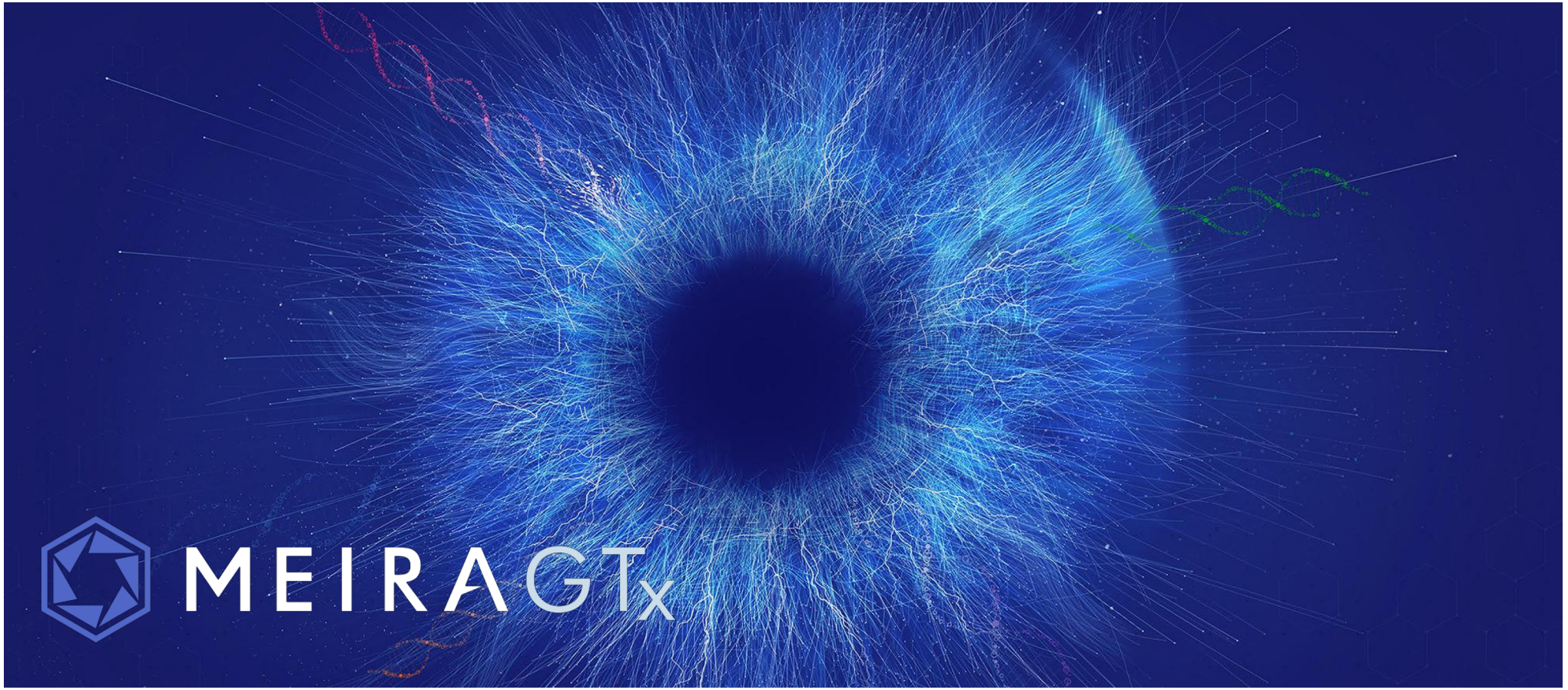


July 20, 2020

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 the development and efficacy of AAV-RPGR, plans to advance AAV-RPGR into Phase 3 clinical trial and anticipated milestones regarding our clinical data and reporting of such data and the timing of results of data, including in light of the COVID-19 pandemic, as well as statements that include the words “expect,” “intend,” “plan,” “believe,” “project,” “forecast,” “estimate,” “may,” “should,” “anticipate” and similar statements of a future or forward-looking nature. These forward-looking statements are based on management’s current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, our incurrence of significant losses; any inability to achieve or maintain profitability, acquire additional capital, identify additional and develop existing product candidates, successfully execute strategic priorities, bring product candidates to market, expansion of our manufacturing facilities and processes, successfully enroll patients in and complete clinical trials, accurately predict growth assumptions, recognize benefits of any orphan drug designations, retain key personnel or attract qualified employees, or incur expected levels of operating expenses; the impact of the COVID-19 pandemic on the status, enrollment, timing and results of our clinical trials and on our business, results of operations and financial condition; failure of early data to predict eventual outcomes; failure to obtain FDA or other regulatory approval for product candidates within expected time frames or at all; the novel nature and impact of negative public opinion of gene therapy; failure to comply with ongoing regulatory obligations; contamination or shortage of raw materials or other manufacturing issues; changes in healthcare laws; risks associated with our international operations; significant competition in the pharmaceutical and biotechnology industries; dependence on third parties; risks related to intellectual property; changes in tax policy or treatment; our ability to utilize our loss and tax credit carryforwards; litigation risks; and the other important factors discussed under the caption “Risk Factors” in our most recent quarterly report on Form 10-Q or annual report on Form 10-K or subsequent 8-K reports, as filed with the Securities and Exchange Commission. These and other important factors could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management’s estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, unless required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. Thus, one should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation. Unless otherwise stated or the context otherwise requires, the information herein is as of July 17, 2020.

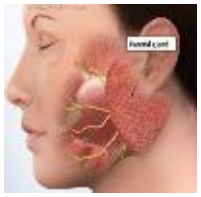
A Vertically Integrated, Clinical Stage Gene Therapy Company

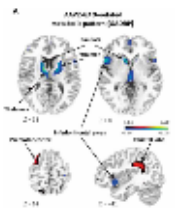
Developing a new pharmaceutical modality designed for the cost-effective treatment of a broad range of serious disorders

Diversified Pipeline of Gene Therapy Candidates

6 ongoing clinical programs:

- Inherited retinal diseases
- Salivary gland
- Parkinson's disease

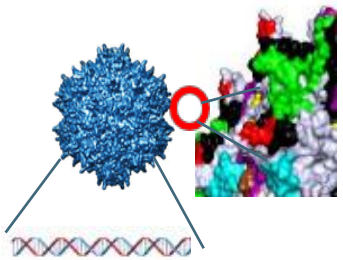


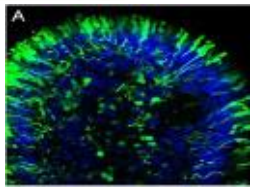


Platform of Core Viral Vector Engineering Capabilities

Viral vector design platform:

promoter, capsid, transgene optimization, ITRs, immunogenicity





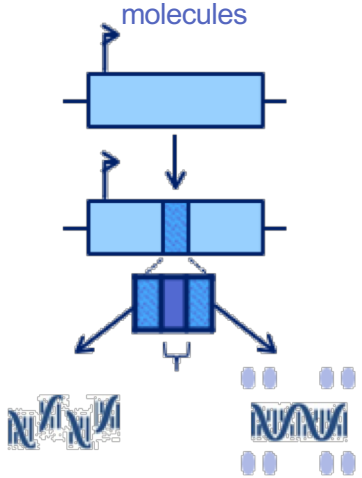
Manufacturing Capacity & Commercial Ready Scalable Process

Flexible and **scalable cGMP manufacturing facility** with capacity for commercial supply for our programs.

Commercial quality Process Development

Next Generation Gene Therapy Riboswitch-Based Gene Regulation

Proprietary technology that may allow for innovative gene therapy treatments whose **expression can be turned on and off** with small molecules



Multiple Therapeutic Targets

OCULAR

Clinical Development
- IRD franchise: XLRP, achromatopsia, *RPE65*-associated retinal dystrophy, LCA4

Research
- Wet AMD, Dry AMD

Gene Regulation
- VEGFR2 Ab – eye drops

NEURODEGENERATIVE

Clinical Development
- Parkinson's disease

Research
- Amyotrophic Lateral Sclerosis (ALS)

Gene Regulation
- CNS expression with BBB penetrant small molecules

SALIVARY GLAND

Clinical Development
- Radiation-induced xerostomia (Grade 2/3)

Research
- Sjogren's Syndrome

Gene Regulation
- Peptide and hormone salivary gland delivery

Human proof of concept demonstrated across ocular, neurodegenerative and salivary gland pipelines

Vector development & optimization technology create opportunities to treat broader indications beyond rare, inherited genetic disorders

MEIRAGTx

Gene Therapy Pipeline

Ocular, Neurodegenerative, Salivary Gland Programs

MeiraGTx Broad Clinical Pipeline

Product	Indication	Preclinical	Phase 1/2	Phase 3
Ocular				
AAV-RPGR* (janssen)	X-linked RP	PRIME, Fast Track, Orphan Drug		lumeos XLRP study
AAV-RPE65	RPE65-Associated Retinal Dystrophy	RPDD, Orphan Drug		
AAV-CNGB3* (janssen)	Achromatopsia	RPDD, PRIME, Fast Track, Orphan Drug		
AAV-CNGA3* (janssen)	Achromatopsia	RPDD, Orphan Drug		
AAV-AIPL1	LCA4	Compassionate use under MHRA Specials License		
A006	Wet AMD			
Neurodegenerative Disease				
AAV-GAD	Parkinson's Disease			
Salivary Gland				
AAV-AQP1	Xerostomia	Orphan Drug		
	Sjögren's Syndrome			

*Co-development program with Janssen Pharmaceuticals pursuant to a collaboration agreement.

Manufacturing

President and CEO, MeiraGTx

Comprehensive Manufacturing Approach to Support Commercial Production

MeiraGTx has internal manufacturing capabilities to support GMP viral vector manufacturing Phase 1/2 through Commercial Production

- **cGMP certified facility:** Flexible scalable, includes fill and finish, QC and warehousing; second facility and internal plasmid production (2020-2021)
- **QA:** Quality Management System supporting Phase 1/2 through commercialization
- **Manufacturing Process:** flexible and scalable; fit for commercialization; global regulatory CMC input; internal QC
- **MSAT facility:** adjacent to London cGMP facility; process development/optimization, QC and potency assay development and validation
- **Non-clinical vector core:** Amsterdam
- **Vector Engineering**
  - Vectors are optimized for **potency** (promoters, capsids, gene sequence) may reduce dose increase efficacy decrease cost of goods
  - Optimized for **producibility** driving yield and increasing production capacity

cGMP Viral Vector Manufacturing Facility

110+ person team developing best-in-class manufacturing technologies to support current and future pipeline

- Manufacturing & Supply: 50+ person team
- MSAT: 20+ person team
- Quality: 40+ person team

Manufacturing flexibility and capacity

- Production of material for 4 potential pivotal programs and several Phase 1/2 clinical studies over the next 18 months

cGMP Certified Manufacturing Facility: Flexible and Scalable

Central London facility

- cGMP certified 29,000 sq. ft multi-product, multi-viral vector manufacturing facility
- Designed to meet MHRA, EMA and FDA regulatory requirements
- Single use philosophy / fully enclosed technologies
- 2 cell suites; 3 viral vector suites
- Independent air handling
- Designed for minimal downtime and maximum flexibility
- Adherent / non-adherent cell lines – HEK293
- Support laboratories: Quality Control
- Adjacent MSAT (Manufacturing Science and Technology) area/pilot plant

