsiveness for at least 12 months, and a UPDRS Part 3 score of ≥25 points in the "off" state.
- Subjects who completed the trial may enroll in a long-term follow-up study (NCT05894343) where they will be monitored for a total of five years post-treatment.

Positive Data from a Randomized, Sham-controlled Clinical Bridging Study: AAV-GAD Was Safe and Well Tolerated with Significant & Clinically Meaningful Improvements Demonstrated for Key Efficacy Endpoints at 26 Weeks

MEIRAGTx

Top-line data summary:

- AAV-GAD was safe and well tolerated with no serious adverse events related to AAV-GAD treatment.
- At Week 26, a statistically significant 18-point average improvement from baseline in UPDRS part 3 “off” medication score was demonstrated in the high dose group (p=0.03), with no significant change in the sham or low dose groups.
- Significant improvement from baseline in the disease-specific, patient-reported quality of life PDQ-39 score was demonstrated in both the high and low dose groups with no change in the sham group at Week 26:
  - In the high dose AAV-GAD group, the PDQ-39 score improved by 8 points from baseline (p=0.02), the low dose group improved by 6 points from baseline (p=0.04), while the 0.2 point worsening in the sham surgery group was not statistically significant.
  - A dose response in PDQ-39 score was observed, with 100% of participants in the high dose group, 60% of participants in the low dose group, and 25% of participants in the sham surgery group reporting an improvement.
  - For the PDQ-39 score, there was a trend to significance between the high dose and sham surgery groups at 6 months (n=4 evaluable per group).

MeiraGTx is engaging in regulatory discussions with the goal of initiating a Phase 3 study in 2025

AAV-GAD Parkinson's Program Status: Q4 2024

- ✓ 100% owned by MeiraGTx
- ✓ Large global market
- ✓ Significant unmet need
- ✓ Positive sham controlled randomized double-blind Phase 2 data
- ✓ Completed randomized, double-blind bridging study with MeiraGTx manufactured material using GMP manufacturing process fit for commercialization
- ✓ Phase 3 ready 1H 2025. Material manufactured using commercial ready process – released mid-2024

Novel, Synthetic, Mammalian Splicing-Based Riboswitch Platform

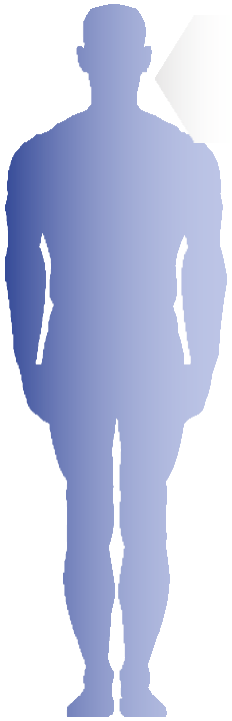
in vivo **delivery of any protein or peptide mRNA sequence from any DNA template in precise dose response to bespoke oral small molecule dosing**

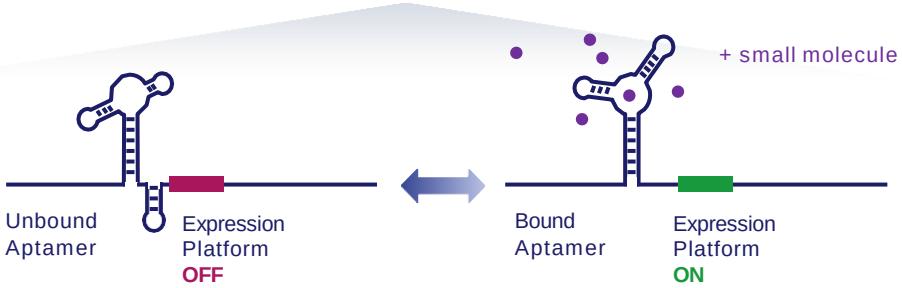
Riboswitch Platform: Precise *in vivo* production of Therapeutic Proteins and Peptides using Oral Small Molecule Inducers

Use cDNA Template For any Protein Sequence to Deliver That Protein, *in vivo*, with Very Precise Control Based on Oral Small Molecule Dosing

1 DNA template with control platform, one time injection

2 Oral pill induces precise production of the peptide or protein therapeutic

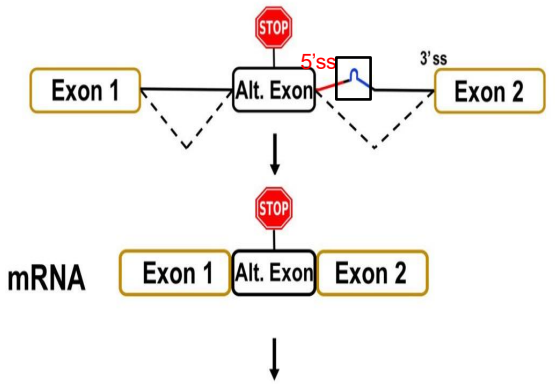




mRNA formation is controlled by alternative splicing cassette via aptamer : small molecule ligand binding

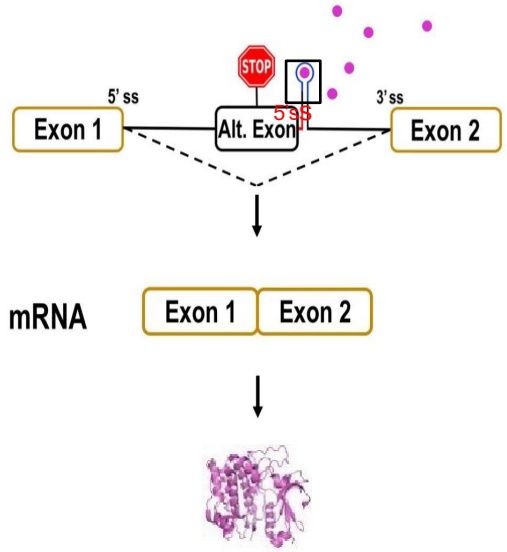
1 small molecule binding leads to the irreversible formation of 1 stable mRNA

No Small molecule (OFF state)



no protein

+ Small molecule (ON state)



protein expressed

Precise and Specific Control of Protein Production From any cDNA Template Driven by Bespoke Oral Small Molecules

Riboswitch technology enables precise control of *in vivo* protein production using bespoke orally-dosed small molecules:

i. Gene Regulation Cassette driven by a novel, synthetic, mammalian, splicing based Riboswitch technology

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

iii. Riboswitch precisely controls mRNA production from any DNA template using bespoke oral small molecules

iv. Oral small molecules activate mRNA and thereby protein production *in vivo* driving exquisitely precise protein *in vivo* therapeutic protein delivery

v. MeiraGTx's Riboswitch control system allows for repeated, durable production of mRNA resulting *in vivo* production of therapeutic protein

vi. Riboswitch can be applied to any transgene and any delivery vector or can be edited into the gene (for gene or cell therapy)

vii. Precise pharmaceutical control of the timing and level of *in vivo* production of therapeutic protein – peptides, hormones, antibodies show *in vivo* dose responsive efficacy in animal models eg: HER2-Ab, Epo, PTH, hGH, GLP1, GLP1-GIP, GLP1-GIP-Glucagon

viii. Allows native form of therapeutics to be produced within the body – in particular naturally short-lived peptides can be delivered in physiological timeframe eg: Gut Peptides

ix. Overcomes the need for manufacture of biologic therapeutics outside of the body

Precise and Specific Control of Protein Production From any cDNA Template Driven by Bespoke Oral Small Molecules

MeiraGTx has applied riboswitch technology in Metabolic Disease to control multiple combinations of peptides, gut peptides, myokines and adipokines and in Cell Therapy to control any CAR or cell fate determining factor via an oral small molecule. In both cases biologic targets that agonize rather than repress receptor signaling and work significantly better when not constitutively active or long-acting. This provides a new technology for delivering short-lived agonists and a new paradigm in drug development of molecules in homeostatic systems where rapid response to changing environmental factors is critical to efficacy.

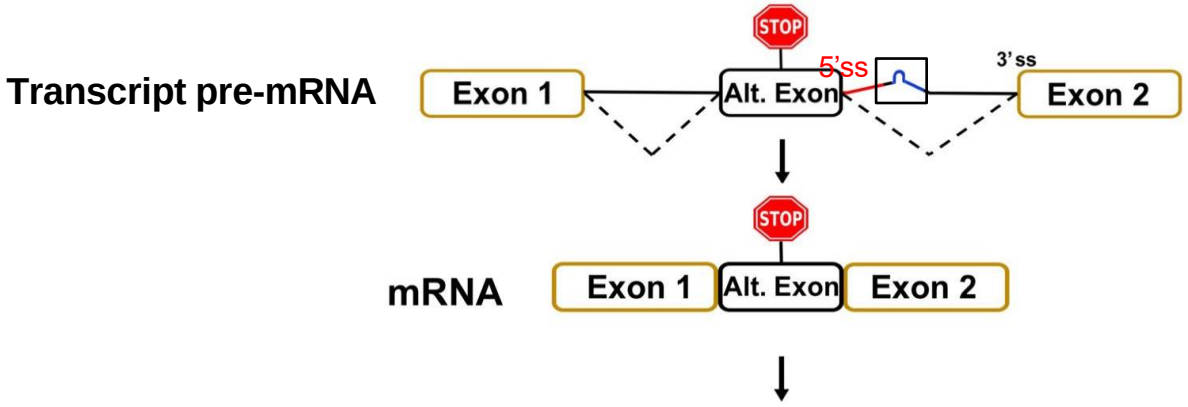
- Metabolic Disease: MeiraGTx has applied riboswitch technology to *in vivo* delivery of peptides to overcome the current issues with gut peptide combinations: manufacturing, efficacy, tolerability, muscle loss, and fat regain. Pulsatile production of short-lived peptides involved in metabolism has a significant impact on efficacy and tolerability. Bespoke combinations can be delivered; myokines to directly impact muscle and bone strength as well as white fat browning and CNS BDNF expression; natural leptin production for systemic and CNS activity to prevent fat regain; *in vivo* delivery of natural short lived peptides that cross BBB has implications for cognitive flexibility and neurodegenerative diseases of aging.

- Cell therapy: precise control of CAR expression timing and levels addresses many issues with current CAR-T therapy, manufacturing efficacy, safety and targeting solid tumors. Significant increase in efficacy of four-fold over approved unregulated CAR-T. Normalizes T-cell profile of CAR-T to that of naïve T-cells and, increases proliferation as well as cytotoxicity and potency *in vivo*.

