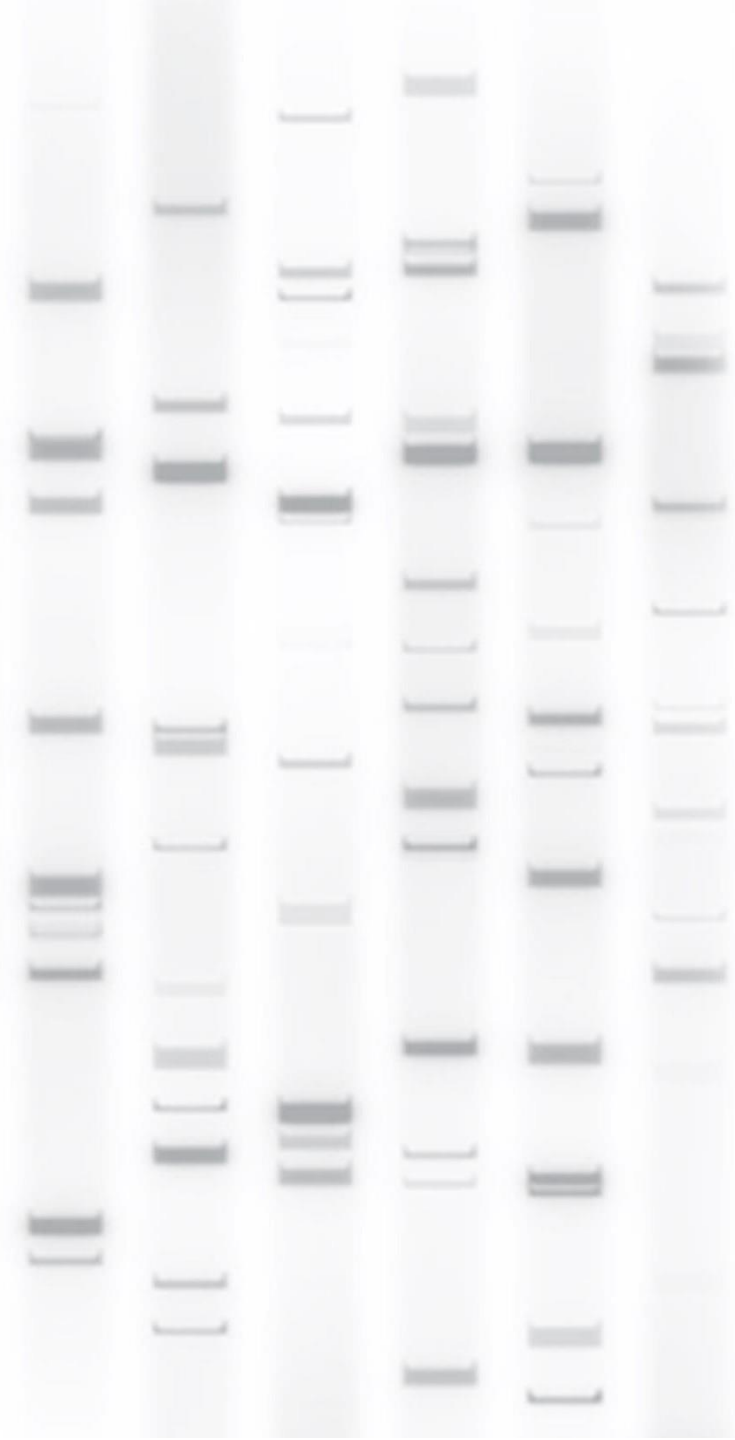
TAYSHA GENE THERAPIES

Bringing New Cures to Life

Corporate Presentation
May 2021



Legal Disclosure

FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are subject to a number of risks, uncertainties and assumptions. Risks regarding our business are described in detail in our Securities and Exchange Commission filings, including in our Annual Report on Form 10-K for the year ended December 31, 2020. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this prospectus involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

Driven by a relentless focus on discovering, developing, and commercializing novel AAV-based gene therapies for devastating disorders of the central nervous system

Taysha Summary Overview

Multiple product candidates with anticipated near-term catalysts to enhance value	– First in human clinical data for TSHA-101 in GM2 gangliosidosis in 2H 2021 – Additional clinical data for TSHA-120 in GAN in 2H 2021 – Open IND for TSHA-118 in CLN1 disease; initiation of Phase 1/2 trial in 2H 2021 – Submit four IND/CTA filings, including Rett syndrome, in 2021 – Advancement of four product candidates in IND-enabling studies, four in discovery in 2021
Portfolio of 26 CNS gene therapy programs across 3 distinct franchises	– Current pipeline of 26 AAV gene therapy programs – Portfolio addressing over 500,000 patients (US+EU) across monogenic CNS diseases, including neurodegenerative diseases, neurodevelopmental disorders, and genetic epilepsies
UT Southwestern Gene Therapy Program strategic alliance	– Led by Drs. Steven Gray and Berge Minassian; established to accelerate R&D, with integration of translational research, clinical development and GMP manufacturing – Exclusive access to resources, expertise, and novel technology platforms for delivery and dosing of gene therapies
Validated capsid, manufacturing system and route of delivery	– Clinically and commercially proven AAV9 vector platform – Highly scalable suspension HEK293 manufacturing process with excellent yield – Intrathecal delivery enables direct targeting to the CNS with validated biodistribution and safety
Proven management team and investor syndicate	– Deep expertise in the development of gene therapies for rare diseases – Key leadership team members and investors previously led the development and commercialization of Zolgensma®, the first FDA-approved gene therapy for CNS disease

Leadership team uniquely positioned to deliver on corporate mission

Leadership

RA Session II *Founder, President & CEO*	avenis, REATA, PTC Therapeutics, bridgebio
Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM *Chief Medical Officer and Head of R&D*	AUDENTES, BIOMARIN, SANOFI GENZYME
Kamran Alam, CPA, MBA *Chief Financial Officer*	avenis, rocket pharma, Lundbeck
Fred Porter, PhD *Chief Technical Officer*	NOVARTIS, gsk, bridgebio
Mishima Gerhart *Chief Regulatory Officer and Head of Quality*	SANOFI GENZYME, REATA
Sean McAuliffe *Chief Commercial Officer*	avenis, Baxalta
Jim Rouse *Chief Information Officer*	avenis, REATA, PTC Therapeutics
Emily McGinnis *Chief Patient Officer & Head of Government Affairs*	avenis, REATA, OVATION
Tim Douros, JD *Chief Legal Officer and Corporate Secretary*	bluebirdbio, CUBIST
Tracy Porter, M.Ed., SPHR *Chief People Officer*	AUDENTES, MEDIVATION, BAYER

Advisors

Steven Gray, PhD *Chief Scientific Advisor*	UTSouthwestern Medical Center
Berge Minassian, MD *Chief Medical Advisor*	UTSouthwestern Medical Center

Board of Directors

Sean Nolan *Chairman*	avenis, INTERMUNE, REATA
Paul Manning	PBM CAPITAL, avenis
Phillip Donenberg	avenis, AVROBIO
Sukumar Nagendran, MD	avenis, REATA
Laura Sepp-Lorenzino, PhD	Intellia THERAPEUTICS, VERTEX
Kathleen Reape, MD	Spark THERAPEUTICS
RA Session II	TAYSHA GENE THERAPIES

Scientific Advisory Board of preeminent international scientific and clinical thought leaders in gene therapy, CNS diseases and drug discovery and development