Expanding manufacturing footprint

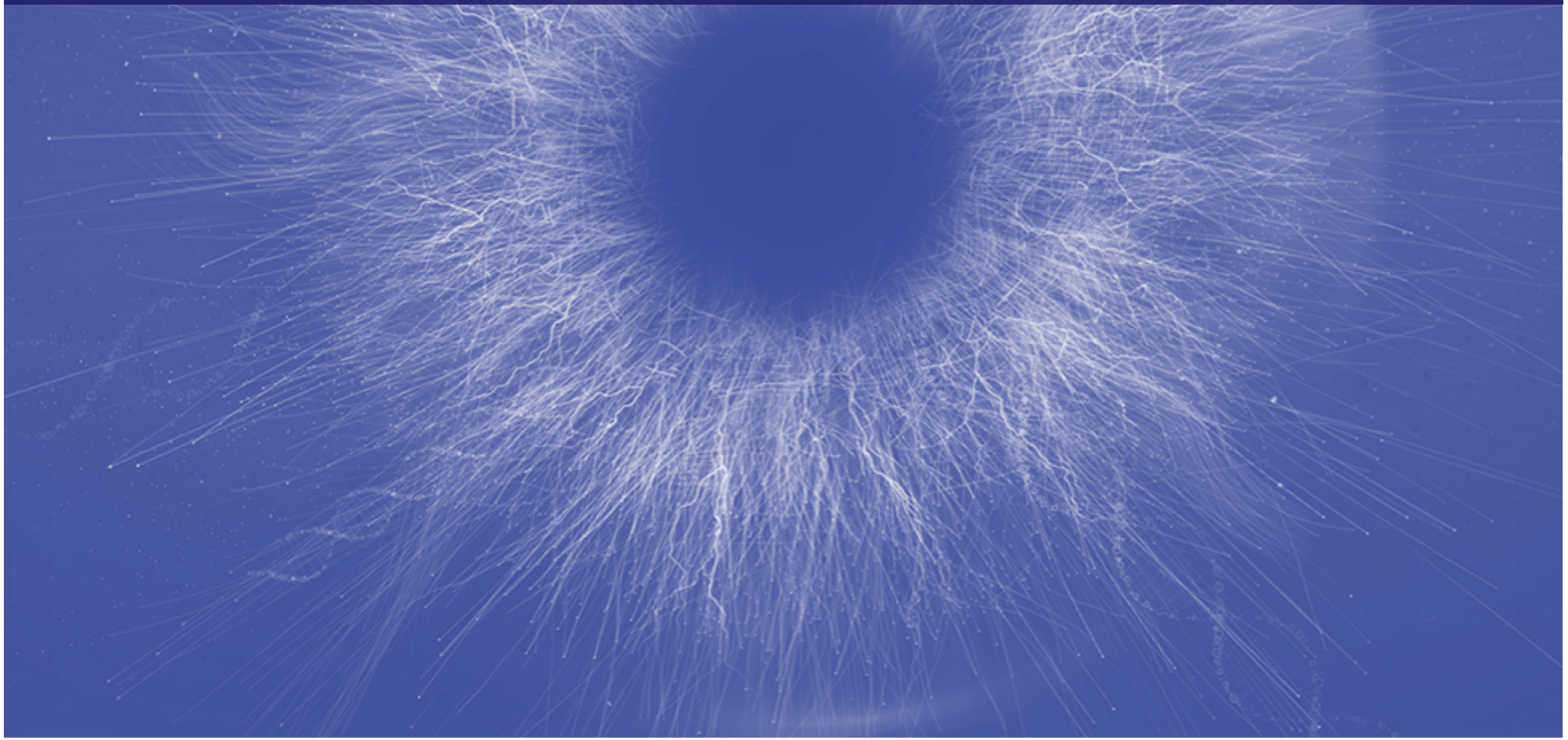
- Construction on 2nd cGMP viral vector manufacturing facility & cGMP plasmid production facility to begin in 2020

London Facility Plan

Britannia Walk Facility - London

MEIRAGTx

Ocular Franchise



Inherited Retinal Disease (IRD) Strategy

Portfolio approach to IRDs

- Over 200,000 patients in each of US and EU with IRDs that may be caused by one of 200 or more different genes
- Synergies in clinical, regulatory, assay development, manufacturing, and commercial

Optimized vector for each genetic indication

- Each with the best selected capsid, cell specific promoter expressing at appropriate level for the molecular profile of the disease

Natural History studies

- Large prospectively designed natural history study for each clinical indication with 2-5 years of data on each patient who enters one of our clinical trials following participation in the natural history study
- Rapid enrollment
- Well characterized patients appropriate for treatment and potential signals of activity
- Well validated endpoints for each disease
- Advanced imaging

Global network of clinical expertise in rare IRD indications

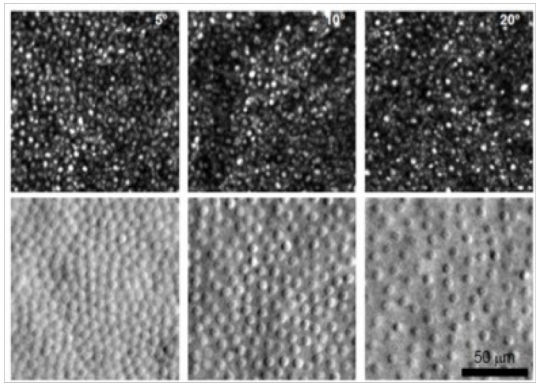
- Clinical programs ongoing: CNGA3-ACHM, CNGB3-ACHM, RPGR-XLRP, RPE65
- Compassionate use program: LCA4
- Deep research and pre-clinical pipeline

MeiraGTx Ocular Programs

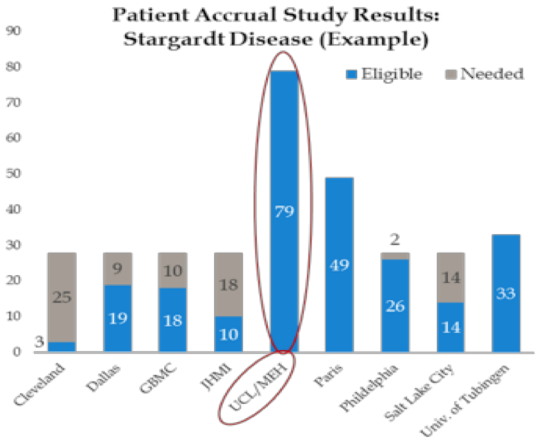
Ophthalmology Partners and Centers of Excellence

- **UCL Institute of Ophthalmology**
  One of the world's leading research institutes pioneering ophthalmology gene therapy
- **Moorfields Eye Hospital**
  Provides access to the world's largest catchment of patients with inherited retinal diseases, well characterized patients, prospective Natural History studies
- US footprint through links with **University of Michigan Kellogg Eye Center, Massachusetts Eye and Ear (MEEI)**, **Casey Eye Institute** and other leading centers
- Partnership with **Foundation Fighting Blindness (FFB)**
- Global expertise in imaging and validated endpoints in each of our target diseases

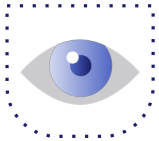
Our Partners Possess World Leading Imaging, Endpoint Development and Validation



Patient Access



Inherited Retinal Disease Worldwide Strategic Collaboration

Clinical development	Janssen commercial infrastructure	Pre-clinical IRD research	Manufacturing and process development
			
Janssen and MeiraGTx collaborating to advance AAV-CNGB3, AAV-CNGA3, AAV-RPGR through clinical development	• Janssen has worldwide exclusive commercial rights to AAV-CNGB3, AAV-CNGA3, AAV-RPGR and future IRD programs • IRD portfolio to benefit from worldwide reach of Janssen commercial infrastructure	• Collaboration leverages MeiraGTx vector design and optimization technology to develop potential gene therapy treatments for multiple IRDs • Janssen to receive exclusive rights to develop & commercialize programs from IRD research collaboration	• Janssen accesses MeiraGTx advanced manufacturing capabilities with clinical and commercial supply agreements • Joint development of novel AAV manufacturing technologies to expedite and optimize development

AAV-RPGR for the Treatment of X-Linked Retinitis Pigmentosa due to RPGR-Deficiency

XLRP

Retinitis Pigmentosa (RP)

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

Disease progression

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

Prevalence and genes

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

AAV-RPGR

- Human rhodopsin kinase promoter (RKp)
- AAV5
- $RPGR^{ORF15}$

Patient Experience




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

Significant vision improvement six months after treatment

- Meaningful improvement from baseline in retinal sensitivity across multiple metrics and modalities in low and intermediate dose cohorts
- Statistically significant improvement from baseline compared to untreated eyes evident at six months post treatment in low and intermediate dose cohorts
- Initial signs of efficacy at three months, with improvements generally sustained or increased at six months

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

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

Data support advancing AAV-RPGR into Phase 3 clinical trial

lumeos XLRP study

Retinal Sensitivity Endpoint

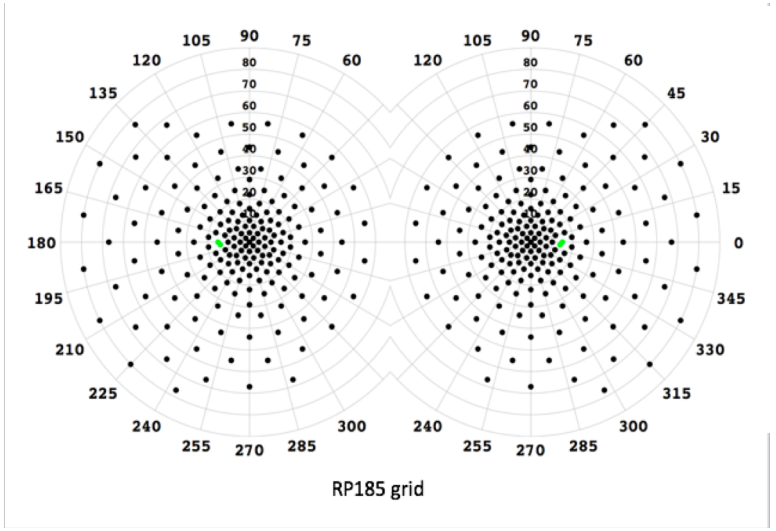
Perimetry performed at baseline (three measurements), three, six, nine and 12 months to assess baseline visual function and change over time

Modalities

- Octopus 900 full-field static perimetry
- MAIA fundus-guided microperimetry (10-2 grid)

Metrics

- Mean retinal sensitivity
- Visual field modeling and analysis (VFMA) derived hill-of-vision
- Pointwise analysis



RP185 grid

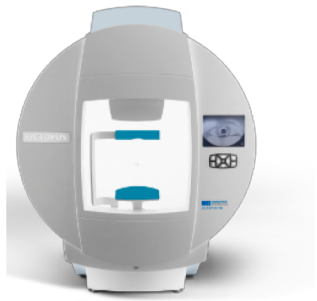
- Customized grid used in the *RPGR* trial and natural history study
- 185 test points with central condensation and good peripheral coverage extending 55.5˚ nasally and superiorly, 67˚ inferiorly and 80˚ temporally