Gene Regulation Cassette Driven by Splicing-Based Synthetic Mammalian Riboswitch

mRNA formation is precisely controlled by alternative splicing cassette via aptamer : small molecule ligand binding

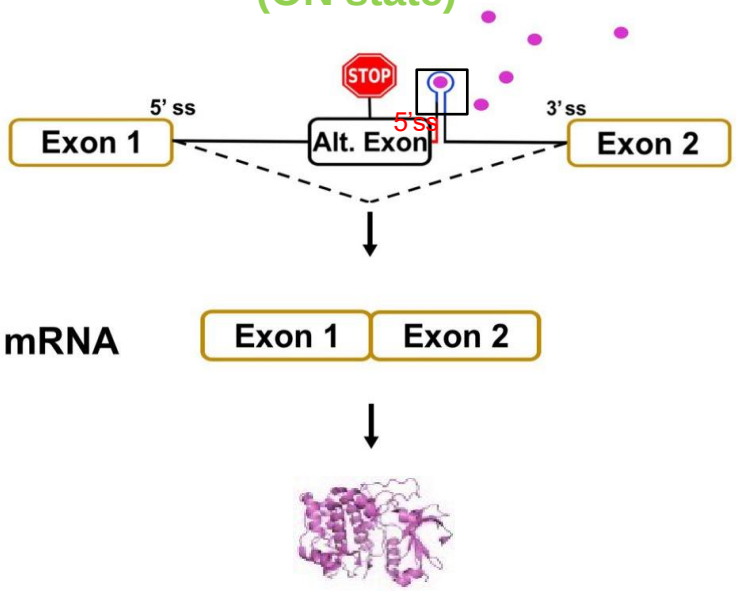
No Small molecule (OFF state)



no protein

- MeiraGTx's regulation cassette is inserted into the cDNA sequence of the transgene
- The cassette comprises an intron-exon-intron sequence which are not part of the cDNA coding sequence
- The exon contains a premature stop codon
- In the absence of the small molecule ("OFF state"), the incorporation of the alternative exon with stop codon into the transcript drives immediate degradation of transcript via the ubiquitous process of nonsense-mediated decay (NMD)
- **Thus, in the absence of the small molecule no messenger RNA is formed**
- **No protein or peptide is expressed**

+ Small molecule (ON state)



protein expressed

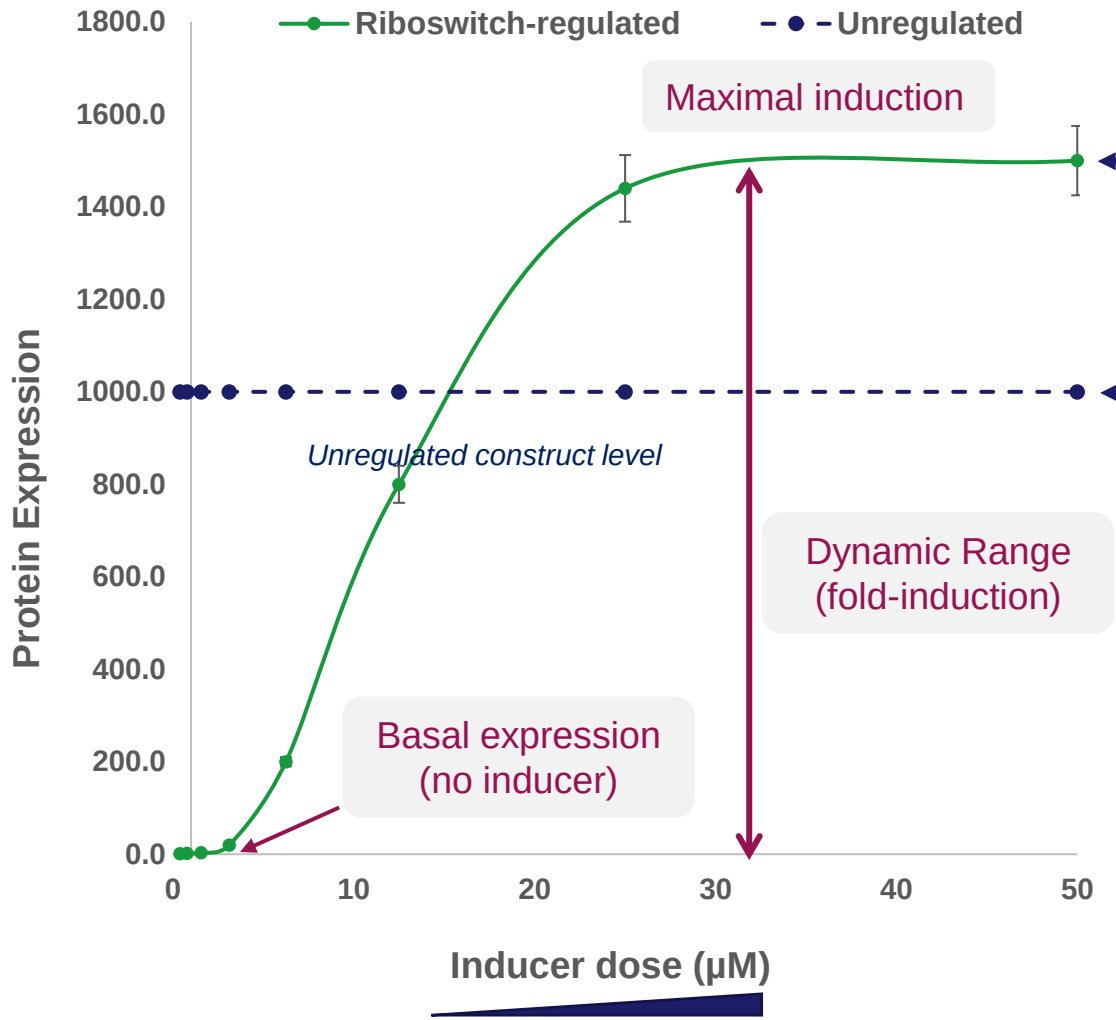
- Incorporated into the regulation cassette is a small molecule responsive 'riboswitch'
- Binding of the small molecule to a specific aptamer sequence in the riboswitch drives stabilization of a hairpin structure
- The hairpin structure incorporates the 5' splice site of the second intron sequence
- When the hairpin is stabilized and the splice site is blocked, the entire cassette is spliced out, leaving a stable mRNA
- **mRNA is translated and protein is produced**

Illustration of Terms Describing Riboswitch Gene Regulation Dynamics

Effective Levels: Protein expression is activated in dose response to the orally delivered small molecule.

Maximal induction exceeds that of the constitutive unregulated construct and is well above the therapeutic levels reached by unregulated

Basal Expression: Protein expression is undetectable in the absence of inducer



Expression level of regulated gene constructs containing the splicing cassette precise dose response to oral small molecule inducer. The level gets to higher than the level of expression of the constitutive unregulated gene construct with the identical promoter.

Expression level of unregulated construct with strong constitutive promoter.

Dynamic Range: Can be >5,000 fold due to low basal expression and high activated expression

Riboswitch Splicing Cassette Drives Precise Control of mRNA Production with Unprecedented Dynamic Range and Precision

MeiraGTx Riboswitch driven splicing cassette drives precise dose responsive control of mRNA formation and thereby protein production from DNA template in response to bespoke orally delivered small molecules

MeiraGTx's Riboswitch Platform is completely novel and superior to all other gene regulation technologies, overcoming the key issues limiting their application:

i. **Basal level**: Protein expression can be switched on **from undetectable baseline** to higher than maximum unregulated expression levels

ii. **Dynamic Range**: In contrast to other gene control systems where dynamic range (basal level to maximal induction) is in the range of 2-fold to 20-fold, MeiraGTx's dynamic range **can exceed 5,000-fold**

iii. **Effective levels**: Using the Riboswitch Splicing Cassette, higher level of expression than constitutive is routinely achieved

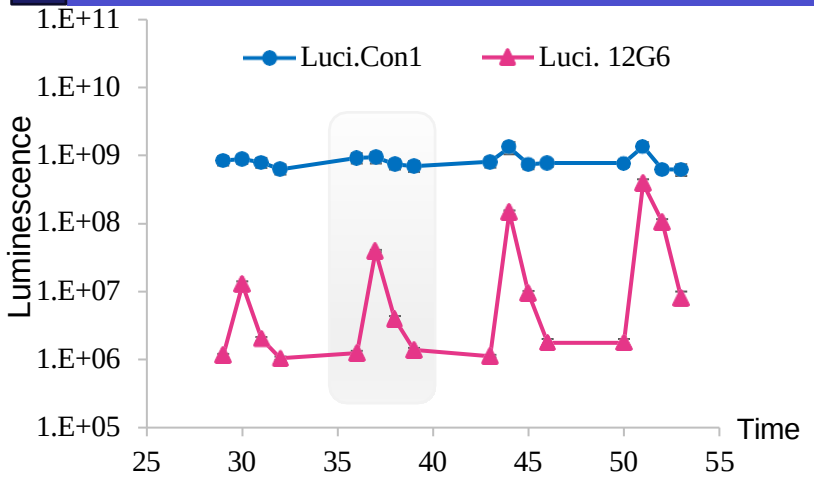
iv. **Exquisite Precision**: Exquisite precision of dose response to oral small molecule dose

v. **mRNA production**: MeiraGTx Riboswitch Splicing Cassette uses RNA configuration to control mRNA production; does not use transcriptional control via promoter

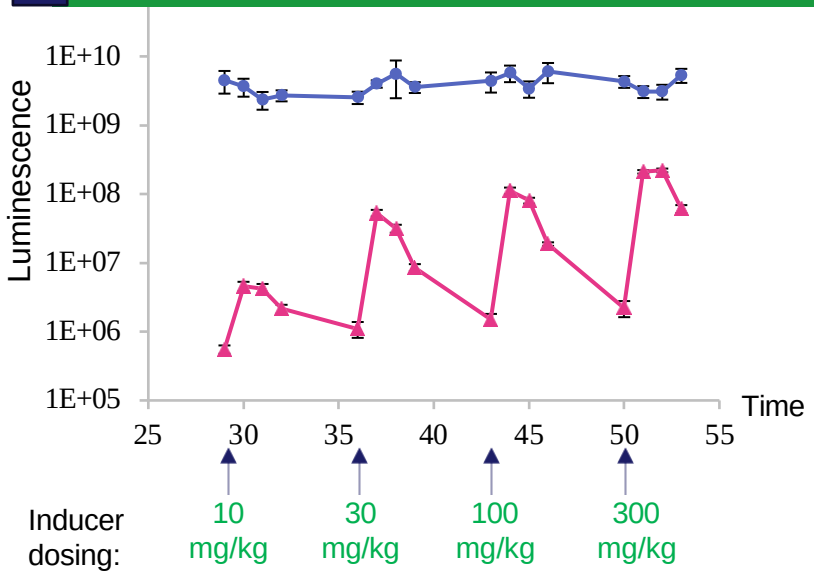
vi. **Different small molecules**: high throughput screening selects multiple small molecule activators that are potent and appear safe

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

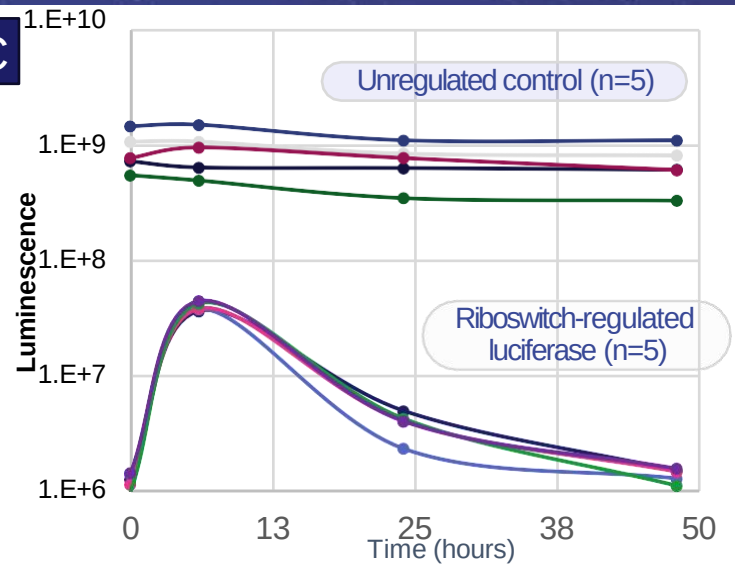


- **Luci.Con1**: constitutive expression – no regulation cassette
- **Luci.12G6:** identical construct to Luci. Con1 but with regulation cassette