Scientific Advisory Board

Deborah Bilder, MD	University of Utah Registry of Autism and Developmental Disabilities (URADD); Utah Regional Education; BioMarin Pharmaceutical
Alan Boyd, BCc, MB, ChB, FRSB, FFLM, FRCP, FFPM	Boyd Consultants; Royal Colleges of Physicians; University of Birmingham Medical School; AstraZeneca; Ark Therapeutics Ltd
Wendy K. Chung, MD, PhD	Columbia University; Simons Foundation Autism Research Initiative (SFARI)
David P. Dimmock, MD	Rady Children's Institute for Genomic Medicine; FDA; CDC
Michael W. Lawlor, MD, PhD	The Neuroscience Research Center at the Medical College of Wisconsin; Solid Biosciences
Gerald S. Lipshutz, MD, MS	David Geffen School of Medicine at University of California, Los Angeles; Wellcome Trust, UK; NIH

Taysha by the numbers

1

differentiated strategic partnership with a world class academic institution

1

pivotal-stage program further diversifying portfolio

4

IND/CTAs expected to be submitted by the end of 2021

26

programs in development with options to acquire an additional 4 programs

500,000+

US+EU patients addressable through current pipeline programs

Diverse pipeline focused exclusively on monogenic disorders of the central nervous system

Neurodegenerative Diseases

Diseases characterized by the progressive degeneration of the structures and function of the CNS and PNS

Neurodevelopmental Disorders

Multi-faceted conditions characterized by impairments in cognition, behavior, and motor function

Genetic Epilepsies

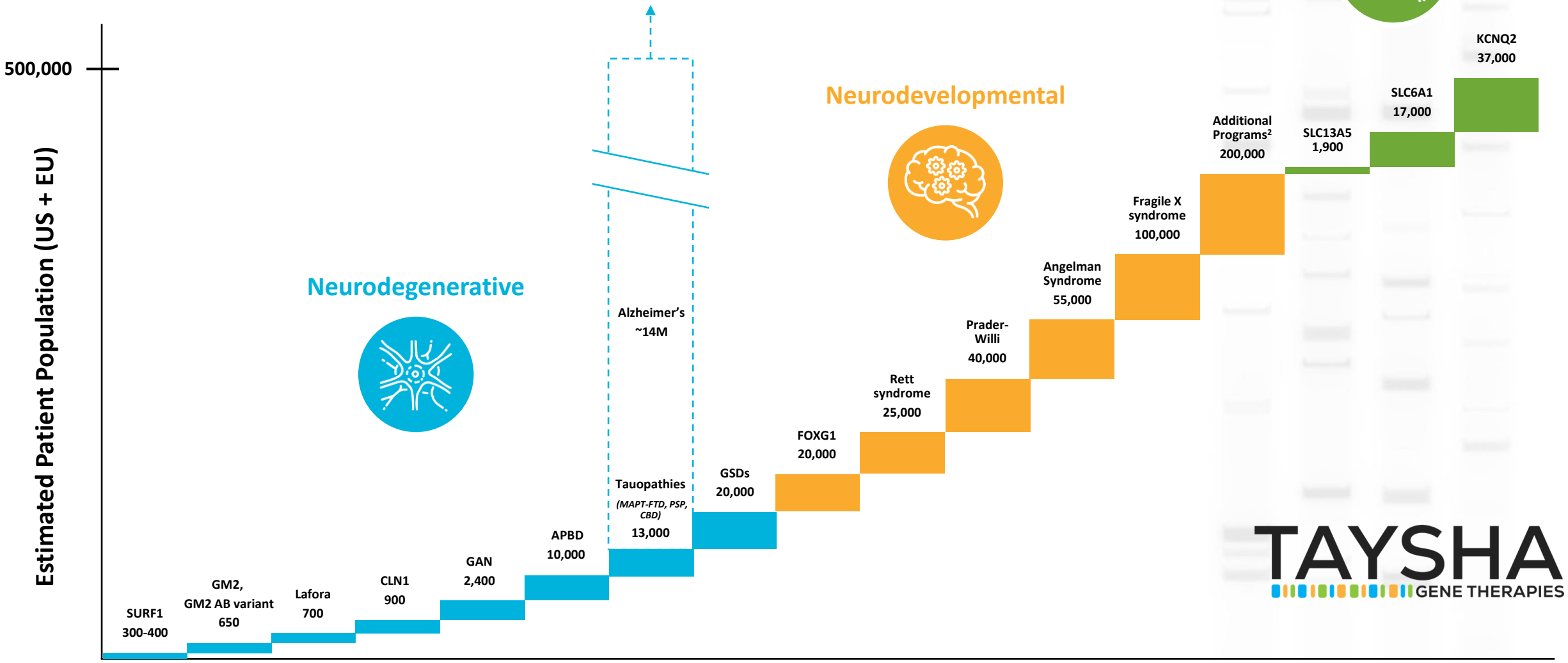
Disorders characterized by recurrent seizures often leading to abnormal development of the brain

Unparalleled gene therapy pipeline focused exclusively on monogenic CNS disorders

PROGRAM		INDICATION	DISCOVERY	PRECLINICAL	PHASE 1/2	Pivotal	GLOBAL COMM. RIGHTS
NEURODEGENERATIVE DISEASES							
TSHA-120	*GRT*	Giant Axonal Neuropathy				Regulatory guidance YE 2021	TAYSHA GENE THERAPIES
TSHA-101	*GRT*	GM2 Gangliosidosis				Currently open CTA	
TSHA-118	*GRT*	CLN1 Disease				Currently open IND	
TSHA-119	*GRT*	GM2 AB Variant					
TSHA-104	*GRT*	SURF1-Associated Leigh Syndrome				IND/CTA submission 2H 2021	
TSHA-112	*miRNA*	APBD					
TSHA-111-LAFORIN	*miRNA*	Lafora Disease					
TSHA-111-MALIN	*miRNA*	Lafora Disease					
TSHA-113	*miRNA*	Tauopathies					
TSHA-115	*miRNA*	GSDs					
Undisclosed	GRT/*shRNA*	Undisclosed					
Undisclosed	GRT	Undisclosed					
NEURODEVELOPMENTAL DISORDERS							
TSHA-102	*Regulated GRT*	Rett Syndrome				IND/CTA submission 2H 2021	TAYSHA GENE THERAPIES
TSHA-106	*shRNA*	Angelman Syndrome					
TSHA-114	*GRT*	Fragile X Syndrome					
TSHA-116	*shRNA*	Prader-Willi Syndrome					
TSHA-117	*Regulated GRT*	FOXG1 Syndrome					
TSHA-107	*GRT*	Autism Spectrum Disorder					
TSHA-108	*GRT*	Inborn Error of Metabolism					
TSHA-109	*GRT*	Inherited Metabolism Disorder					
Undisclosed	GRT	Undisclosed					
Undisclosed	mini-gene	Undisclosed					
GENETIC EPILEPSY							
TSHA-103	*GRT*	SLC6A1 Haploinsufficiency Disorder					TAYSHA GENE THERAPIES
TSHA-105	*GRT*	SLC13A5 Deficiency					
TSHA-110	mini-gene	KCNQ2					
Undisclosed	mini-gene	Undisclosed					