MAIA, macular integrity assessment

Statistically Significant Improvement in Retinal Sensitivity in Low and Intermediate Dose Cohorts

Parameter	Treated-Untreated Eye Difference (90% CI adjusted for baseline)
Mean Retinal Sensitivity (dB)	
Low Dose Cohort	0.69 (–0.28, 1.66)
Intermediate Dose Cohort	1.02 (0.75, 1.31)*
High Dose Cohort	–1.00 (–1.87, 0.38)
Central Visual Field Progression Rate (Central 30° Hill-of-Vision [V30], dB-sr/y)†	
Low Dose Cohort	1.10 (0.10, 2.10)*
Intermediate Dose Cohort	1.26 (0.65, 1.86)*
High Dose Cohort	–0.81 (–1.52, 0.47)

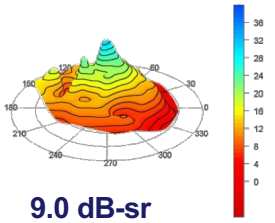
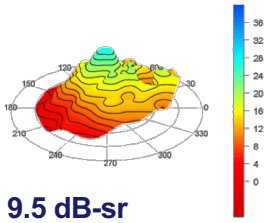
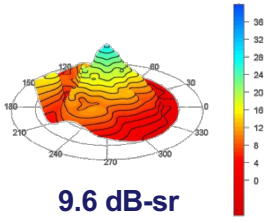
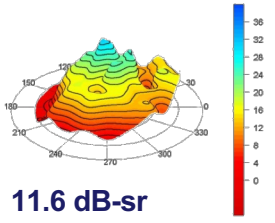
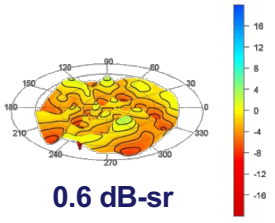
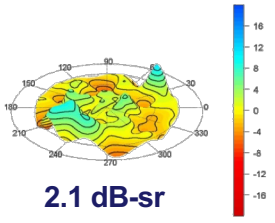
Response was treated-untreated eye adjusted for baseline (double-delta)
* Statistically significant effects at a one-sided 5% level
† Currently, at least 6 months of data and up to one year of data
Excludes one subject with panuveitis in the low dose



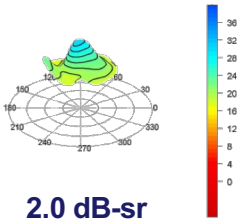
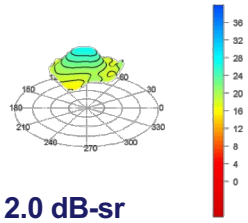
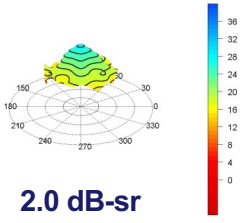
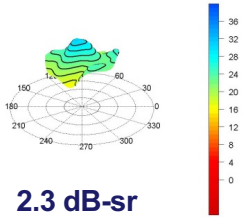
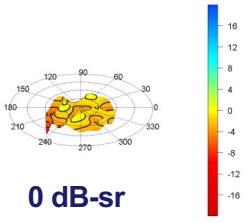
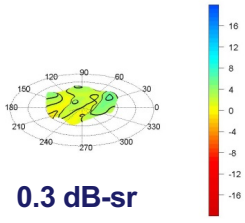
Octopus 900
Static Perimetry

Subject 01-007 – Improved Retinal Sensitivity

VFMA-Derived Central 30° Hill-of-Vision (V30)

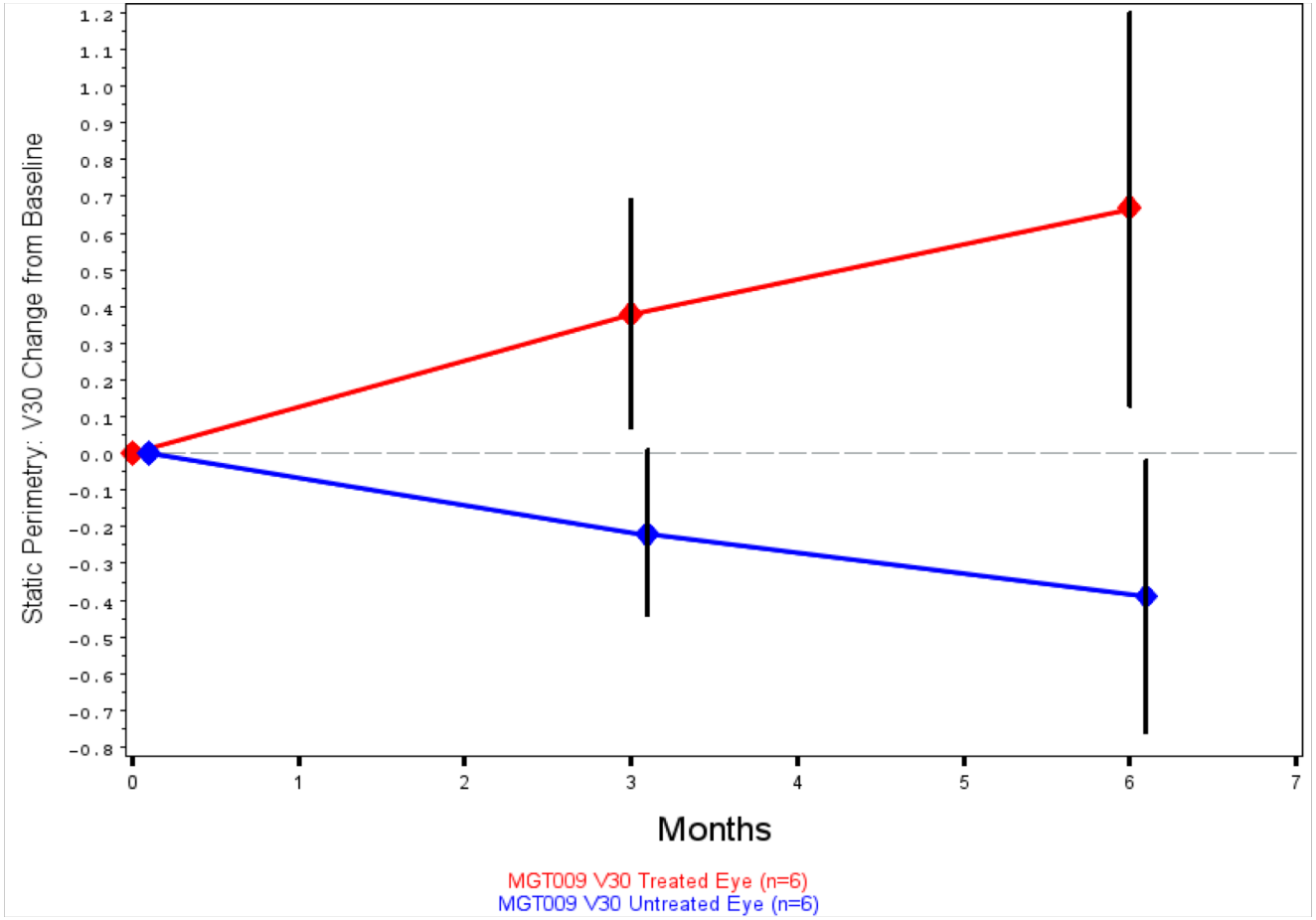
	Untreated eye	Treated eye
Baseline	 9.0 dB-sr	 9.5 dB-sr
Six month	 9.6 dB-sr	 11.6 dB-sr
Six month difference	 0.6 dB-sr	 2.1 dB-sr

VFMA-Derived Central 10° Hill-of-Vision (V10)

	Untreated eye	Treated eye
Baseline	 2.0 dB-sr	 2.0 dB-sr
Six month	 2.0 dB-sr	 2.3 dB-sr
Six month difference	 0 dB-sr	 0.3 dB-sr

VFMA, visual field modeling and analysis.

Statistically Significant Improvement in Central Retinal Sensitivity Observed in Treated Eyes



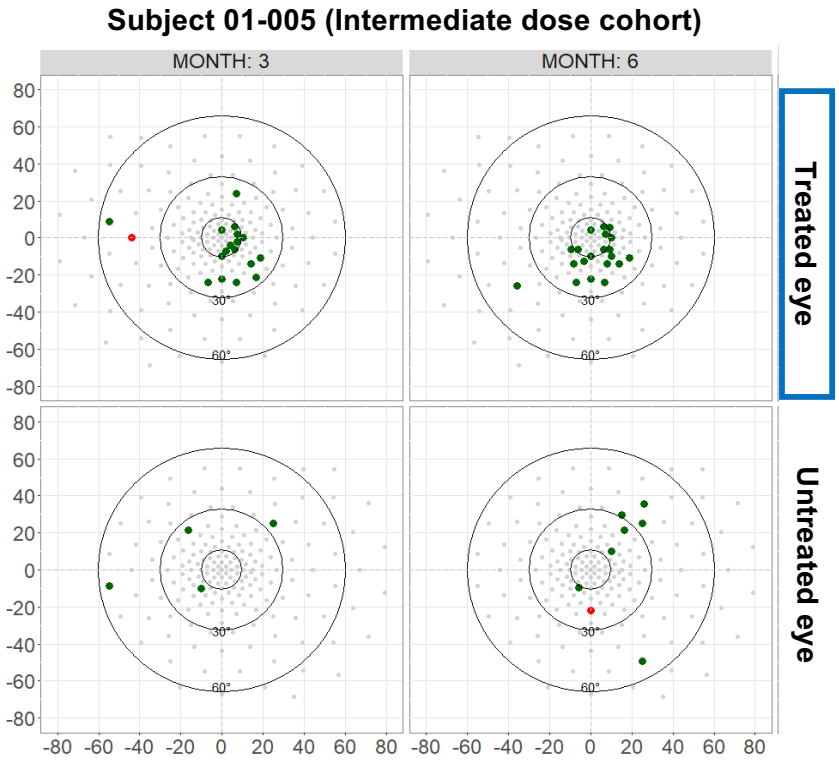
Low and Intermediate Dose Subjects (n=6)*

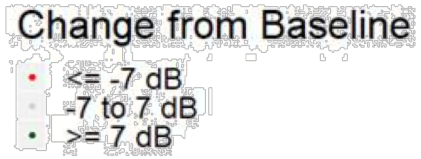
- Central retinal sensitivity increased in the treated eye group vs. baseline (0.67 dB-sr [90% CI: 0.13, 1.20]), while it decreased in the untreated eye group (–0.39 dB-sr [–0.76, –0.02])
- Statistically significant difference between treated and untreated eyes (1.06 dB-sr; P<0.05)