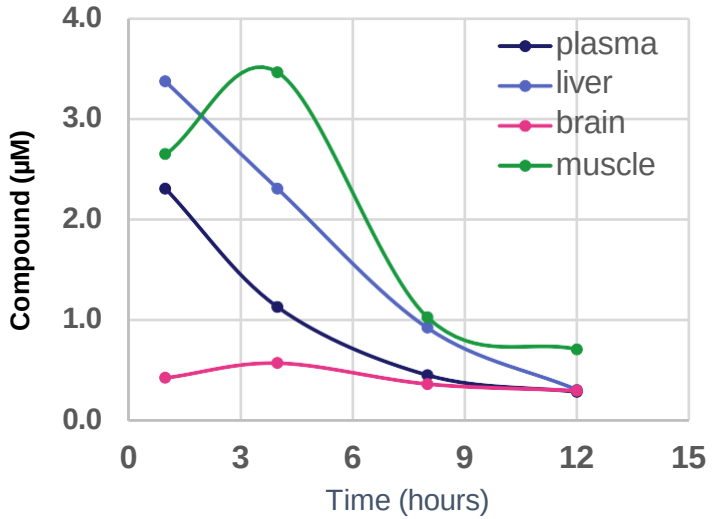
Liver Expression: tail vein injection AAV-luciferase
Muscle Expression: direct intramuscular injection of AAV-Luciferase

- 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**)
- **Figure C** is a blow up of the individual mice in each cohort at 30mg/kg dose in Figure A – indicated by the gray box in Figure A. This illustrates the restriction of expression with small molecule dosing between individual mice.
- On a mouse-by-mouse basis there is about 0.4 log range of expression between the 5 mice from constitutively active unregulated control 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.
- **Figure D** shows the differential tissue distribution of the small molecule inducer when delivered orally. The different shapes of the induced luciferase curves in Fig. A (liver) and Fig. B(muscle) precisely reflect the different tissue biodistribution to liver and muscle. A sharp peak for liver (blue) vs. slow accumulation and then exit from muscle (green).

C



D



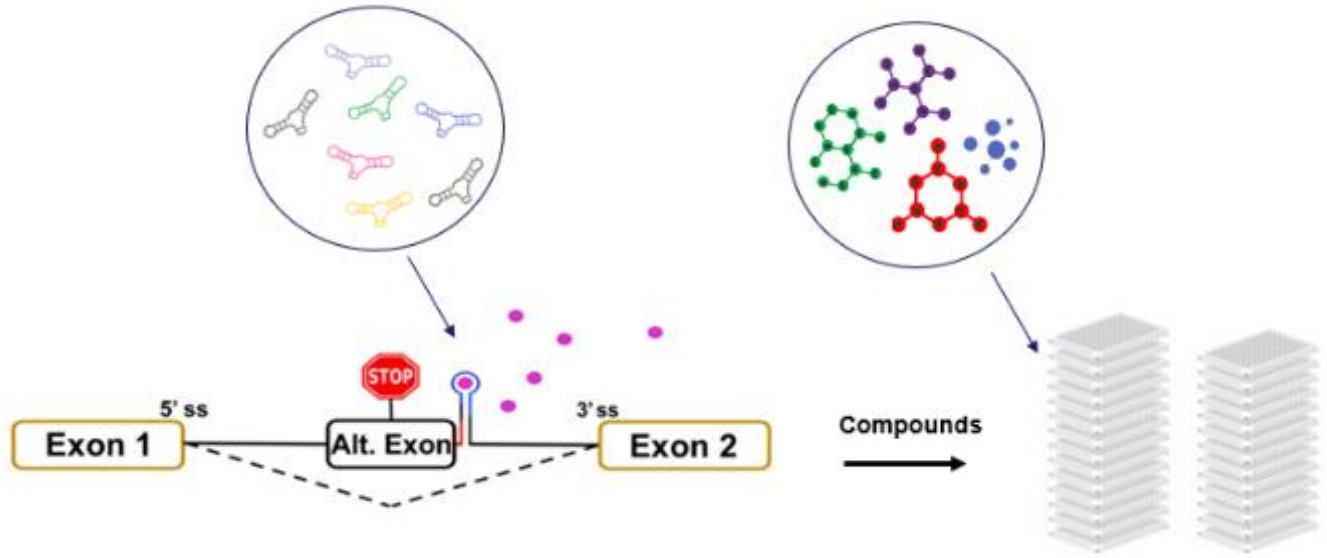
- Tissue distribution of orally delivered small molecule inducer shows short term accumulation in muscle, whereas clearance from liver is linear. This is directly reflected in the different profiles of regulated luciferase expression in the liver and muscle (Figures A and B)

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
- ~350 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. Additional BBB-penetrant compounds have been identified and are being evaluated.
- 5 compounds demonstrated high Eye exposure levels when dosed orally
- 4 compounds are in pre-clinical development: showed good PK/safety profile in non-GLP rat, dog, and/or NHP studies.
- **Most advanced candidate in IND enabling studies in 2024**

Riboswitch Drives *in vivo* Efficacy Demonstrated with Multiple Vectorized Targets: Vectorized Antibodies, Peptides and Hormones, Receptors in Cell Therapy and DNA and RNA Targeting Nucleases

MEIRAGTx

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (eye)
- 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, Amylin, Oxyntomodulin
- Myokines
- Adipokines eg: leptin

Gene/RNA Editing Nucleases

- Cas9
- CasRx

Tight control of CAR expression via oral small molecule inducer results in significant improvement in CAR-T phenotype and function

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

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RiboCAR: Solution to Key Issues Remaining for Current CAR-T and Other Cell Therapies

The precision of control both the timing and the levels of CAR using MeiraGTx's technology is unprecedented and drives significant improvements in CAR-T manufacturing, efficacy and safety compared to the currently unregulated CAR-T

Advantages of RiboCAR:

Manufacturing:

- Using MeiraGTx Riboswitch Cassette, CAR is not expressed during CAR-T production.
- In contrast to unregulated CAR-T, RiboCAR-T retain naïve T-cell phenotype and do not express increased exhaustion markers.
- RiboCAR-T cells retain proliferative ability while unregulated CAR-T fail to proliferate over time.

Efficacy of CAR-T:

- By tightly controlling CAR receptor density and timing of expression, excessive tonic signaling and high CAR receptor density is avoided.
- RiboCAR-T are 3-4x more potent *in vivo* and *in vitro* than the currently approved CAR-T with constitutively expressed CAR.
- This is demonstrated for CAR targeting solid tumors as well as liquid.

Safety:

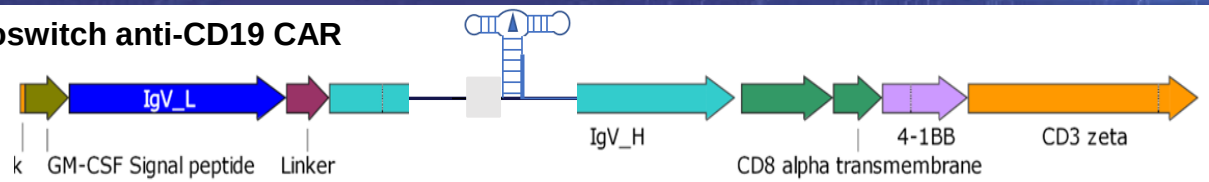
- Precise control of timing of CAR expression allows for improved safety as well as efficacy in both solid and liquid tumors - potentially allowing solid tumor treatment currently limited by lethal safety concerns using constitutive CAR-T.

Applicability:

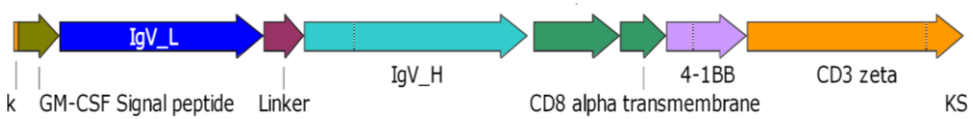
- RiboCAR provide superior CAR-T for liquid tumors, solid tumors and auto-immune disease, delivered by knock in or lentivirus.

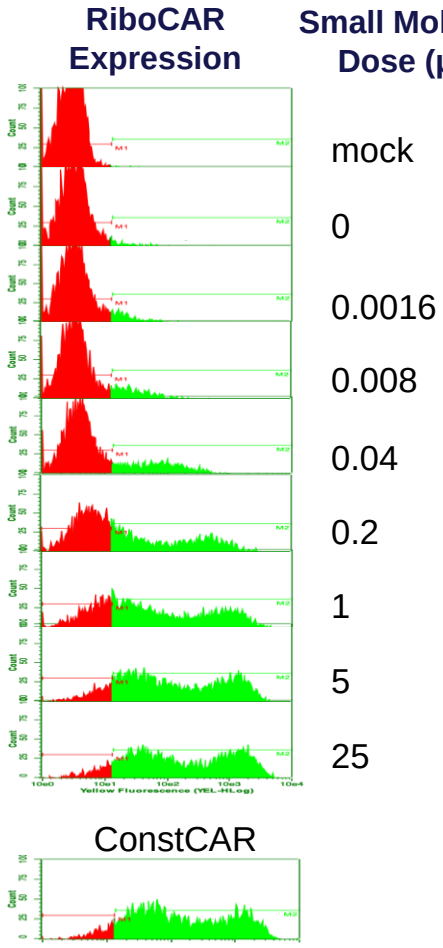
Chimeric Antigen Receptor Cell Surface Expression Precisely Controlled by Small Molecule Dose in HEK 293 cells