GRT: Gene replacement therapy **miRNA**: microRNA **shRNA**: short hairpin RNA

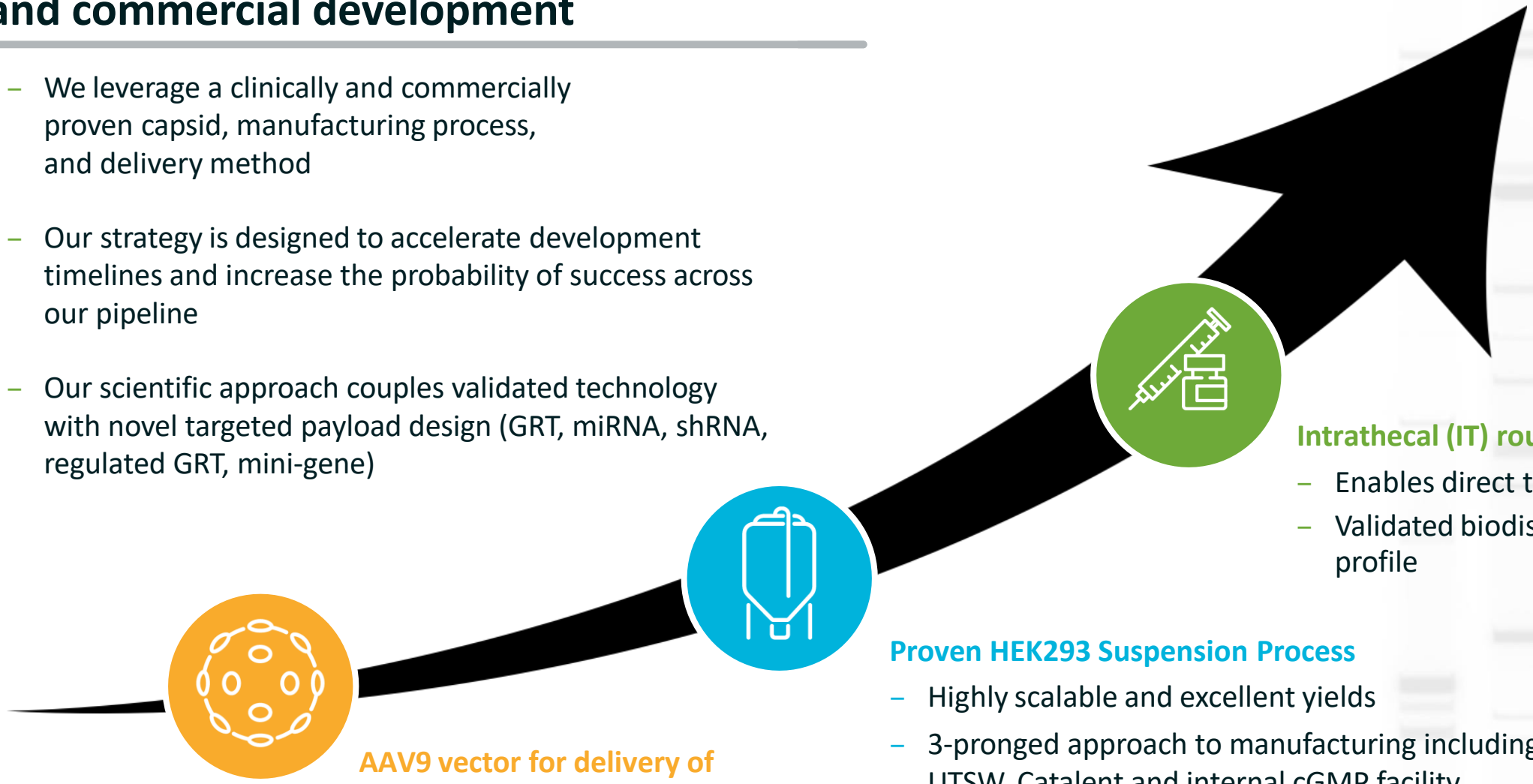
Our three distinct franchises have the potential to address over 500,000+ patients (US+EU)



[1]Tauopathies only include MAPT-FTD, PSP, CBD
[2]Additional programs include TSHA-107, TSHA-108 and TSHA-109

Our strategy is focused on rapid clinical and commercial development

- We leverage a clinically and commercially proven capsid, manufacturing process, and delivery method
- Our strategy is designed to accelerate development timelines and increase the probability of success across our pipeline
- Our scientific approach couples validated technology with novel targeted payload design (GRT, miRNA, shRNA, regulated GRT, mini-gene)



AAV9 vector for delivery of therapeutic transgene

- Demonstrated safety and efficacy across multiple CNS indications

Proven HEK293 Suspension Process

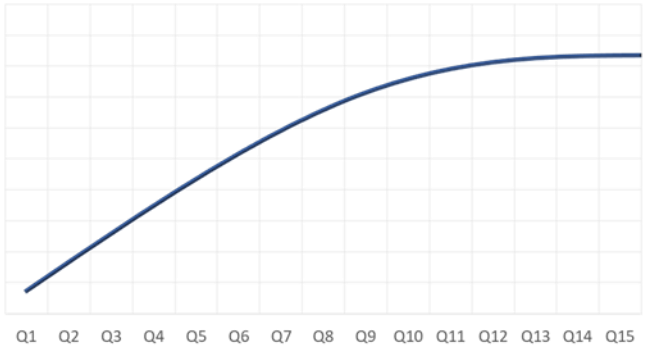
- Highly scalable and excellent yields
- 3-pronged approach to manufacturing including UTSW, Catalent and internal cGMP facility

Intrathecal (IT) route of administration

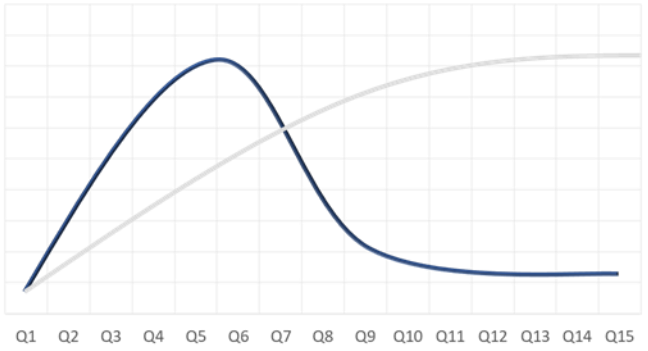
- Enables direct targeting to CNS
- Validated biodistribution and safety profile

Creating a sustainable business model for gene therapy

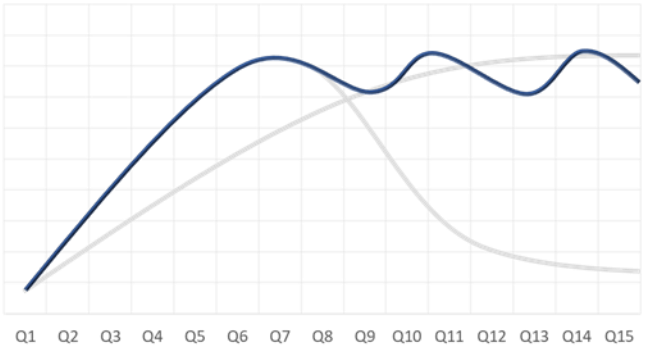
Traditional chronic dosing business model



One-time dosing business model



Taysha's sustainable gene therapy platform business model



Approach and ability to deliver various payloads

Gene Replacement

- Replace gene of interest to treat diseases or disorders with limited gene expression
- Comprised of a codon-optimized DNA transgene that encodes the wild type gene of interest
- Transgene (or mini-gene) coupled with a promoter selected to ensure expression in the cell or tissue-type of interest

Regulated Gene Replacement

- Regulate expression of a therapeutic transgene
- Built-in regulation system to replace dose-sensitive genes safely and at therapeutic levels
- Uses miRARE, our novel miRNA target panel

Vectorized RNA

- Transgenes designed to express miRNA (small, non-coding sequences of RNA that result in silencing of gene expression)
- Transgenes designed to express short-hairpin RNA (shRNA), which reactivate a silenced gene upon binding to the target of interest