*Excludes one subject with panuveitis in the low dose

Evidence of Retinal Sensitivity Improvement Using Pointwise Analysis

Representative Example of Pointwise Analysis

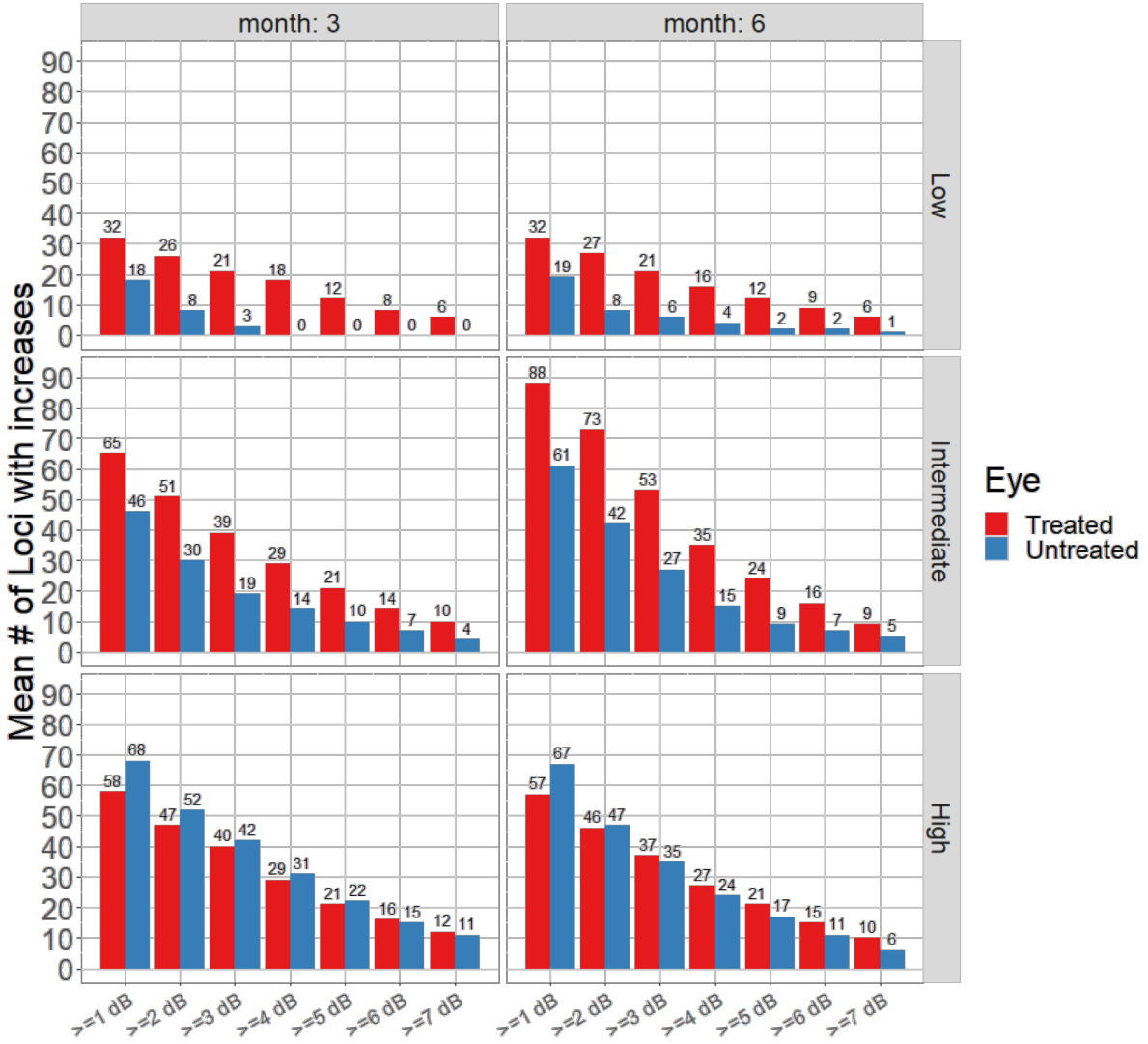




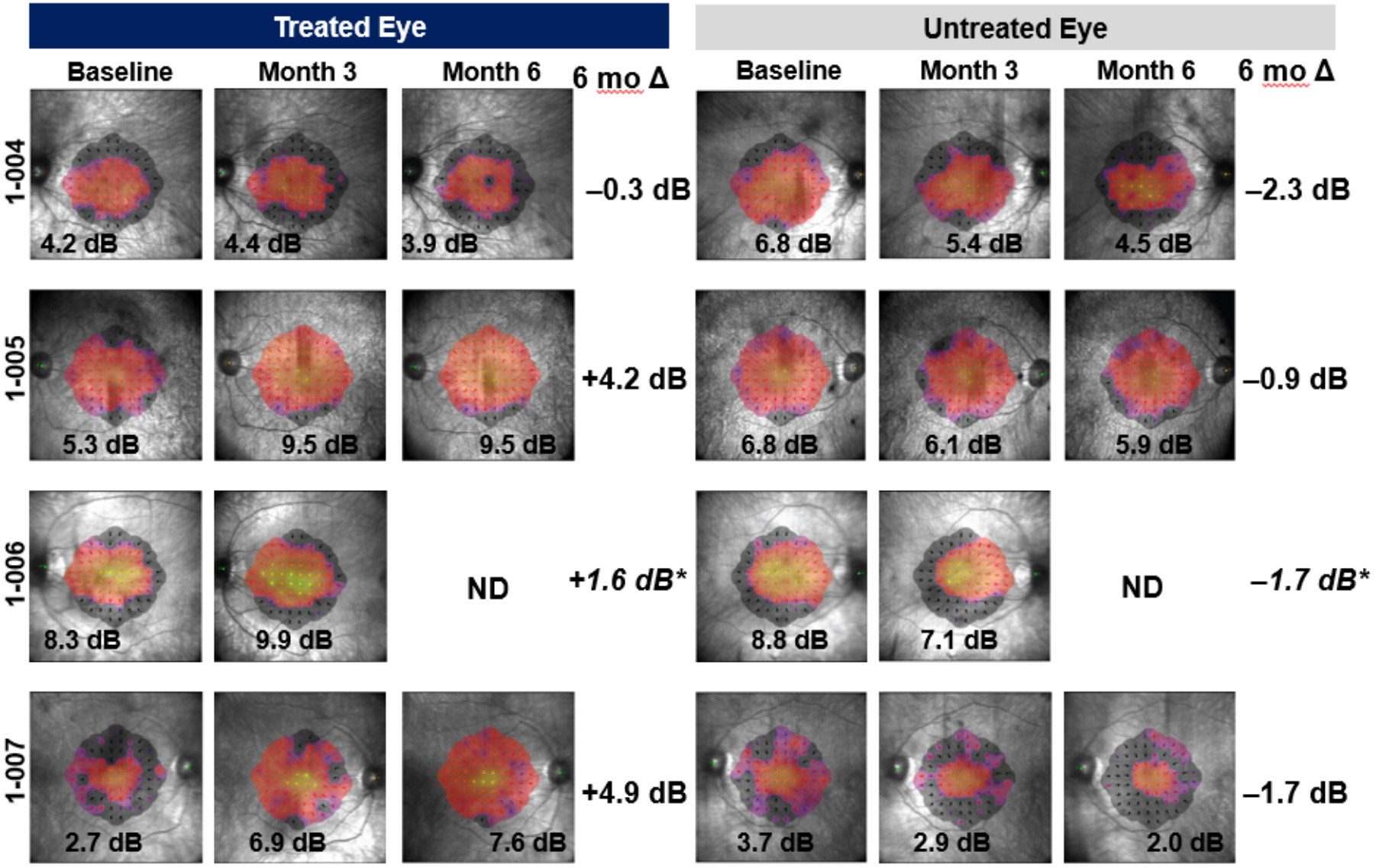
FDA definition of clinically meaningful improvement in diseases characterized by visual field loss: ≥ 5 loci improving ≥ 7dB

Increased Retinal Sensitivity in Treated Eyes in Low and Intermediate Dose Cohorts

- In low and intermediate dose cohorts, efficacy signals were observed at first post-treatment assessment at three months, with improvements sustained or increased at six months
- No improvement compared to untreated eyes demonstrated in high dose cohort



Retinal Sensitivity Improvements on Mesopic Microperimetry: Intermediate Dose Cohort



*3 month change from baseline. Subject did not complete 6 month microperimetry assessment

Dose Escalation Six-Month Data Conclusions

- **Low and intermediate dose cohorts achieved clinically meaningful improvements in retinal sensitivity, evident across multiple metrics (mean sensitivity, volumetric, and pointwise) and modalities (full-field static perimetry and microperimetry)**
  - In low (n=3) and intermediate (n=4) dose cohorts, 5/7 subjects demonstrated improvement or stability in retinal sensitivity in the treated eye at six months
  - Efficacy signals were observed at first post-treatment assessment at three months, with improvements sustained or increased at six months

- **Safety data obtained to date suggest that AAV-RPGR is generally safe and well tolerated, the majority of the adverse events were anticipated due to the surgical procedure**

- **Given the robust safety and efficacy signals observed, these doses are being further explored with analyses at additional data time-points in the ongoing randomized, controlled dose-expansion phase of the study**

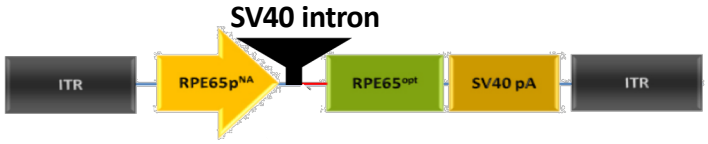
AAV-RPE65 for the Treatment of *RPE65*-Associated Retinal Dystrophy

RPE65-Associated Retinal Dystrophy

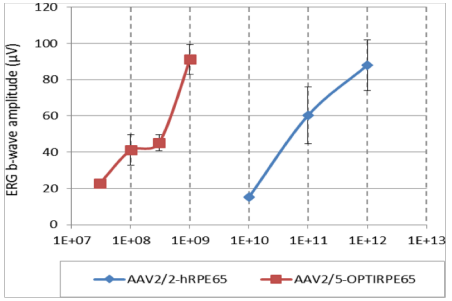
- **Rod-cone dystrophy**
  - Ultra-rare, severe IRD caused by mutations in the *RPE65* gene
  - RPE65 expressed in retinal pigment epithelium (RPE), supporting cells of photoreceptors
  - RPE65 required for recycling of the visual pigments allowing photoreceptors to sense light
- **Disease progression**
  - Complete lack of rod function and night blindness from birth
  - Reduced cone function early in life
  - In addition to diminished photoreceptor function, both rods and cones degenerate progressively
  - Complete retinal degeneration and blindness in early adulthood
- **Natural history study ongoing**
  - >30 patients well characterized

AAV-RPE65: optimized and highly potent cell-specific vector

- **Increased efficiency of transduction, transcription and translation**
  - RPE strong cell-specific promoter
  - Optimized transgene sequence
  - AAV5 capsid selected over AAV2 capsid



Georgiadis et al 2016 *Gene Therapy*



In RPE65-deficient mice, AAV2/5-OPTIRPE65 restores retinal function at 300-1,000-fold lower doses than unoptimized AAV2/2-RPE65 vector

AAV-CNGB3 & AAV-CNGA3 for the Treatment of Achromatopsia

Achromatopsia (ACHM)

- **Retinal defect**
  - Complete absence of cone photoreceptor function from birth
- **Disease characterization**
  - Very poor visual acuity from birth (typically 20/200)
  - Photophobia (disabling aversion to light)
- **Prevalence and genes**
  - Overall ACHM prevalence is around 1/30,000 in US
  - Total patients in US, EU5 and Japan:~24,000
  - CNGB3 (~50% of cases), CNGA3 (~40% of cases)
- **Natural history study ongoing**
  - >90 patients well characterized