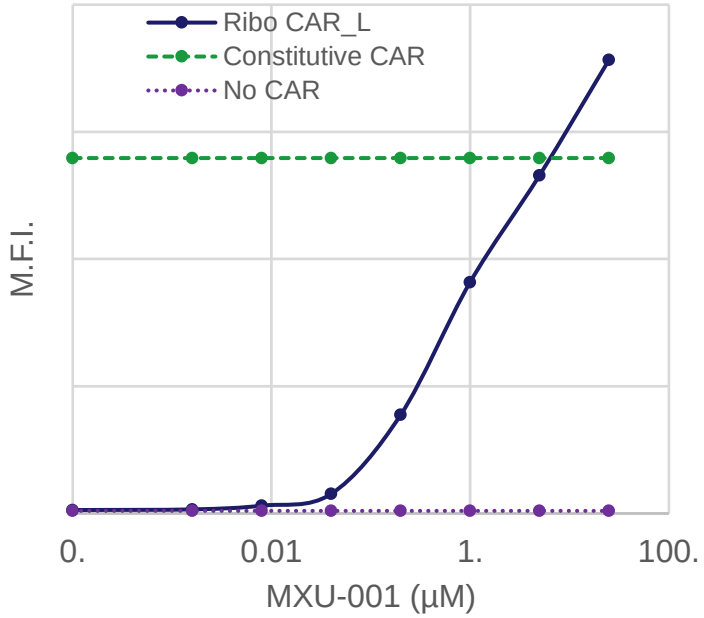
Riboswitch anti-CD19 CAR



Constitutive anti-CD19 CAR





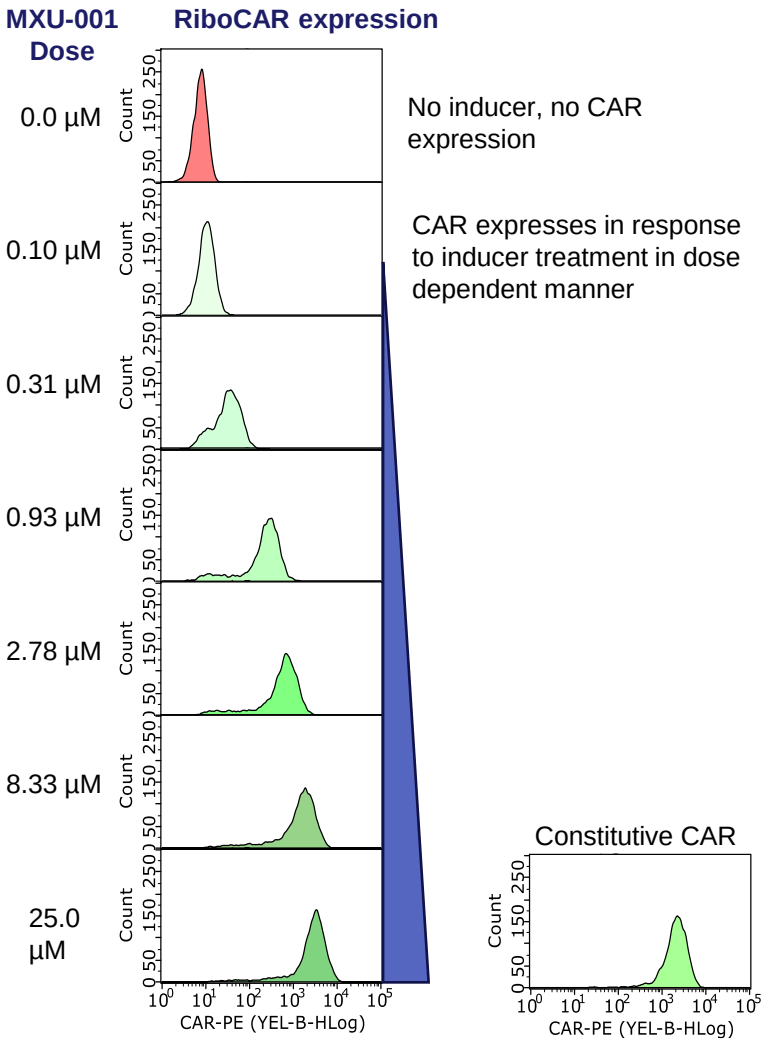


- HEK 293 cells were transfected with CAR constructs
- Transfected cells were treated with small molecule inducer MXU-001 at different doses
- HEK 293 cells were stained with anti-FMC63 antibody 48 hours after transfection
- CAR expression was measured by Flow cytometry
- **CAR expression was induced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

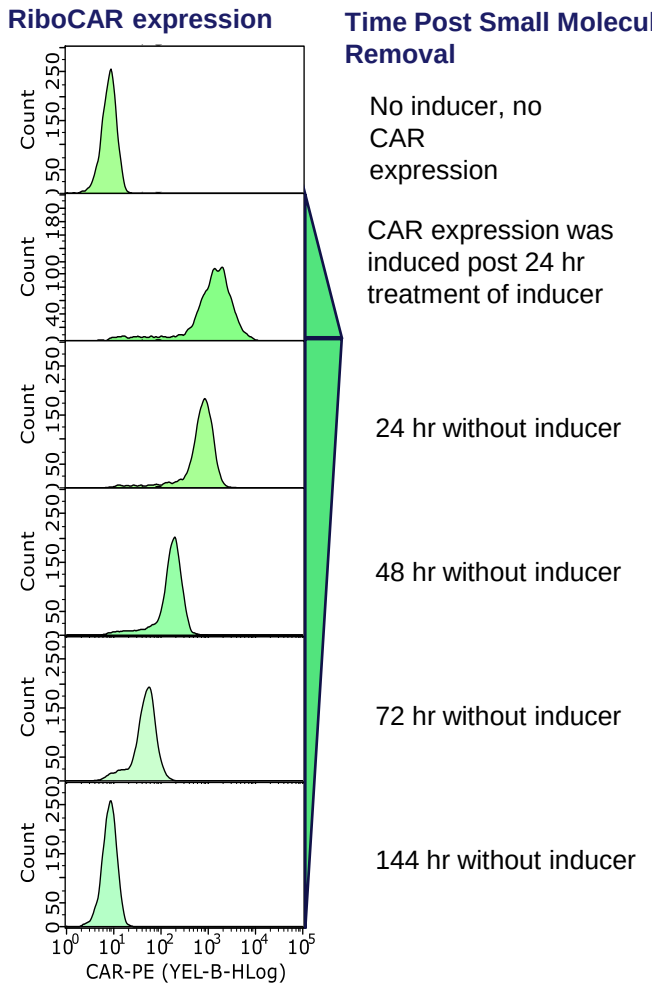
Riboswitch Regulates Chimeric Antigen Receptor Cell Surface Expression in Jurkat T Cells when Knocked into TRAC Locus

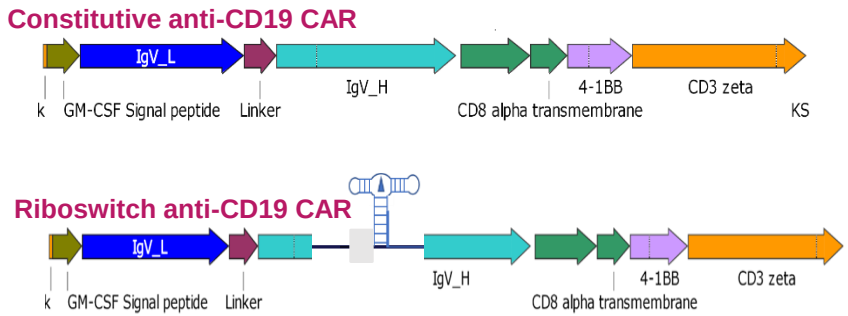
MEIRAGTx

CAR expression activated in response to small molecule dose



CAR expression switches off when small molecule removed

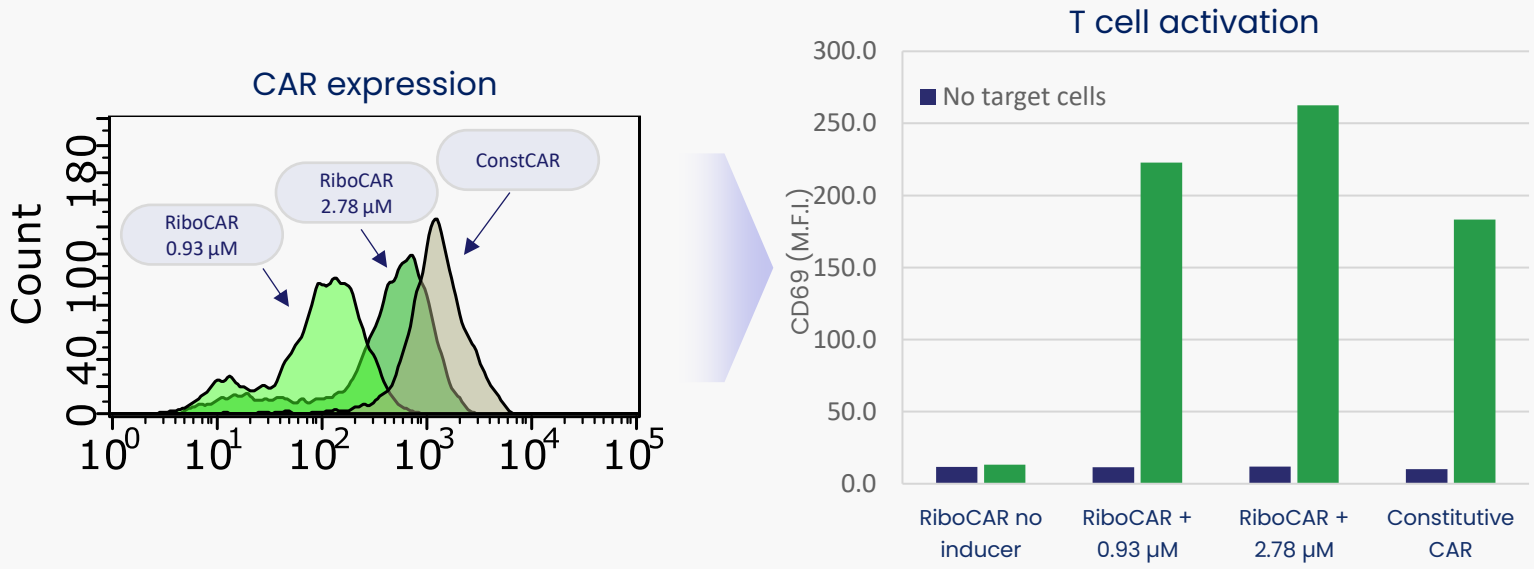




- **RiboCAR or constitutive CAR was targeted to TRAC locus by CRISPR/cas9-mediated knock-in**
- Stable lines of Jurkat T cells containing RiboCAR or constitutive CAR were established
- Jurkat T cells were treated with MXU-001 at different doses
- Jurkat T cells were stained with anti-FMC63 antibody 48 hours after MXU-001 treatment
- CAR expression was measured by Flow cytometry
- CAR expression was induced by MXU-001 in dose-dependent manner
- CAR expression declined to undetectable levels post small molecule removal

Jurkat T cells TRAC locus knock in: Riboswitch-Regulated Chimeric Antigen Receptor Induces CAR-T Activation in Response to Antigen

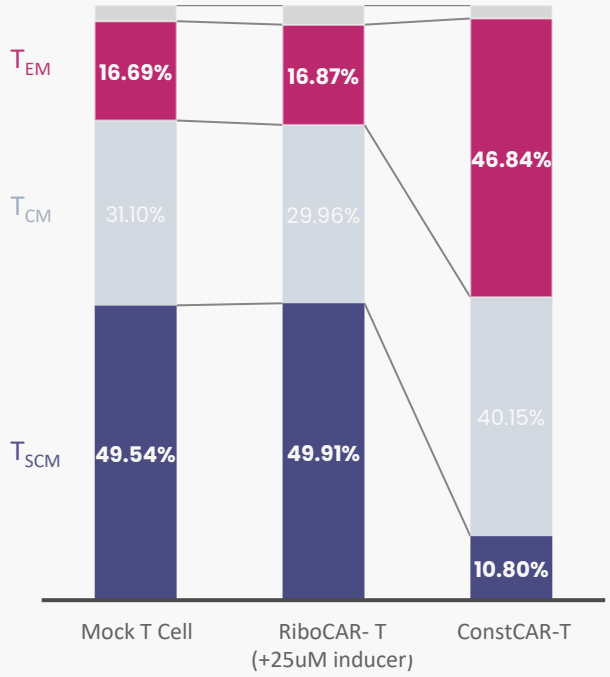
RiboCAR-T cells exhibit higher levels of activation at lower levels of CAR expression vs. ConstCAR-Ts