Mini-Gene Payloads

- Many genes are too large to fit in AAV capsids
- Mini-genes designed to overcome limited AAV packaging capacity
- Collaboration with Cleveland Clinic to advance next-generation mini-gene payloads initially for genetic epilepsies and neurodevelopmental disorders

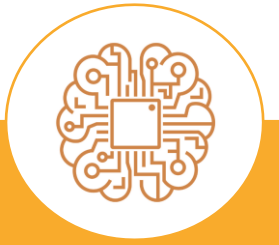
Novel platform technology that powers our research engine

Novel AAV Dosing Platform

- Potential to facilitate redosing via vagus nerve
- Efficient targeting of vagal neurons demonstrated in adult rats, with potential to improve autonomic nervous system symptoms in humans
- Normal vagal nerve fibers and neurons post AAV delivery to the vagus nerve in dogs

miRARE Platform

- Novel miRNA target panel derived from high-throughput miRNA profiling and genome mining
- Designed for safely regulated transgene expression levels in the brain
- Needed in disorders like Rett syndrome where high doses of transgene-expressing vectors may be harmful while low doses may avoid toxicity but be subtherapeutic
- Built-in regulation system harnesses endogenous systems



Novel Capsid Identification

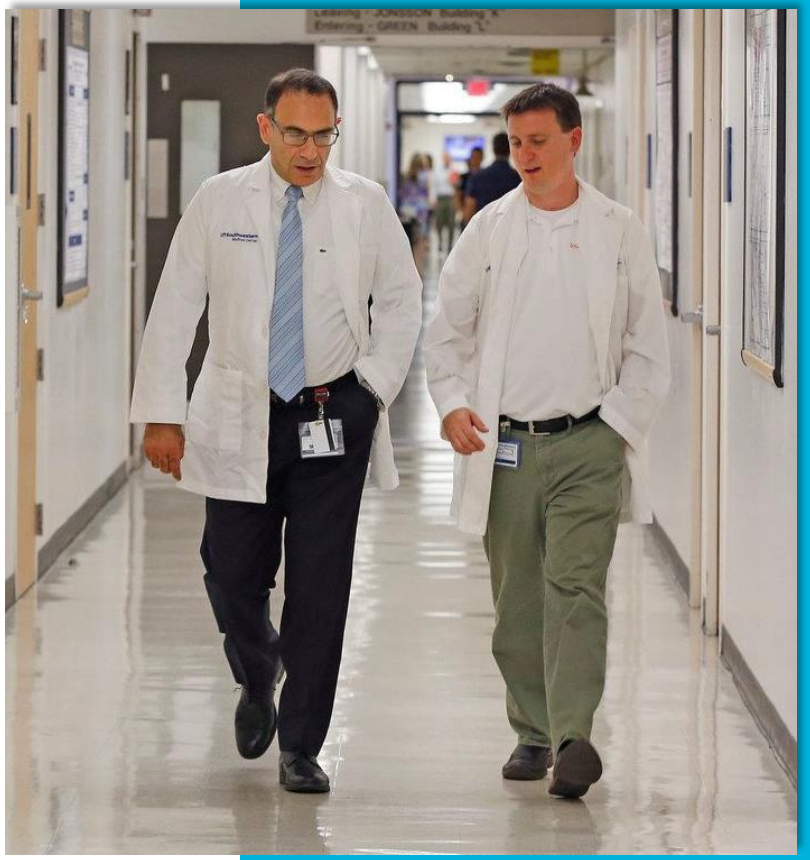
- Improves targeted delivery through use of machine learning, capsid shuffling and directed evolution
- Allows rapid identification of capsids with improved properties in mice and Non- Human Primates (NHPs) to maximize translational relevance
- Potential to drive new product candidates with novel biodistribution and transduction profiles into pipeline

Our strategic partnership with UTSW

UT Southwestern Medical Center

We have access to a world-class team of scientists and cutting-edge technology through an exclusive, worldwide royalty-free license to discover, develop, and commercialize gene therapies led by:

- **Berge Minassian, MD**, Division Chief of Child Neurology
  - Pediatric neurologist with expertise in neurodegenerative diseases, neurodevelopmental disorders, and genetic forms of epilepsy
  - Discovered *MECP2* CNS isoform (Rett syndrome)
- **Steven Gray, PhD**, Director of Viral Vector Core, Associate Professor Dept of Peds
  - AAV-based vector engineering expertise and optimizing CNS delivery of transgenes
  - Administered the first AAV9-based therapy to patients via intrathecal route
- Exclusive access to a flexible, scalable, and well-characterized GMP manufacturing suite that utilizes a suspension HEK293 process
- Exclusive access to next generation platform technologies, including novel redosing platform, transgene regulation (miRARE), and capsid development



Manufacturing strategy allows flexibility and scalability to support broad pipeline

UT Southwestern Medical Center®

- Support the UTSW viral vector core to supply early-phase clinical material
  - Active technical collaboration and knowledge sharing for process information and analytical methods
  - First program is ongoing
- Capabilities
  - 50L tox production
    - 200L available by EOY
  - 500L GMP manufacturing
    - GMP operations began in December 2020
  - In-house support for critical release and stability testing

Catalent®

- Establish collaborations with leading CDMO to provide additional capacity for early-phase and pivotal supply
  - Strategic partnership in place with Catalent Gene Therapies
    - Two programs ongoing
    - Able to leverage process, methods and materials across programs
- Current Capabilities
  - 200/400L tox production
  - 800L GMP manufacturing
  - Full support for release and stability testing