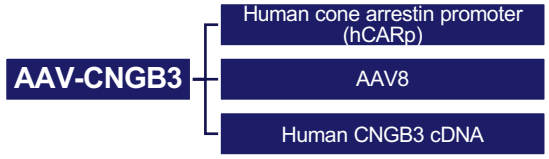
Patient Experience

Normal

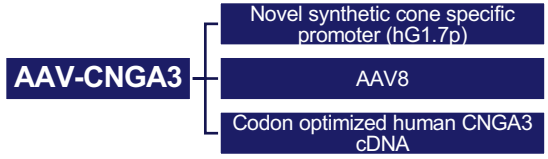
Achromatopsia

Ongoing clinical trials

- **Phase 1/2 trial of AAV-CNGB3**
  - 23 patients treated (11 adults, 12 children)
  - Dosing complete, follow up ongoing

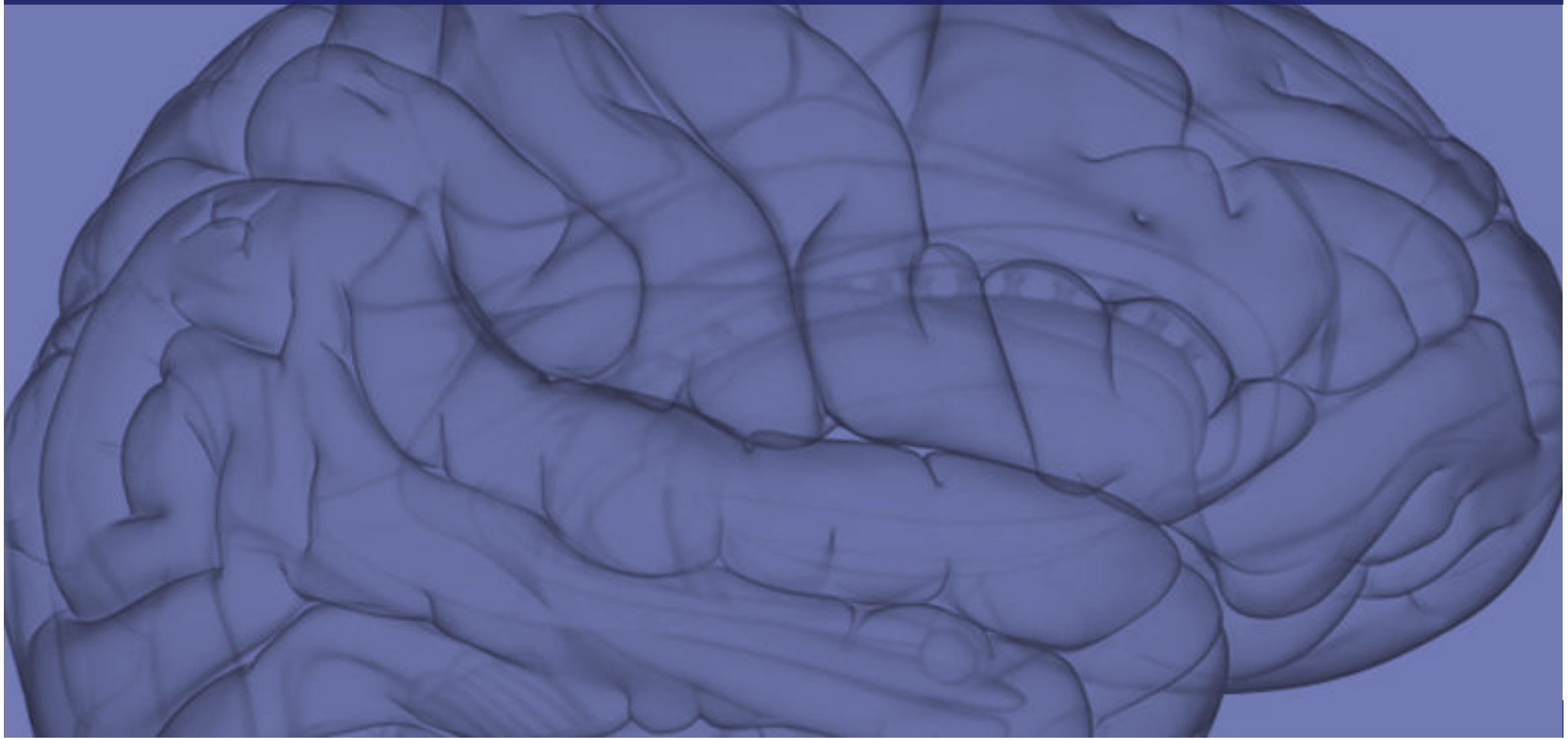


- **Phase 1/2 trial of AAV-CNGA3**
  - Dose escalation began in pediatric patients
  - Enrolling children aged 3-15



MEIRAGTx

AAV-GAD for Parkinson's Disease



AAV-GAD Rationale: Patient Population

Current Treatment for Parkinson's Disease

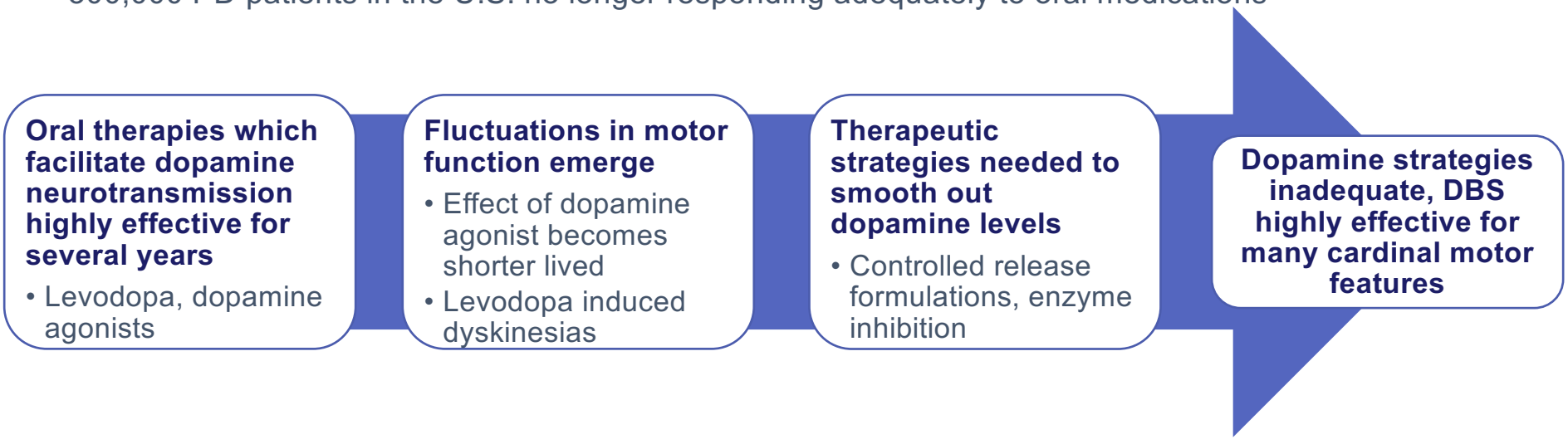
Medical therapy: Dopamine replacement (L-Dopa, agonists)
Surgical therapy: Subthalamic nucleus (STN) deep brain stimulation (DBS)

Medical therapy over time associated with high rates of complications

- Chronic treatment requires ongoing adherence and out-of-pocket costs
- Symptomatic relief for around 5 years with reduced benefit over time
- Increased doses required over time with high rates of non-adherence and increased side effects
- Motor fluctuations, dyskinesias, cognitive/affective side effects

High unmet medical need

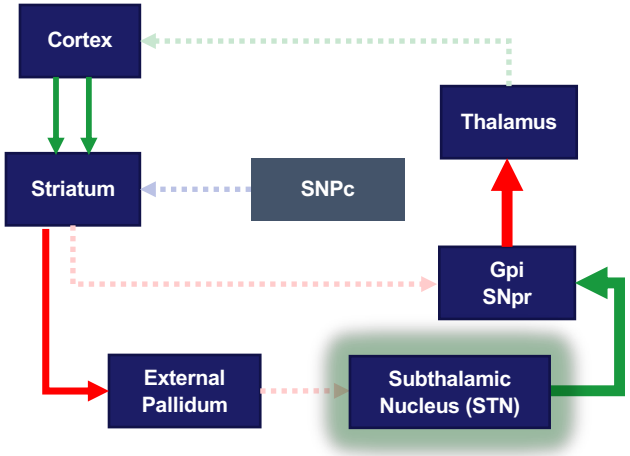
- 300,000 PD patients in the U.S. no longer responding adequately to oral medications



Local delivery of AAV-GAD into the subthalamic nucleus circumvents the dysregulation of the basal ganglia circuitry that occurs as dopaminergic signaling fails in Parkinson's disease

Rationale for STN as Target for Localized AAV-GAD Treatment in Parkinson's Disease

Dysregulation of basal ganglia in PD leads to STN overactivity due to reduced GABA



Dopamine

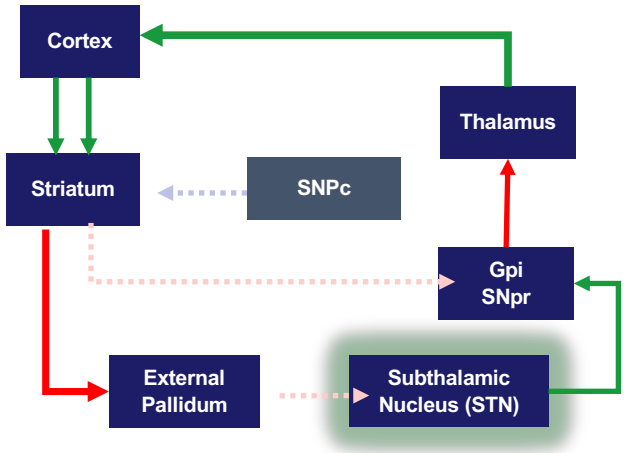
Glutamate (+)

GABA (-)

STN is a key structure downstream of dopamine circuitry which is overactive in PD

- DBS specifically targets STN to modulate basal ganglion circuitry output
- Direct STN infusion of muscimol, a GABA agonist, reduces motor symptoms in human PD

AAV-GAD gene therapy to STN rebalances basal ganglia circuitry to normalize outflow



Dopamine

Glutamate (+)

GABA (-)

STN AAV-GAD restores glutamate/GABA imbalance in the basal ganglia

- Normalizes STN neuronal firing
- Releases brake on the thalamus and improve motor function

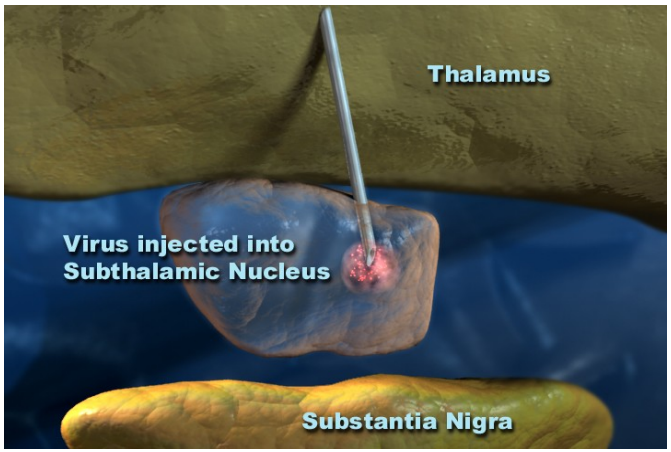
AAV-GAD Gene Therapy Approach – Local Delivery to STN