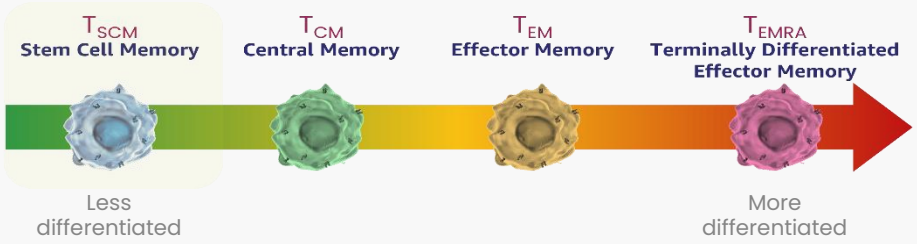
- RiboCAR Jurkat T cells treated with low doses of inducer express lower levels of CAR compared to ConstCAR-Ts
- The same RiboCAR-T cells express higher levels of the early activation marker, CD69, vs. ConstCAR-Ts
- RiboCAR Jurkat T cells demonstrate stronger activation in response to target cell antigen stimulation
- Controlled lower levels receptor density appear to increase RiboCAR potency compared to constitutive CAR

Primary human T-cells: Riboswitch Controlled CAR-T Cells Are Enriched in Naïve/Stem Cell-Like Memory Phenotype and Display Reduced Exhaustion Markers

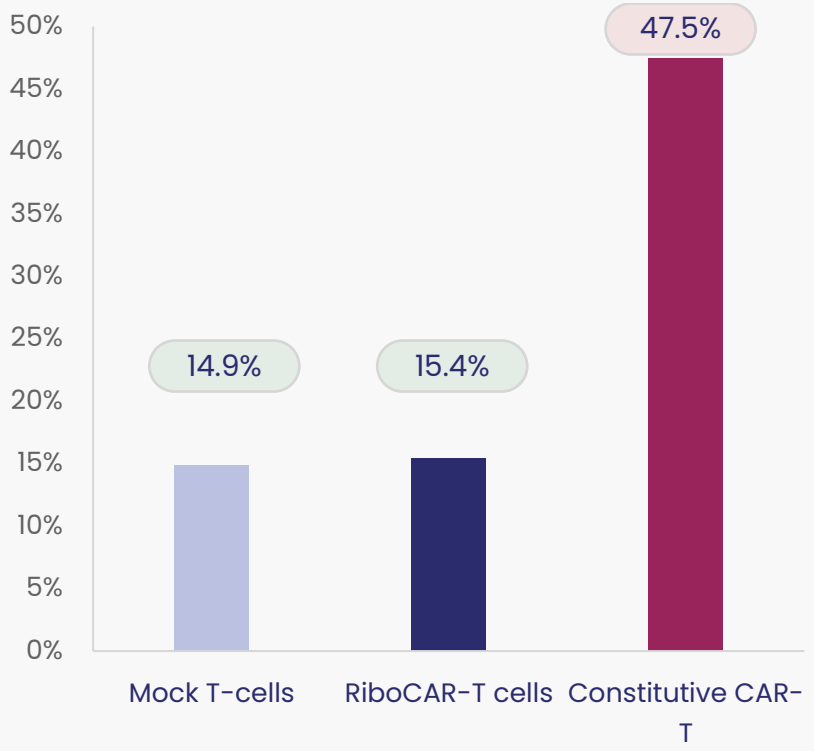
Primary Human RiboCAR-T cells have a significantly higher proportion of naïve/Stem cell-like phenotype



- CAR-T products rich in less differentiated T-cell subsets (such as stem cell-like memory (T_{SCM}) T cells) exhibit superior expansion, long-term persistence, reduced inflammatory response, and therefore better clinical response in patients[1,2]
- Compared to constitutive CAR-T cells, primary human RiboCAR-T cells exhibit a significantly higher proportion (~5-fold) of naïve/stem-like memory phenotype (CD62L+CD45RA+), and lower proportion of differentiated T effector memory (T_{EM}) cells



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

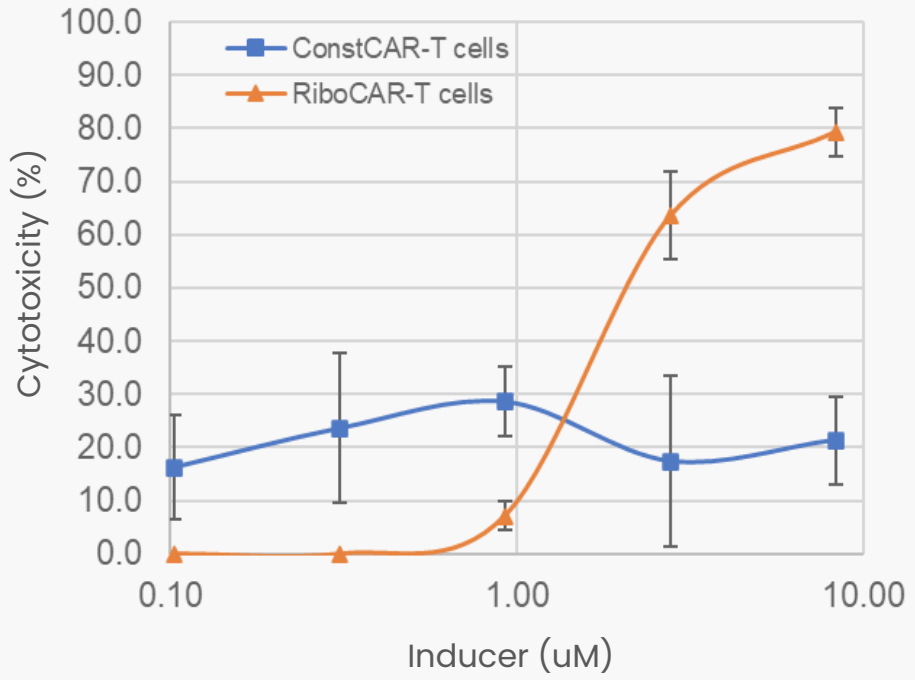


- Exhausted CAR-T cells exhibit decreased proliferative capacity, impaired anti-tumor activity, and attenuated persistence[1].
- RiboCAR T-cells exhibit significantly lower levels of the exhaustion marker, CD39, vs. constitutive CAR

1. O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol (2016) 16:553–65. doi: 10.1038/nri.2016.70
2. Bantug GR, Galluzzi L, Kroemer G. The spectrum of T cell metabolism in health and disease. Nat Rev Immunol (2018) 18:19–34. doi: 10.1038/nri.2017.99

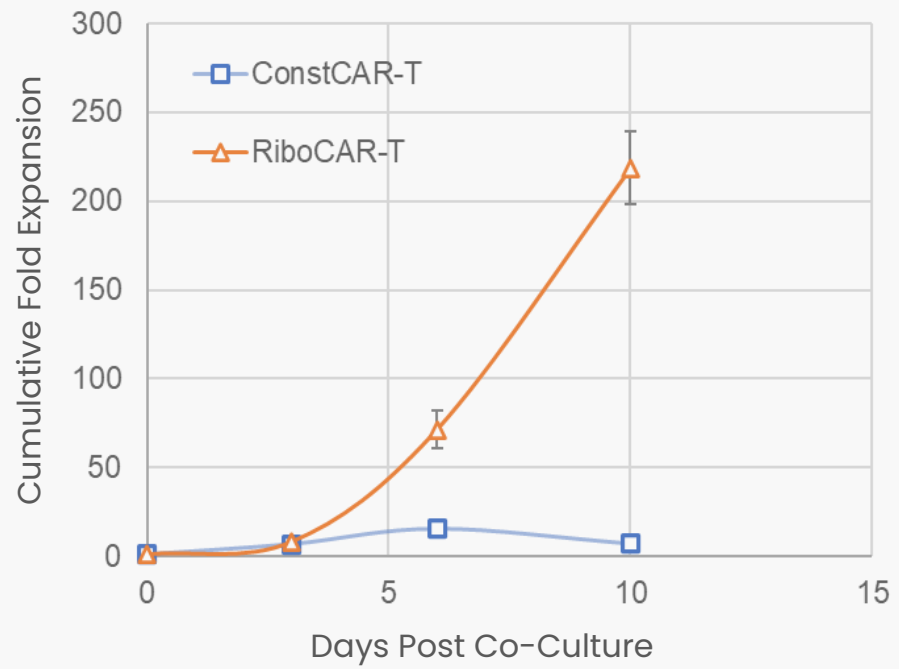
Riboswitch-Controlled Primary RiboCAR-T Cells Outperform ConstCAR-T Cells in anti-Tumor Activity *in-vitro*

RiboCAR-T cells exhibit superior cytotoxic activity in a dose-dependent manner



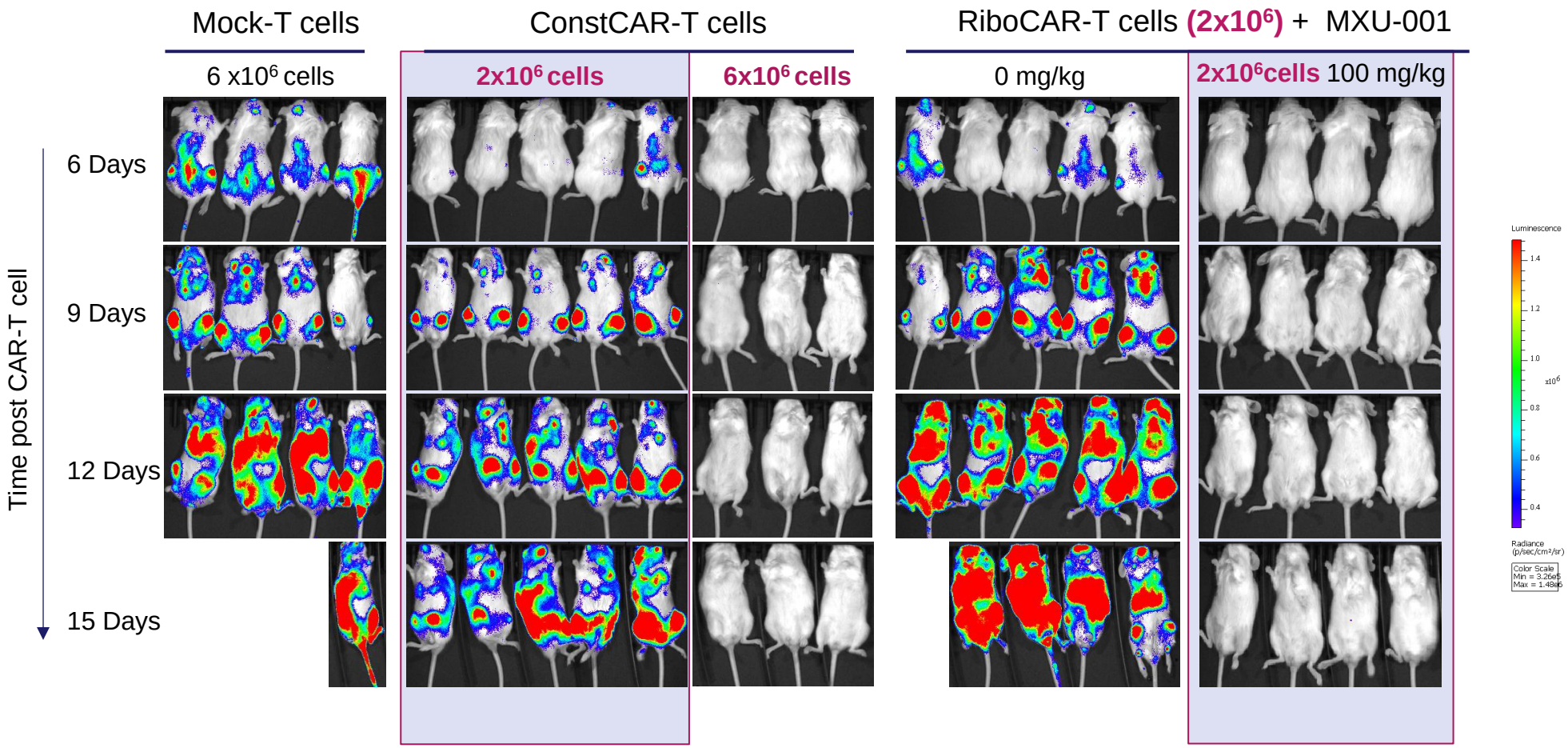
RiboCAR-T cells or ConstCAR-T cells were co-cultured with Raji-ffLuc cells at 2:1 E:T ratio in the presence of various concentration of inducer for 48 hours. Luciferase activity was measured for cytotoxicity assessment.