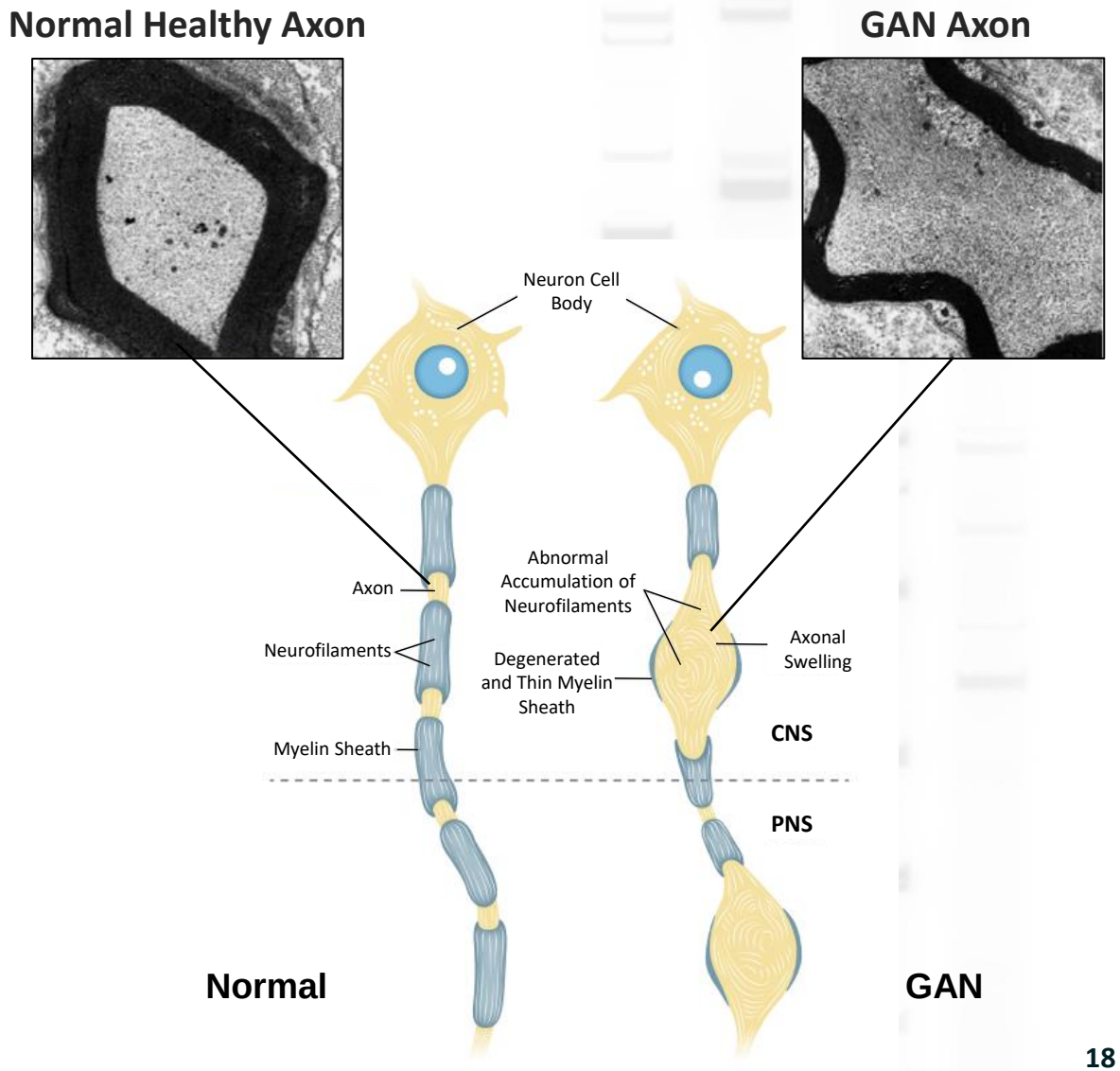
TAYSHA GENE THERAPIES

- Build internal manufacturing facility to support clinical and commercial manufacturing
  - Initial build includes two vector manufacturing trains, one fill/finish suite, QC and technical development labs
  - Building secured in Durham, NC
    - Growing hub for gene therapy manufacturing
- Facility timing
  - Kicked off 1Q 2021
  - Office and development labs operational in 1Q 2022
  - GMP ready in 2023

Neurodegenerative Disease Franchise

Rationale for targeting the *GAN* gene

- Mutations affect production of the protein gigaxonin
  - Leads to accumulation of neurofilaments in giant axons causing signal interruption and neurodegeneration
- Genetic changes in the *GAN* gene have been shown to cause Giant Axonal Neuropathy
- Good candidate for gene transfer approach
  - Small gene that is easy to package into AAV9 capsid
  - High transduction to target organ
  - Low-level expression may restore function
  - A clear model for other disorders with similar mechanism such as GM2 gangliosidosis, CLN1 disease, SURF1-associated Leigh syndrome and amyotrophic lateral sclerosis (ALS)

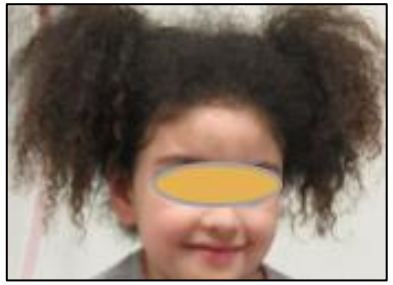


Giant axonal neuropathy (GAN) is a rare inherited genetic disorder that affects both the central and peripheral nervous systems

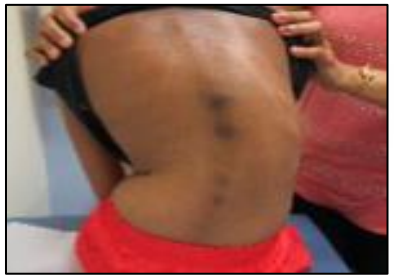
TSHA-120
GAN

- Rare autosomal recessive disease of the central and peripheral nervous systems caused by loss-of-function gigaxonin gene mutations
- Majority of children with GAN show symptoms and features before age 5
  - Dull, tightly curled hair
  - Progressive scoliosis
  - Contractures
  - Giant axons
  - Spinal cord atrophy
  - White matter abnormality
- No approved disease-modifying treatments available
- Symptomatic treatments attempt to maximize physical development and minimize deterioration
- Early- and late-onset phenotypes – shared physiology
  - Late-onset often categorized as Charcot-Marie-Tooth Type 2 (CMT2), with lack of tightly curled hair and CNS symptoms, and relatively slow progression
  - Represents 1% to 6% of all CMT2 diagnosis
  - Late-onset poor quality of life but not life-limiting
- Estimated prevalence of GAN is 2,400 patients (US+EU)