Product

- **Glutamic acid decarboxylase (*GAD*) is the rate-limiting enzyme in the synthesis of GABA**
  - GAD catalyzes the conversion of glutamate to GABA
  - Key enzyme found in all inhibitory neurons and regulates excitability

Preclinical Data

- **STN AAV-GAD improves motor function and normalizes motor circuits in rodent and primate PD models[1,2]**
- **Extensive preclinical rodent and primate efficacy, safety and toxicology package supports translation into human subjects**



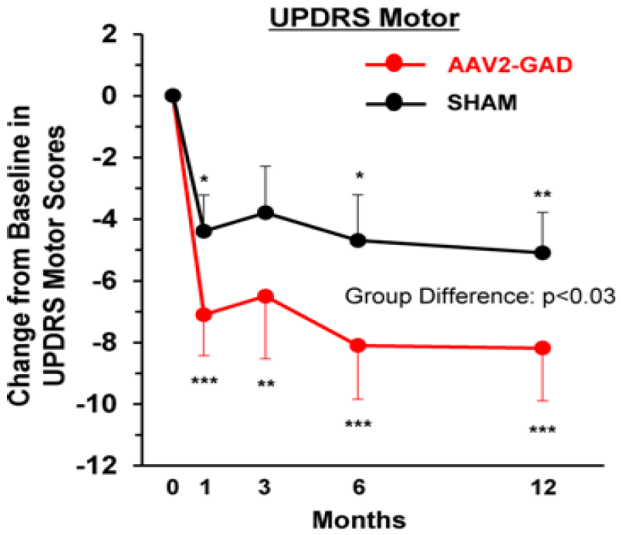
1. Luo J. Subthalamic GAD Gene Therapy in a Parkinson's Disease Rat Model. Science. 2002; 298:425-429.
2. Emborg ME. Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism. J Cereb Blood Flow Metab. 2007; 27:501-509

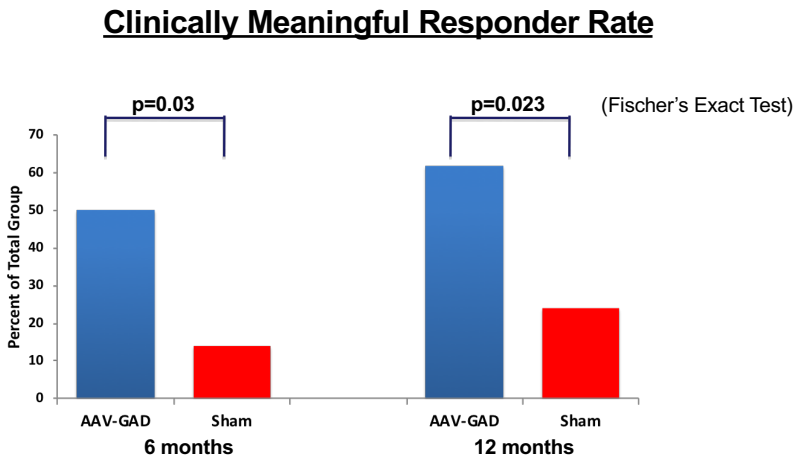
Phase 1 Study of AAV-GAD STN Gene Therapy

- **Study design**: dose escalation study of unilateral STN AAV-GAD delivery in 12 patients (3 cohorts of 4 subjects each)
- **Safety findings**:
  - Unilateral STN AAV-GAD was safe and well tolerated
  - No evidence of induction immune response or effect on outcome of pre-immunity in two patients
- **Efficacy findings:**
  - Significant improvement in both “off” and “on” UPDRS largely limited to hemibody opposite treated hemisphere
  - Effects seen starting at 3 months (trend at 1 month) and stable to one year
  - No decline in neuropsych scores or other non-motor parameters
  - Functional imaging demonstrated significant improvement in abnormal circuitry function specific only to treated hemispheres
- **Safety & efficacy findings together supported entry into Phase 2**

Phase 2 Study of AAV-GAD STN Gene Therapy

- **Study Design**: Randomized (n=45,1:1) double-blind study of bilateral STN AAV-GAD vs. Sham surgery
- **Efficacy findings**:
  - Met primary endpoint: Per protocol group showed significantly greater improvement in off-medication UPDRS part 3 for AAV-GAD subjects compared with sham
  - Positive secondary endpoints for AAV-GAD included greater responder rate at 6 and 12 months
- **Safety findings**:
  - No adverse effects related to AAV-GAD across all time points
  - Worsening PD as an adverse event in 35% of sham vs. 0% GAD further supports efficacy
- **Functional imaging with same findings as phase 1 and new biomarker specific to AAV-GAD treated subjects, which significantly correlated with clinical outcome**



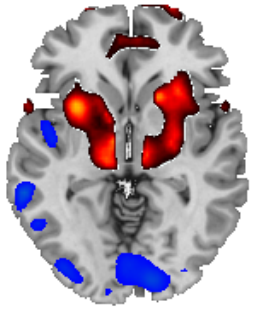


Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133

Development of Objective FDG-PET Biomarker: GADRP

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

- Measure changes in specific brain regions of interest
- Determine interactions between brain regions during disease progression
- Determine interactions between brain regions as a biomarker of response to therapy



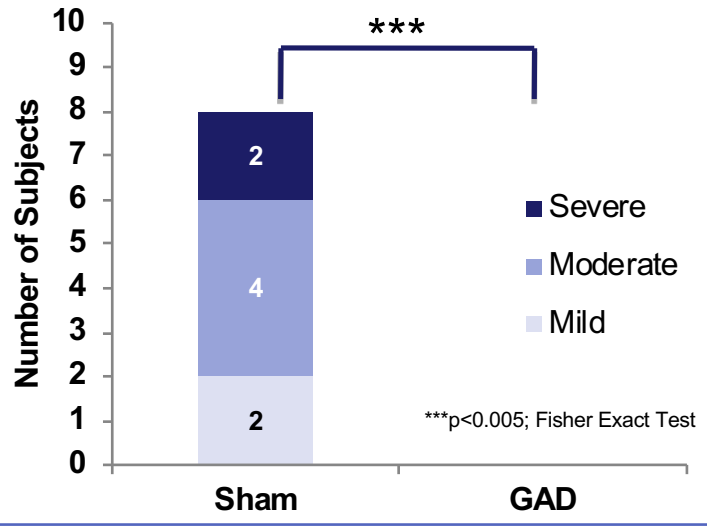
Functional Imaging – GAD Related Pattern (GADRP)

- Subjects that respond to AAV-GAD have a unique FDG-PET imaging pattern (GAD related pattern, GADRP)
- GADRP reflects corrective changes is polysynaptic brain circuitry in response to AAV-GAD treatment
- Statistically significant correlation between UPDRS motor ratings and GADRP expression ($p < 0.009$)
- GADRP expression correlates with UPDRS response only in AAV-GAD treated subjects and does not develop in Sham responders
- The GADRP is a unique imaging biomarker that objectively distinguishes AAV-GAD treatment-driven responses from placebo responses in Sham subjects
- AAV-GAD is the first gene or cell therapy for PD to have an objective imaging biomarker of treatment effect that is significant relative to sham surgery patients and correlates with clinical improvement

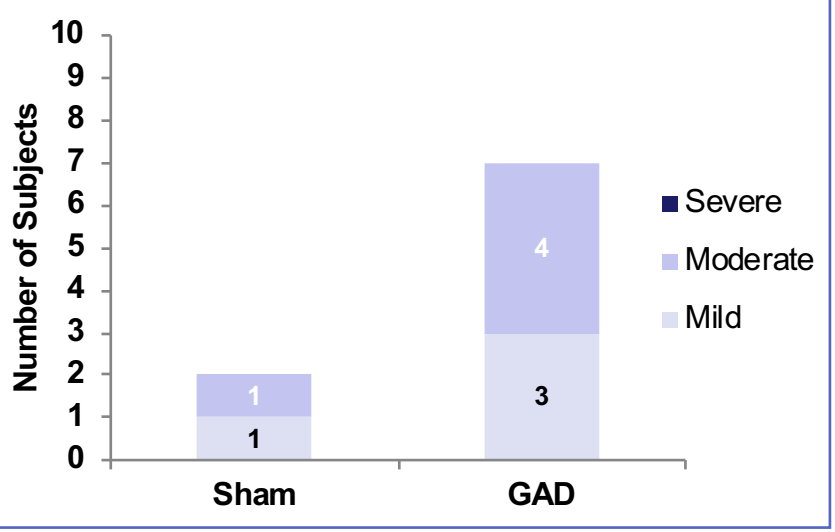
Niethammer M. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. Sci. Trans. Med. 2018; 10(469). pii: eaau0713

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

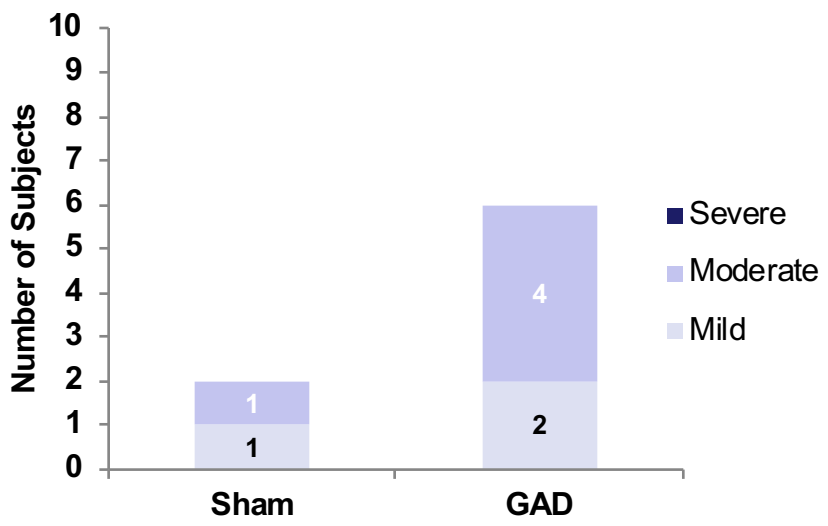
Worsening of Parkinson's Disease



Headache



Nausea



Serious Adverse Events*
(Number of Subjects)

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

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

Summary of Key AAV-GAD Features

- **AAV-GAD is the only gene or cell therapy:**
  - To meet primary clinical efficacy endpoint in a randomized, blinded multi-center PD trial
  - With an imaging biomarker supporting efficacy which correlates with clinical outcome
  - With a routine and brief surgical procedure that requires minimal OR time, virtually no special training, no general anesthesia
- **Improvement in off-medication clinical ratings, ON time without dyskinesia and complications of medical therapy without declines in neuropsychological function or speech**
- **Consistency in clinical outcomes and imaging from phase 1 to phase 2**
- **AAV-GAD could be accessible to more patients than current standard of care**
  - Absence of retained hardware
  - No need for specialized post-op care
- **Non-dopaminergic strategy**
  - AAV-GAD potentially applicable to large patient population not adequately treated with currently available therapies