RiboCAR-T cells exhibit superior expansion capacity following repeated tumor cell stimulation



CAR-T cells were stimulated with MMC-treated Raji cells at 1:1 ratio in the presence of inducer. Stimulation was repeated every 3 days under the same conditions.

Primary human T cells: *in vivo* Riboswitch-Controlled RiboCAR-T Cells Outperform ConstCAR-T Cells in anti-Tumor Activity



- 1x10^6 Raji-ffLuc cells were injected into NSG mice.
- 4 days after Raji-ffLuc cell injection, the indicated CAR-T cells were injected into mice.
- Mice were dosed with the small molecule inducer with the indicated doses orally and daily starting the day before CAR-T cells injection.
- Tumor growth was monitored every 3 days using bioluminescence imaging.

Riboswitch-Controlled RiboCAR-T Cells Outperform ConstCAR-T Cells in anti-Tumor Activity

Summary of Data:

- CAR expression level and timing is precisely controlled by riboswitch via a small molecule inducer in dose dependent manner.
- In the absence of small molecule CAR expression is undetectable; levels of CAR can be induced to at least as high as constitutive CAR expression.
- Absence of CAR during CAR-T production improves T-cell phenotype and ability to proliferate.
- RiboCAR-T cells generated in the absence of CAR inducer appear to have more naïve/stem cell memory T cell phenotype in culture compared to ConstCAR-T.
- RiboCAR-T cells generated in the absence of CAR do not display increased exhaustion markers.
- RiboCAR-T cells appear more potent in cancer cell killing activity *in vitro*.
- RiboCAR-T cells have higher tumor cell stimulated expansion capacity *in vitro.*
- *In vivo,* RiboCAR-T cells are 3 to 4 fold more potent than ConstCAR-T requiring significantly fewer cells for increased tumor killing.

Conclusions:

- **Riboswitch regulated CAR provides a mechanism for precise, rapid and reversible control of CAR-T safety.**
- **Production of RiboCAR-T without CAR expression results in larger numbers of CAR-T with increased naïve/stem cell memory T cell phenotype**
- **RiboCAR-T are 3-4 fold more potent than ConstCAR having implications for manufacturing yield, efficacious dose as well as safety**
- **RiboCAR-T cells have an inherent safety switch due to the loss of CAR expression on small molecule withdrawal.**
- **Riboswitch Control can be applied to any receptor or signaling gene in any cell therapy context allowing exquisite control of cell therapy potency and safety.**

In vivo Delivery of Hormones and Peptides: incretins, myokines and adipokines - individually and in combinations

Riboswitch Drives *in vivo* Efficacy: Vectorized Antibodies, Peptides and Hormones, Receptors in Cell Therapy and DNA and RNA Targeting Nucleases

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (eye)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
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- **Myokines**
- **Adipokines eg: leptin**

Gene/RNA Editing Nucleases

- Cas9
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In vivo Delivery of Peptide Therapeutics Addresses Many Issues in Current Pharmacological Treatment of Metabolic Disorders

Efficacy:

- Native/natural short acting peptides
- More efficacious combinations
- Short acting physiological delivery with physiological receptor engagement - significantly improved efficacy - improved weight loss and post prandial glucose control – CKD and CV disease (supportive of work at Imperial eg: Jones et al. Nature Com (2018) 9:1602)
- *In vivo* delivery of short acting agonist peptides (via 1x per day oral small molecule) results in significantly improved efficacy compared higher levels of the same constitutively active peptides as well as significant improvement of glucose control even with glucagon present daily for 10 weeks

Tolerability:

- Higher potency of natural short acting peptides are efficacious at lower peptide levels and avoid tolerability and safety concerns of durable/ long-acting synthetic peptides more tolerable.
- Natural/native peptides not have the off target or receptor on target effects of small molecule receptor agonists – tolerability is a major issue.

Muscle Loss:

- ***In vivo* production of native myokines** that drive improved muscle strength, fat metabolism, mood.
- In contrast to Myostatin and Activin inhibiting antibodies which cannot increase already depleted levels of muscle/exercise derived peptides.
- Natural peptides are BBB penetrant - *in vivo* delivery allows active levels to be achieved that act on peripheral and CNS sites and mediate the global effects of myokines on BDNF expression, appetite and cognitive flexibility.

Fat re-gain:

- ***In vivo* delivery of natural Leptin** – avoiding the disastrous consequences of immune response to injected metreleptin.
- Natural Leptin can cross the BBB which may not so readily occur with agonist antibodies.

In vivo Delivery of Peptide Therapeutics Addresses Many Issues in Current Pharmacological Treatment of Metabolic Disorders

Neurodegenerative and Psychiatric diseases of Aging / Obesity:

- *In vivo* delivery of myokines, peptides, hormones that have CNS impact – particularly in aging and as muscle mass declines, delivery of non-synthetic peptides at therapeutic level allows them to cross the BBB and have important CNS effects eg: appetite, BDNF activation, cognitive flexibility

Sleep and Circadian Rhythm:

- Pulsatile *in vivo* delivery of peptides in line with role in Circadian rhythm which is disrupted in obesity, diabetes and by a western diet

Patient Access, Manufacturing & COGS:

- **Manufacturing, cost, access**
- *In vivo* delivery - the body makes the peptides, circumvents the ex-vivo peptide manufacturing with injection or oral dosing
- **ORAL:** Oral Peptides currently use 250-350x more peptide than current injectables; current small molecules have tolerability and efficacy issues
- *In vivo* delivery is activated with oral dosing with safe, bioavailable, easy to manufacture small molecule inducer (4 such molecules in IND enabling studies)

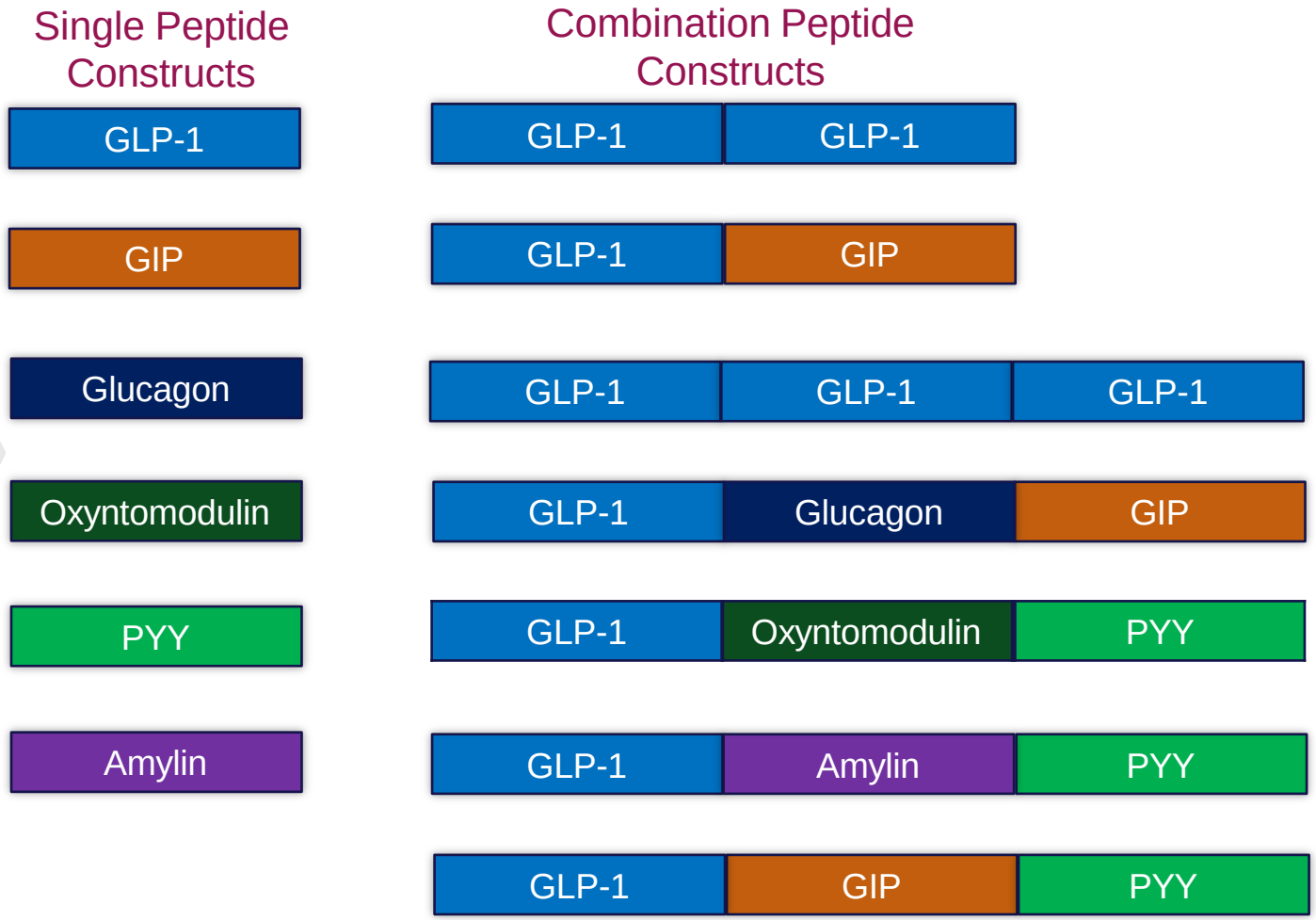
Cell Engineering for *in vivo* delivery:

- Riboswitch gene regulation works well in cell therapies. Riboswitch regulated transgenes can be engineered into cells rendering that gene precisely controllable by oral small molecule. The production of the biologic therapeutics by the therapeutic engineered cell can be precisely controlled by the oral drug, and the engineered cells within the body provide a controlled source of the secreted biologic therapeutic.