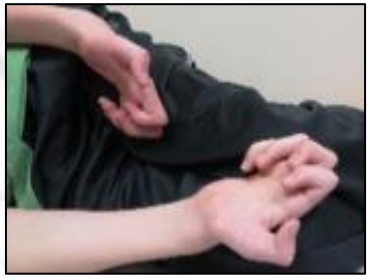
Tightly Curled Hair



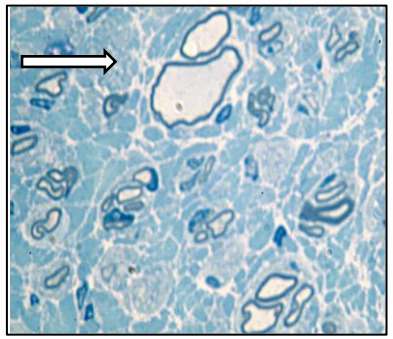
Progressive Scoliosis



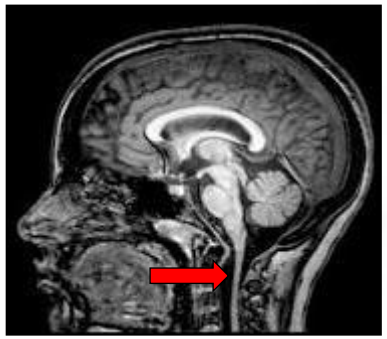
Contractures



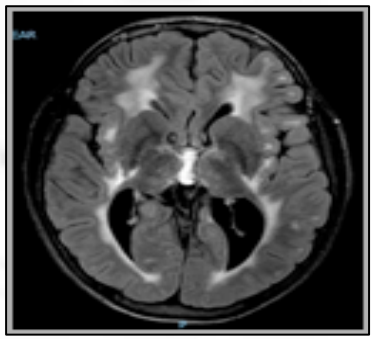
Giant Axons



Spinal Cord Atrophy



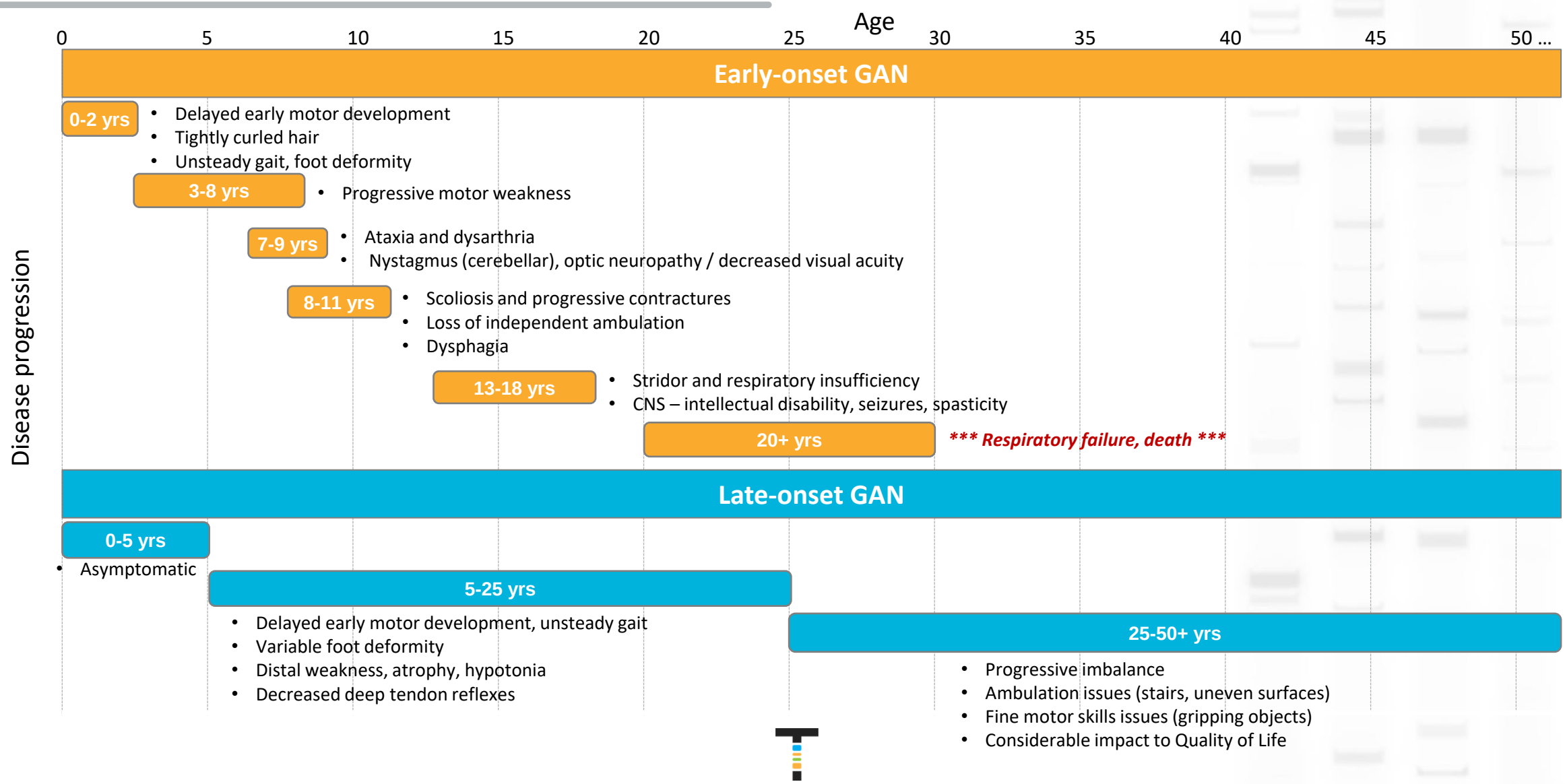
White Matter Abnormality



Murphy SM et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry 2012;83:706–10.
Gess B et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. Neuromuscul Disord 2013;23:647–51.
Antoniadi et al 2014
Bacquet J et al. Molecular diagnosis of inherited peripheral neuropathies by targeted next-generation sequencing: molecular spectrum delineation. BMJ Open. 2018

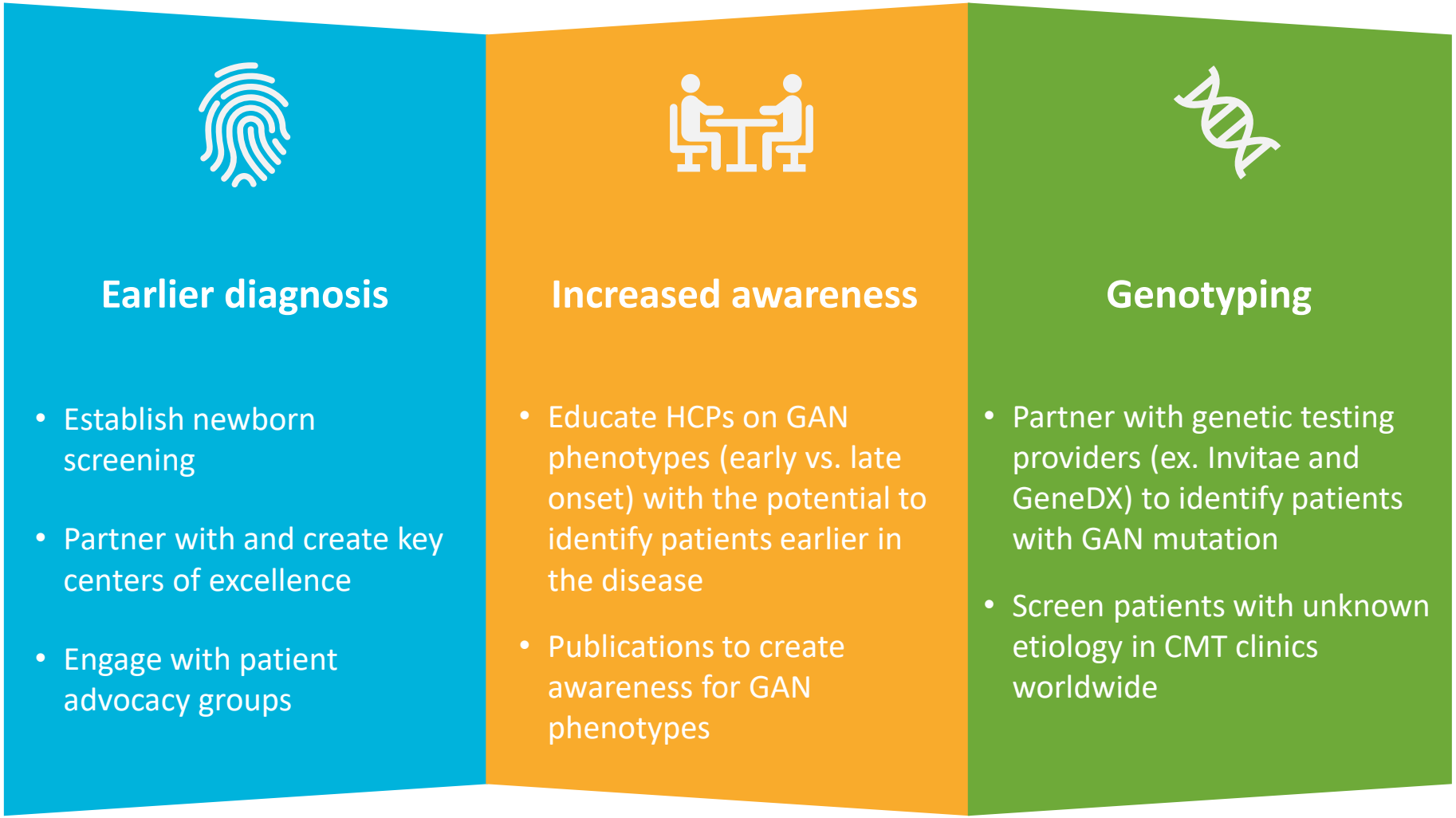
GAN natural history and disease progression

TSHA-120
GAN



Maximizing patient access and identification to address the estimated 2,400 patients in US and EU

TSHA-120
GAN



Earlier diagnosis

- Establish newborn screening
- Partner with and create key centers of excellence
- Engage with patient advocacy groups

Increased awareness

- Educate HCPs on GAN phenotypes (early vs. late onset) with the potential to identify patients earlier in the disease
- Publications to create awareness for GAN phenotypes