MEIRAGTx

Salivary Gland

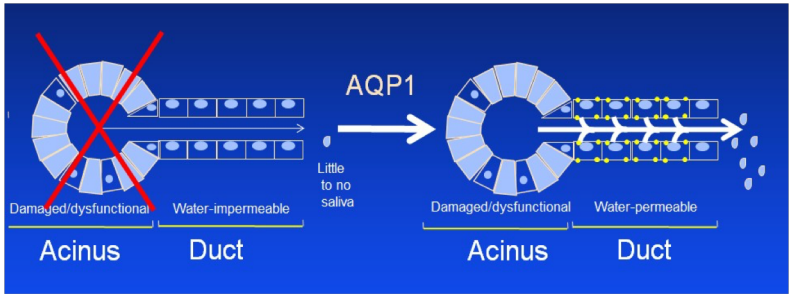
AAV-AQP1 for Radiation-Induced Xerostomia (RIX)

Significant unmet medical need: xerostomia persisting >2 years after radiation therapy for oral cancer

- 170,000 existing patients in the U.S.
- 50,000 new cases of head and neck cancer/yr treated in US
- 85% of radiation-treated patients experience reduced saliva production, of whom 40% have persistent Grade 2/3 RIX
- Serious, debilitating complications: dental caries, enamel erosion, oral infections, sleep disturbances, difficulty talking, chewing, swallowing, weight loss and malnutrition

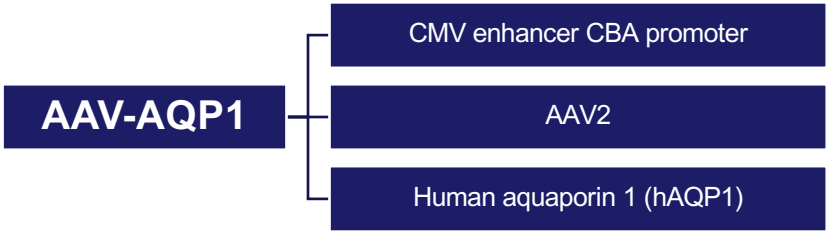
Strategy for the repair

- Water-impermeable duct cells generate an osmotic gradient (lumen > interstitium)
- Introduction of human aquaporin 1 gene (hAQP1) into duct cells via viral vector, making duct cells permeable to water
- Allows water to flow into the salivary duct and out to moisten the mouth



Salivary gland as target for gene therapy

- Non-invasive: allows local administration and avoids systemic exposure
- Isolated and encapsulated
- Small volume of vector



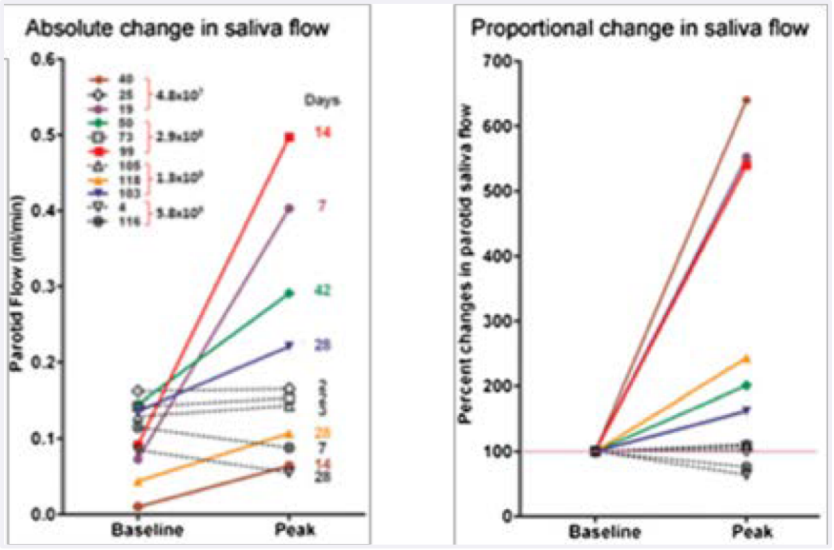
Human Proof-of-Concept Established: Phase 1 trial of AdhAQP1

Adenoviral-mediated aquaporin-1 cDNA transfer for radiation-induced salivary hypofunction

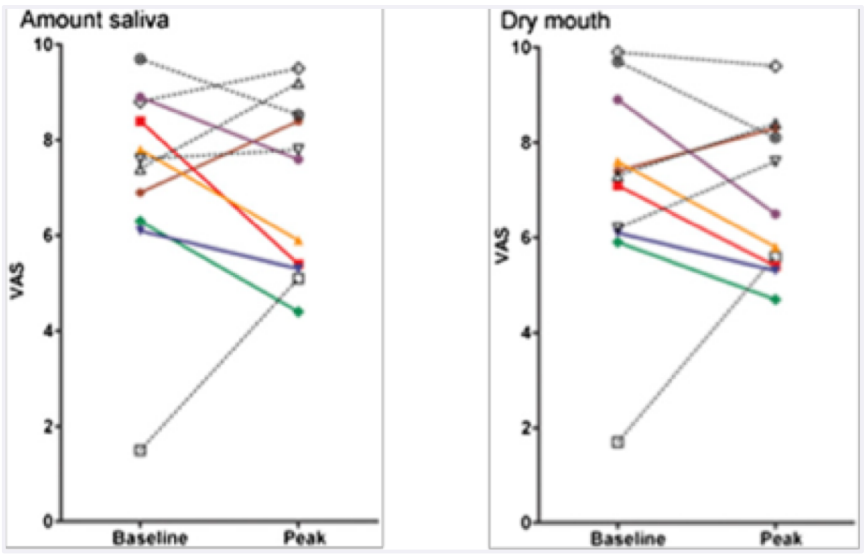
- AdhAQP1 treatment was well tolerated: no SAEs
- Responses seen in 2 of 3 patients in each of the first 3 cohorts
- 60% to 540% increase in parotid flow in responding patients
- 5 of 6 patients also reported subjective improvement in symptoms

NIH
National Institute of Dental and Craniofacial Research

Change in parotid salivary flow rate

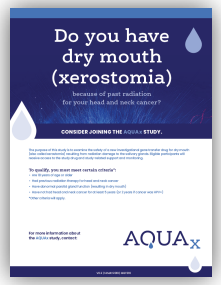


Visual analogue scale (VAS)



Baum BJ et al. *PNAS,* 2012.

Ongoing Clinical Trials of AAV-AQP1 for the Treatment of Radiation-Induced Xerostomia



Multi-center Phase 1/2 Trial – AQUAx (NCT04043104)

- Dose escalation ongoing

National Institutes of Health

Phase 1 trial at NIH (NCT02446249)

- Dose escalation ongoing

Clinical trial overview			
Grade 2/3 Xerostomia	History of radiation therapy for head and neck cancer	Disease-free of head and neck cancer for at least 5 years (at least 2 years if HPV+)	Aged 18+

- **Design:** 3+3 dose escalation
- **Administration:** AAV-AQP1 is slowly injected into a single parotid salivary gland
- **Study period:** Patients will complete assessments at the clinical trial site over the course of one year
- **Primary endpoint:** safety
- **Secondary endpoint:** parotid gland salivary output

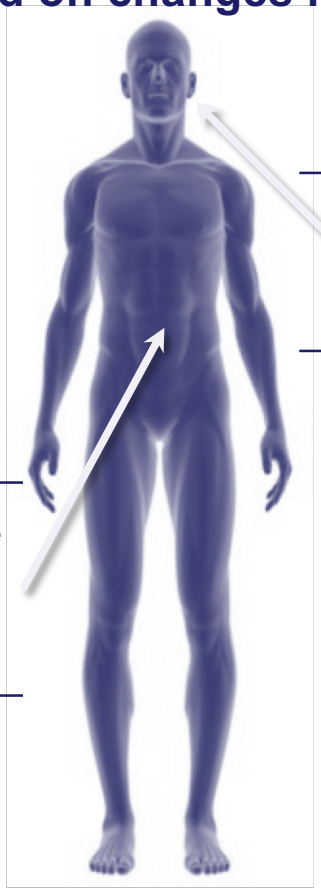
MEIRAGTx

Gene Regulation

Riboswitch Based Gene Regulation Platform

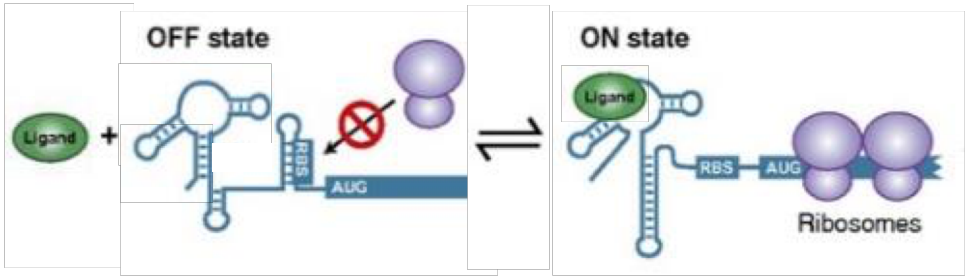
RIBOSWITCH: Small molecule responsive switch based on changes in RNA conformation on RNA small molecule binding

- Modular switch based on rationally designed synthetic riboswitches that function in mammalian cells at high dynamic range
- Regulate a chosen transgene in vivo using a different small molecule for each transgene
- Platform can regulate multiple/any gene: antibodies, hormones, cytokines
- Multiple regulation cassettes with high dynamic range
- Multiple different aptamers with novel small molecule activators
- Demonstrated regulation in vivo



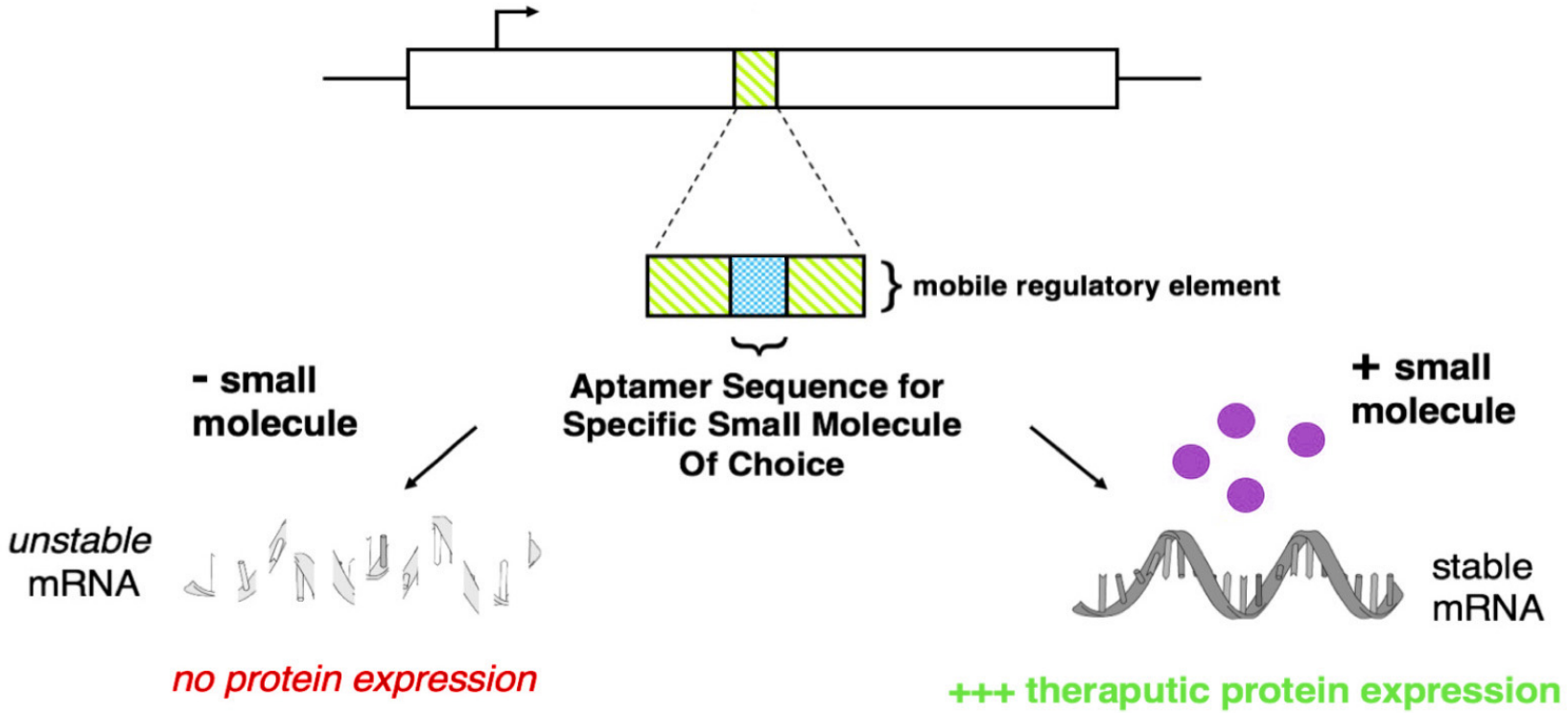
1 Insert the gene for a therapeutic protein