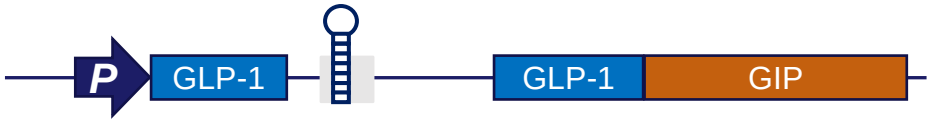
In vivo delivery Cassette Controls the Expression of Combinations of Gut Peptides, GLP-1 plus GIP and PYY

In vivo delivery of natural gut peptides:

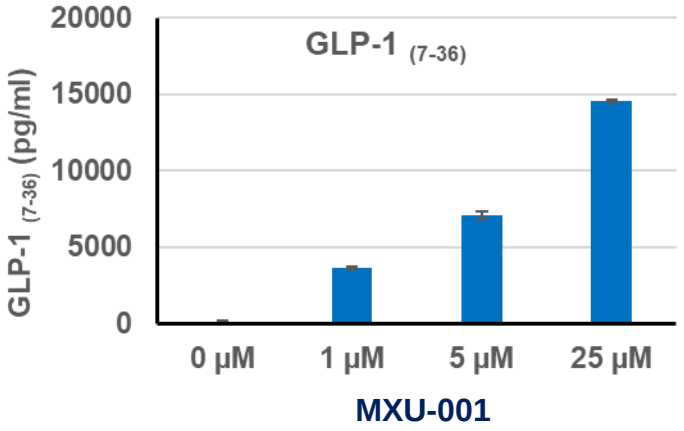
- Expressing gut peptides has been challenging
- MeiraGTx has achieved high expression of natural gut peptides, alone or in combination
- The riboswitch platform provides tight and controlled expression of unmodified, wild-type peptides
- Delivery of multiple combinations of peptides can be achieved in single vector. These can be constructed and tested rapidly head to head to provide fast *in vivo* proof of concept of efficacy and benefit on muscle mass, metabolism, and feeding as well as behavior and CNS impact.

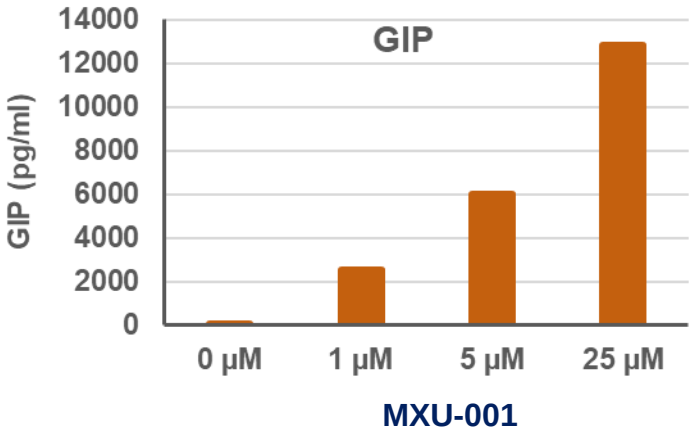


Gene Regulation Cassette Controls the Expression of Combinations of Gut Peptides, GLP-1 plus GIP and PYY

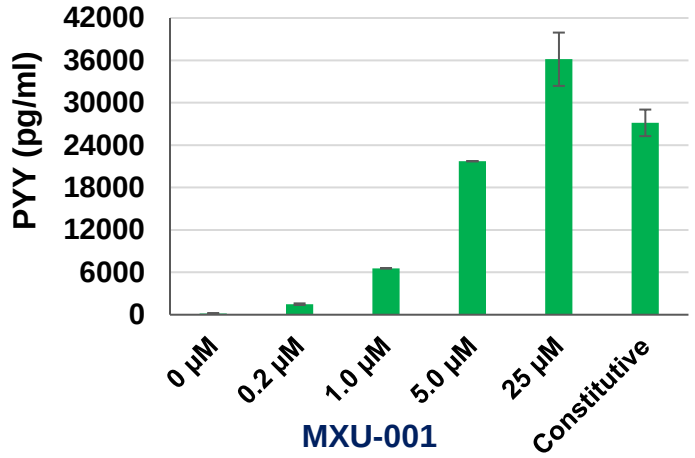


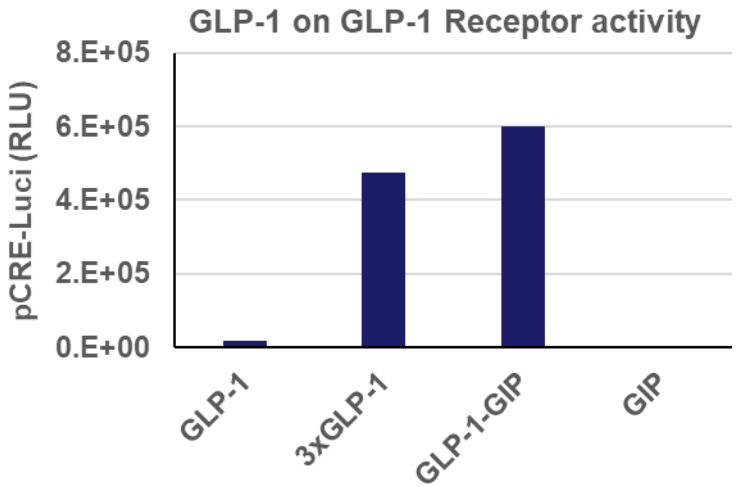
MXU-001-induced expression of GLP-1 and GIP from above construct

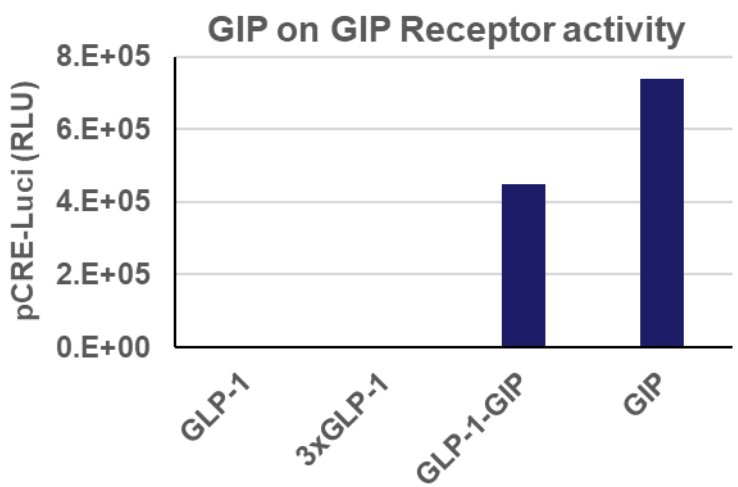




MXU-001-Induced expression of PYY from above construct



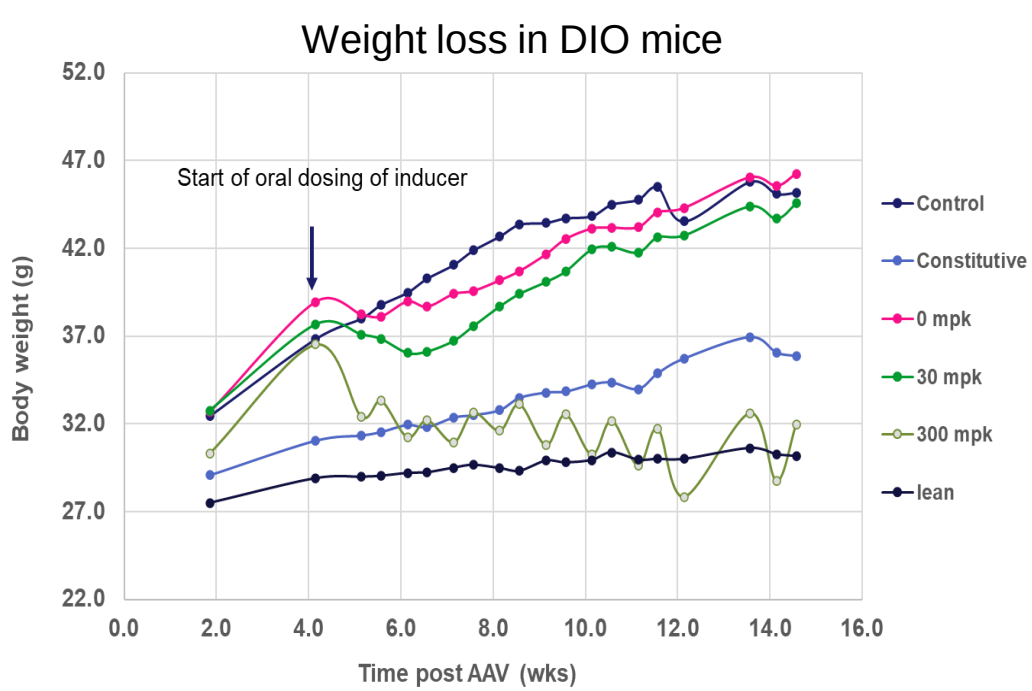


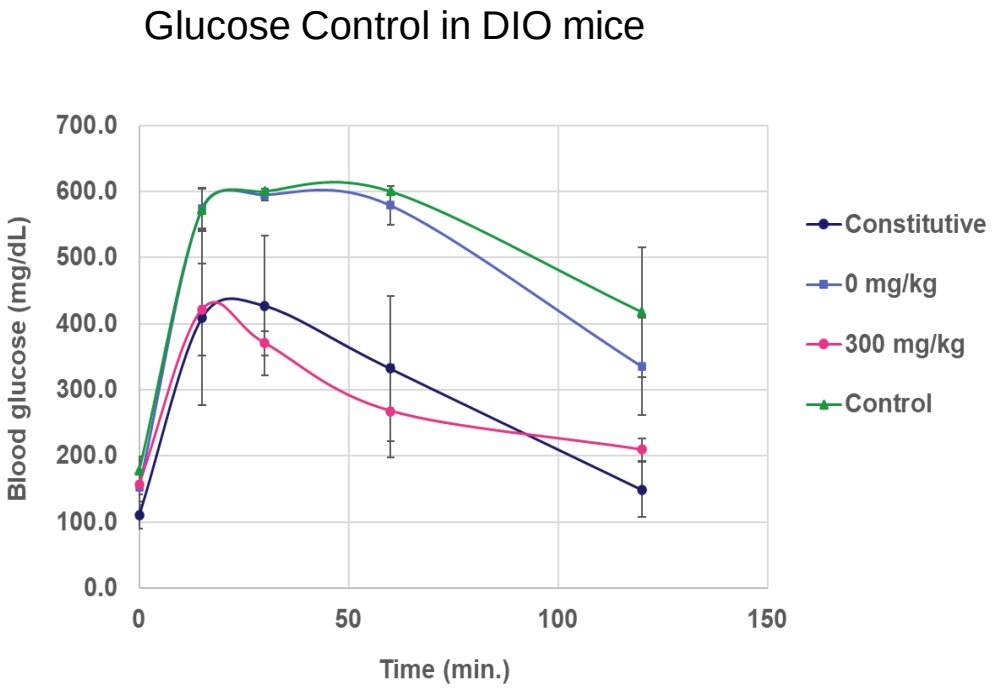


- In addition to expression levels, the biological activity of peptides expressed from constructs containing GLP1, GIP, or combinations of these peptides was demonstrated.
- Data from the following constructs are shown: 1 copy of GLP1 (GLP-1); 3 copies of GLP1 (3xGLP1); combination of GLP1 and GIP (GLP1-GIP); or GIP alone (GIP).
- Supernatants from cells expressing each construct were collected and tested on HEK293 cells expressing either the GLP-1 receptor or GIP receptor. Activation of receptor is indicated by luciferase expression.
- Supernatant from cells expressing GLP1 alone activated GLP-1 receptor cells, but not GIP receptor cells.
- Supernatants containing GIP alone activated GIP receptor cells, but not GLP-1 receptor cells.
- Supernatants containing GLP-1 and GIP activated both GLP-1 receptor cells and GIP receptor cells.