Genotyping

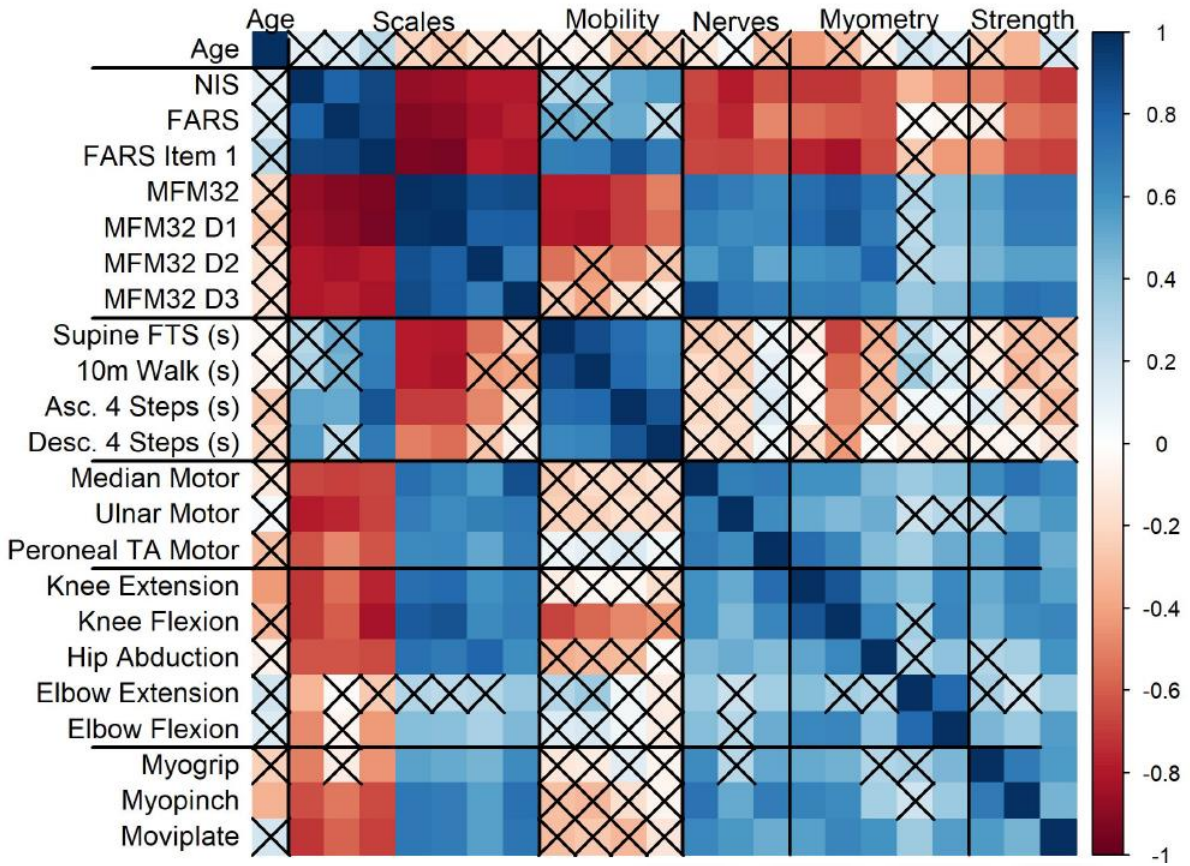
- Partner with genetic testing providers (ex. Invitae and GeneDX) to identify patients with GAN mutation
- Screen patients with unknown etiology in CMT clinics worldwide

Murphy SM et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry 2012;83:706–10.
Gess B et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. Neuromuscul Disord 2013;23:647–51.
Antoniadi et al 2014
Bacquet J et al. Molecular diagnosis of inherited peripheral neuropathies by targeted next-generation sequencing: molecular spectrum delineation. BMJ Open. 2018

Primary efficacy endpoint is the Motor Function Measure (MFM32) – a validated quantitative scale

- Validated instrument used in multiple regulatory approvals
- A 32-item scale for motor function measurement developed for neuromuscular diseases
- Assesses severity and progression of motor function across a broad spectrum and in 3 functional domains
  - Standing, transfers and ambulation
  - Proximal and axial function
  - Distal function
- 32 items scored between 0 and 3 for a maximum score of 96
  - A higher score means that an individual was able to complete the task
  - Sometimes, the score is converted to a percentage
- A 4-point change is considered clinically meaningful in the following indications:
  - DMD
  - SMA
  - LAMA2-related muscular dystrophy
  - Cerebral palsy

Correlation Matrix Measuring Strength and Frequency of Correlations Across Various Motor and Demographic Assessments

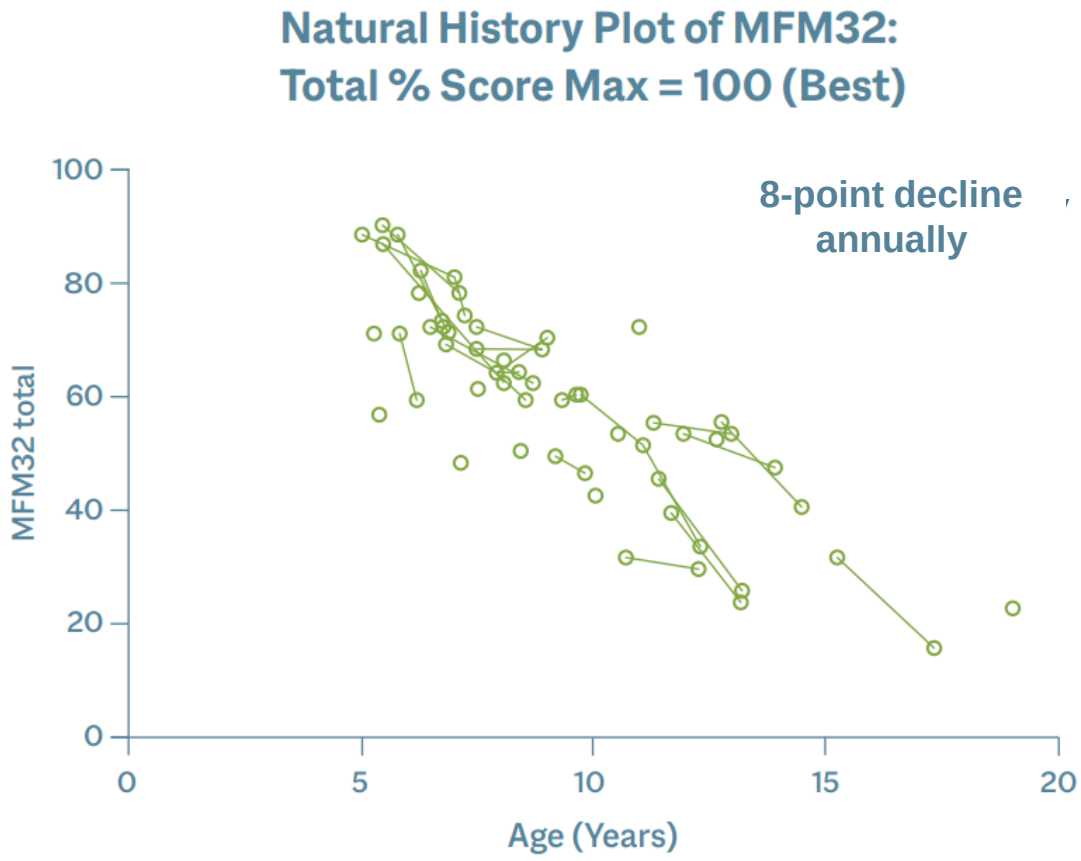


GAN natural history study data as a dependable comparator for future studies

TSHA-120
GAN

- 45 GAN patients (2013-present) ages 3-21 years
  - Can be accessed for treatment study
  - Will be used as comparator for treatment study
- MFM32
  - MFM32 total score shows uniform decline between patients of all age groups over time
  - Average decline is ~8 points per year
  - 4-point change is considered clinically meaningful
- MFM32 selected as primary endpoint due to least variability and its use in confirmatory trials