2 Oral small molecule for ongoing gene expression

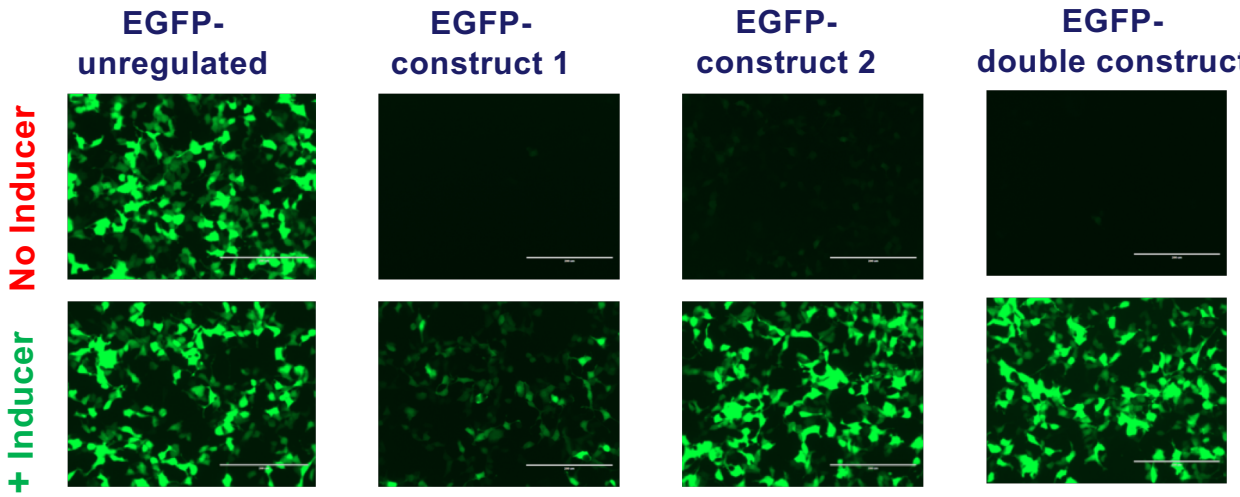


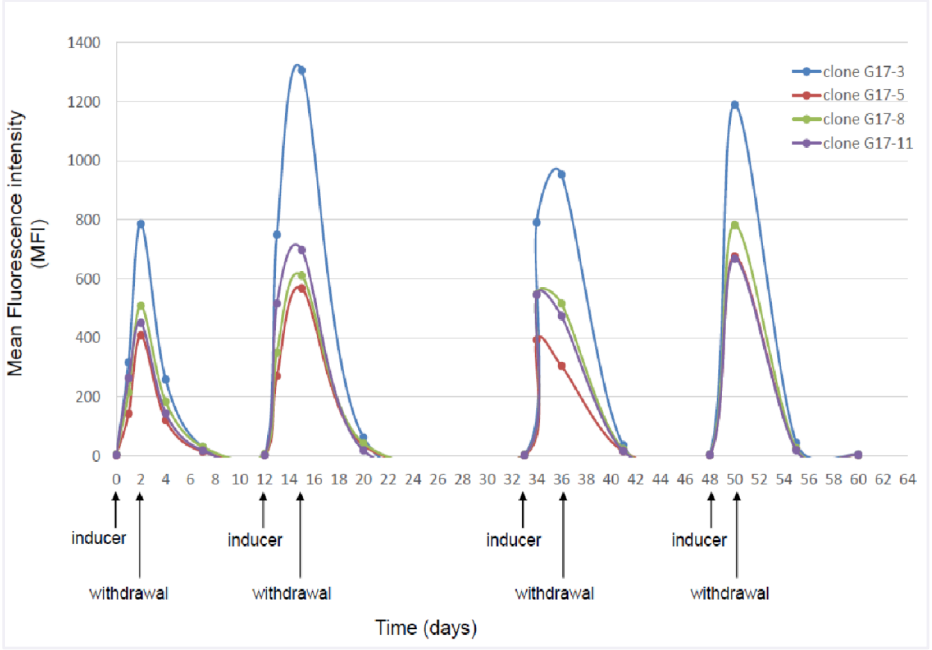
Regulation of Transgenes using Proprietary Riboswitch Technology

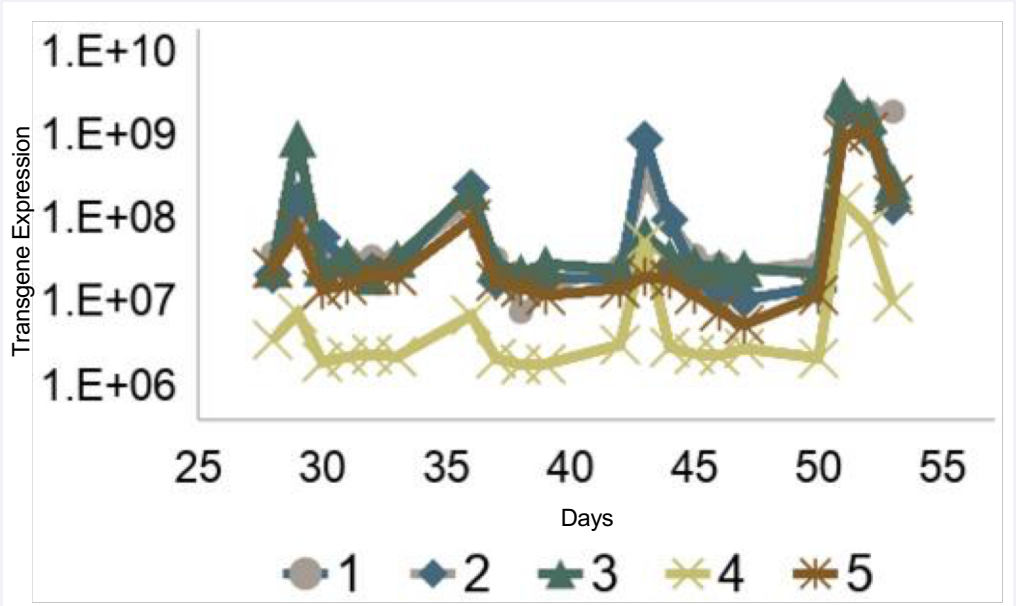
Regulation driven by specific small molecule / RNA binding driving functional changes in RNA configuration, splicing and translation



Regulation of Transgene Expression

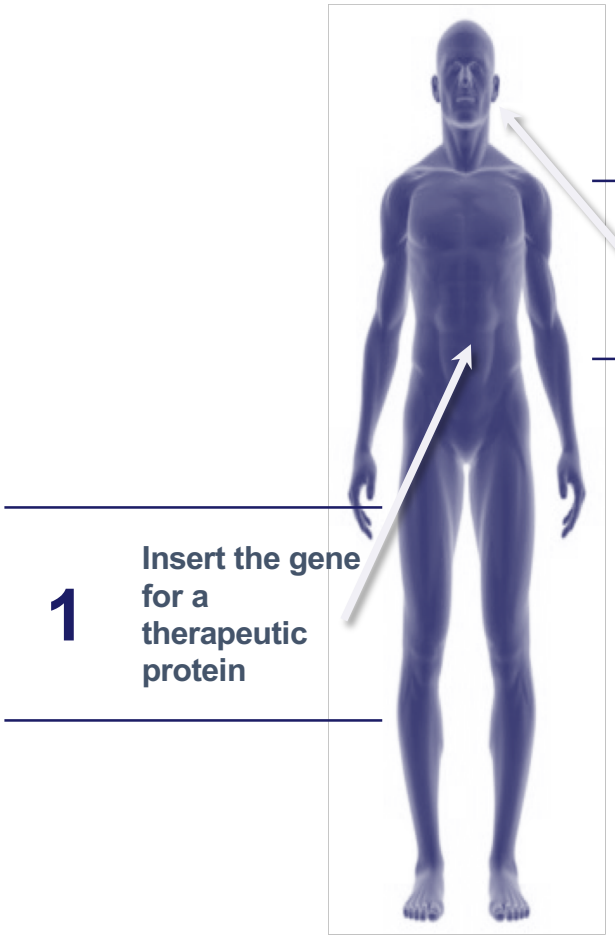


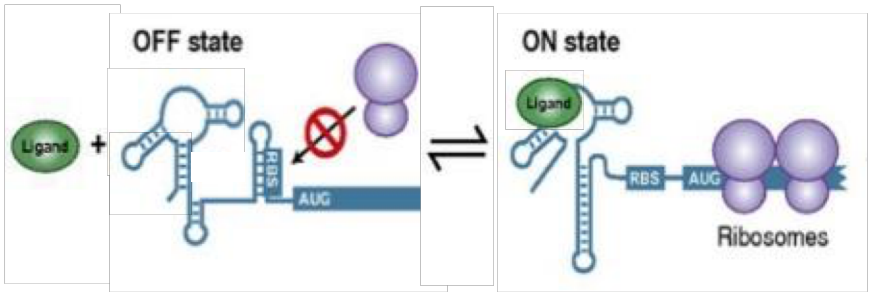




Summary: Gene Switch Platform

- Gene is active only when small molecule present
- Riboswitch – uses RNA shape
- Promoter control intact
- Short or long acting small molecule
- Optimized dosing of biologics delivered from a local source
- Short acting peptides to be dosed effectively (gut peptides) for enhanced efficacy
- Activation in sites hard to access with biologics – cross BBB
- Gene therapy is no longer necessarily a 1x treatment
- New world of potential targets
- New model of pricing for gene therapy and biologics





MEIRAGTx