In vivo Delivery of GLP1-GIP via Daily Oral Small Molecule Dosing Significantly Improves Weight Loss and Glucose Control compared to Continually Active GLP1-GIP

GLP1-GIP: comparison of constitutive expression of the dual peptides compared to daily *in vivo* delivery induced by oral small molecule





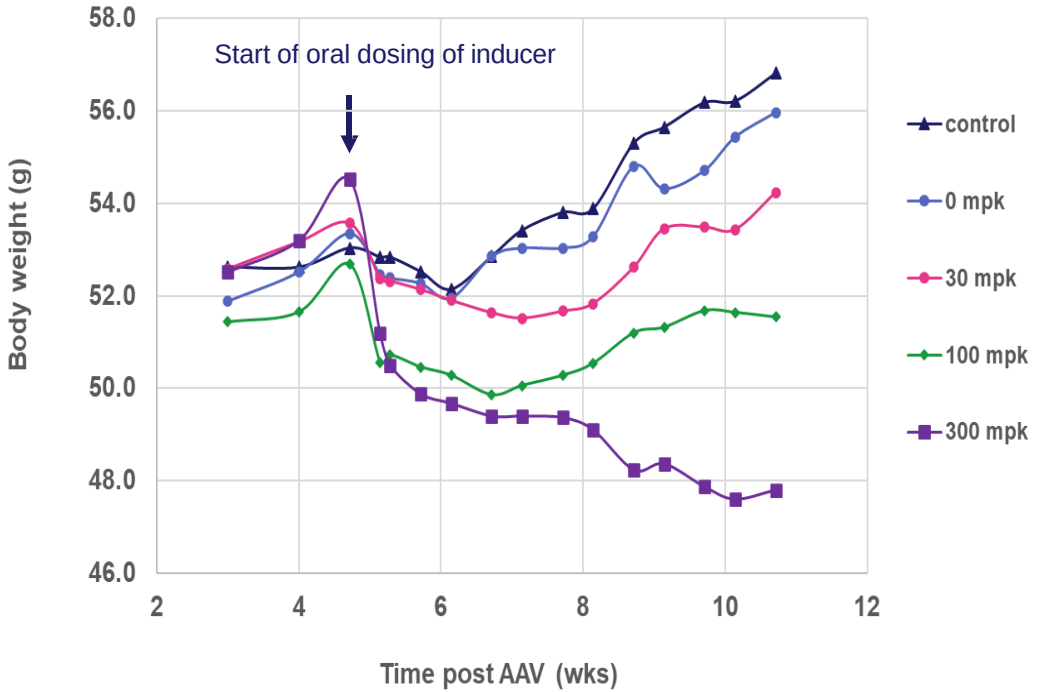
- Untreated DIO animals (male black 6 high fat diet) gain weight persistently over the 15 weeks of the experiment (dark blue line) *In vivo* delivery of GLP1-GIP from the constitutive vector (light blue line) results in reduced weight compared to control DIO animals (dark blue line)
- The regulated construct in the absence of the small molecule (pink line, 0mg/k) shows no difference from the DIO mice
- A low dose of the small molecule delivered orally daily on week days does not result in meaningful weight loss (green line)
- Daily oral dosing of the small molecule at an increased dose (grey line) results in rapid and persistence weight loss with the DIO mice reaching lean weight (black line) 6-8 weeks after small molecule dosing has begun
- The zig zag line reflects the fact that the animals were only dosed on weekdays and not on weekends, indicating that in the absence of the small molecule GLP1-GIP production diminishes

- In control untreated DIO animals (green line) poor glucose control following a glucose challenge is observed
- No improvement in glucose control is observed in animals with the regulated GLP1-GIP construct in the absence of oral dosing of the small molecule (light blue line 0mg/kg)
- Glucose control is clearly improved when GLP1-GIP is constitutively present (dark blue line)
- When animals receive GLP1-GIP via the daily dose of the small molecule rapid glucose control is seen in these animals (pink line)

In vivo Delivery of GLP1-GIP-Glucagon via Daily Oral Small Molecule Dosing Significantly Improves Weight Loss and Glucose Control compared to Continually Active GLP1-GIP-Glucagon

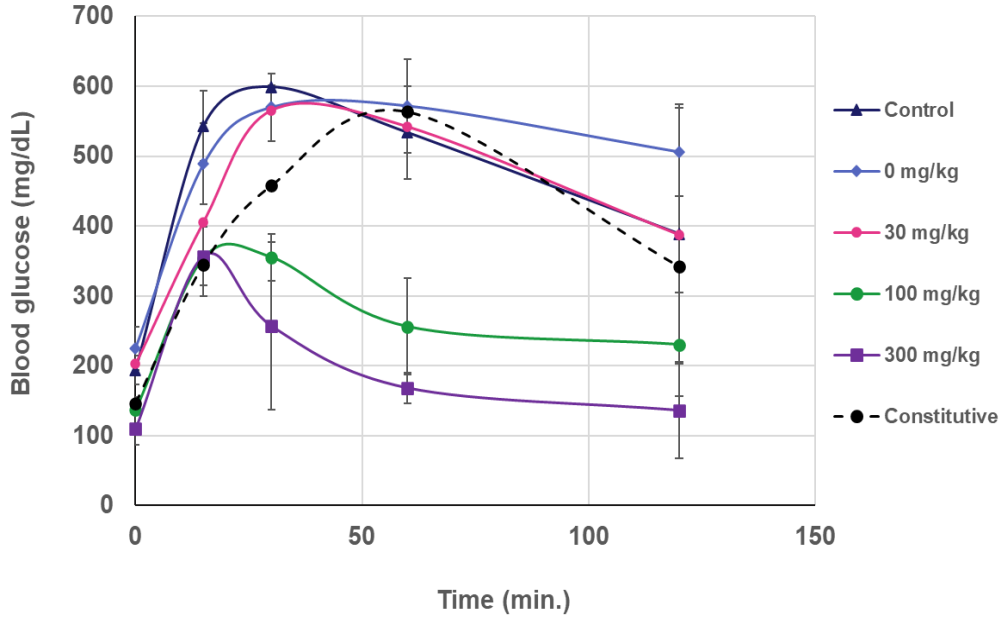
GLP1-GIP-Glucagon (GGG)

Weight loss in DIO mice



- Untreated DIO show persistent weight gain over 10 weeks (black line - control)
- The regulated construct in the absence of the small molecule (blue line, 0mg/k) shows no difference in weight gain from the DIO mice
- A low dose of the small molecule delivered orally daily every day including weekends (pink line) results in some initial weight loss.
- Increased weight loss is seen at a higher dose of small molecule (green line)
- When the daily oral small molecule dose is further increased (purple line) persistent and significant weight loss is observed
- In this experiment the animals received a single oral dose of the small molecule every day including weekends

Glucose Control in DIO mice



- Untreated DIO animals show poor glucose control post the glucose challenge (black line - control)
- The regulated construct in the absence of the small molecule (blue line, 0mg/k), and the animals treated with the low dose of small molecule (pink line) shows no difference from the DIO mice in glucose control
- At an increasing doses of the oral small molecule a dose response is seen with respect to glucose control with the higher dose giving the most rapid glucose control (purple line). This experiment was carried out following 6 weeks of *in vivo* daily delivery of GGG via oral small molecule induction
- In contrast, animals with persistent GGG activity showed complete failure of glucose control (dotted line)

MeiraGTx: Late Stage Clinical Pipeline and Comprehensive End-to-End Capabilities and Technologies in Genetic Medicine

Focus on *in vivo* delivery of vectorized biologic therapeutics addressing unmet needs in prevalent disorders

Diverse clinical pipeline

4 late-stage clinical programs pivotal/Phase 3

- **Retinitis Pigmentosa: Phase 3 dosing complete**. Recently acquired by JNJ.
- Commercial manufacturing agreement
- **AIPL1 associated retinal dystrophy: potential approval in 2025**

Disease modifying effects in prevalent, non-inherited indications:

- **Radiation Induced Xerostomia: potentially pivotal**
- **Parkinson's Disease: Phase 3 ready**

End-to-end GMP manufacturing

Flexible and Scalable

- **2 GMP facilities**, both commercial scale
- **Plasmid production for GMP**
- **QC facility** with commercial license
- **Fill and Finish,** warehouse and supply chain
- **Specials License**
- Industry leading **proprietary manufacturing platform process**
- **AI-driven optimization** of new vector process based on 8 years data, 20 different vectors and >50 GMP runs

Next generation vector optimization

Potency, safety, dose, COGS

- **Capsids:** Muscle, CNS, eye, liver,
- **Promoters:** ubiquitous, muscle, CNS, eye, liver
- **Proprietary Vectorization Technology:** Peptides and antibodies with 2-10x increased potency from same promoter
- **AI-driven in silico cloning** now drives capsid and promoter optimization
- **Organoid testing for HUMAN function**

Transformative Riboswitch technology

***In vivo* delivery of any biologic therapeutic via oral small molecule**

- **Precise dose Response** of protein expression to oral small molecule dosing
- **Gene, tissue, vector agnostic:** *in vivo* efficacy for antibodies, peptides, hormones and cell therapy demonstrated
- **GLP-1, GLP-1-GIP, GLP1-GIP-Glucagon, Amylin, PYY combinations**
- **CAR-T: for liquid and solid tumors, as well as autoimmune disease**

Expected Near Term Global BLA Filings based on current studies **in 2025 (RPGR, AIPL1), 2026 (AQP1), 2027 (GAD)**

Large markets, unmet patient need, strong data, physician and patient demand, low cost of goods

Deep pre-IND pipeline: ALS, MC4R obesity, Stargardt's, AMD, Glaucoma

Speed: New vector to tech transfer within 2-3 months, reducing to 6 weeks with AI

Regulatory Interactions: deep global experience

Avoid CDMO bottlenecks & quality failures

Saves 3 years in development timeline of any product from IND to BLA–significantly increasing ROI on every product

Significantly reduced Cost of Goods

Improvements in potency > 3 logs

Maximize outcomes for patients: lower dose, improved safety and efficacy

Vast reduction in COGS : 3 log lower dose, 3 log lower cost of goods

Affordable therapies increasing access to effective treatments in common diseases

Metabolic disease: leapfrogs current approaches, with transformative impact on:

- **Efficacy** and **tolerability**
- **Muscle loss** and fat regain
- **Neurodegenerative** disease
- **Manufacturing**, cost and patient access

Next-generation Cell Therapy: transforms efficacy, safety, manufacturing and durability in liquid and solid tumors as well as autoimmune disease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