- **Natural history data: 8-point decline annually in MFM32**
- **4-point change in MFM32 considered clinically meaningful**

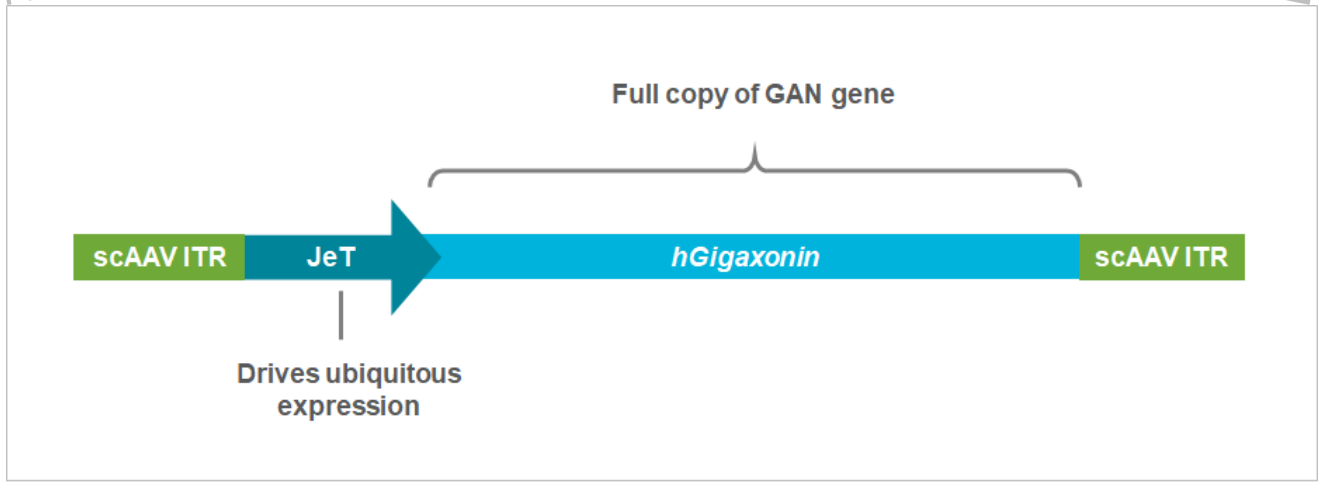


Bönnemann, C. et al; 2020

TSHA-120 program overview and construct

- Construct invented by Dr. Steven Gray (UTSW)
- AAV9 viral vector with engineered transgene encoding the human gigaxonin protein
- Self-complementary AAV capsid (scAAV) for rapid activation and stable expression
- JeT promoter drives ubiquitous expression
- Designed to deliver a functional copy of the GAN gene with optimal tropism and rapid expression
- Received orphan drug and rare pediatric disease designations
- Clinical study ongoing at NIH, led by Carsten Bönnemann, MD

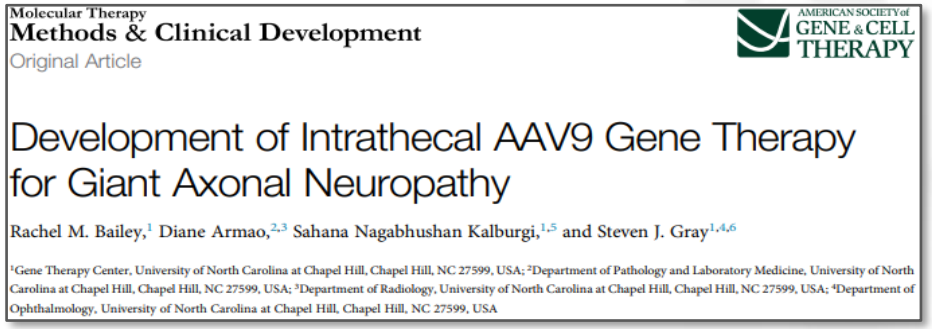
AAV9 capsid
Brain tropism & favorable safety profile



Preclinical data supported intrathecal dosing of TSHA-120

Comprehensive preclinical results demonstrated:

- Function of gigaxonin demonstrated *in vitro* and *in vivo*
- Phenotypic rescue in GAN mice after intrathecal injection, improving motor function and nerve pathology
- No toxicities in mice or non-human primates (NHPs) up to 1 year post injection
- No toxicities observed in rats at a 10-fold overdose up to 6 months post injection
- Improved DRG pathology in GAN knockout (KO) mice
- Preclinical data published in several scientific journals


Molecular Therapy
Methods & Clinical Development
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Development of Intrathecal AAV9 Gene Therapy for Giant Axonal Neuropathy

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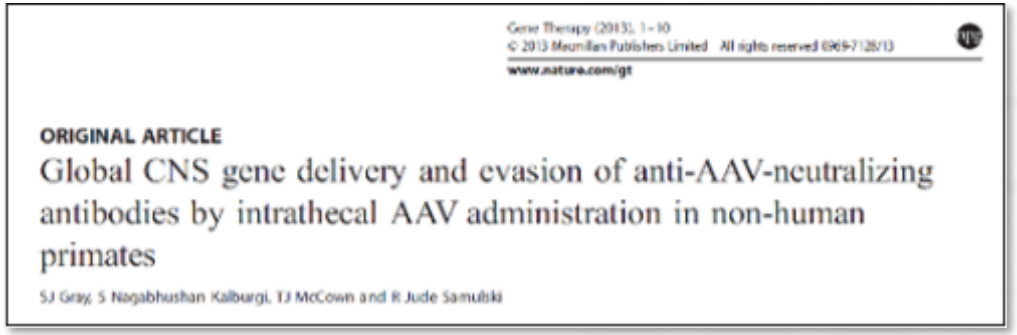
Gene Therapy (2013), 1–10
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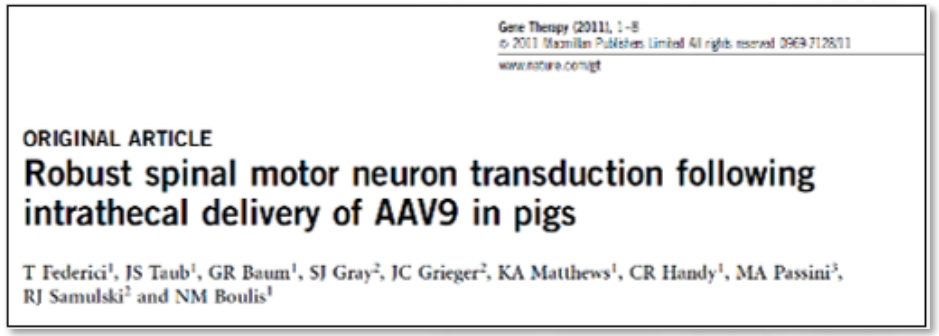
ORIGINAL ARTICLE

Global CNS gene delivery and evasion of anti-AAV-neutralizing antibodies by intrathecal AAV administration in non-human primates

SJ Gray, S Nagabhushan Kalburgi, TJ McCown and R Jude Samulski


Gene Therapy (2011), 1–8
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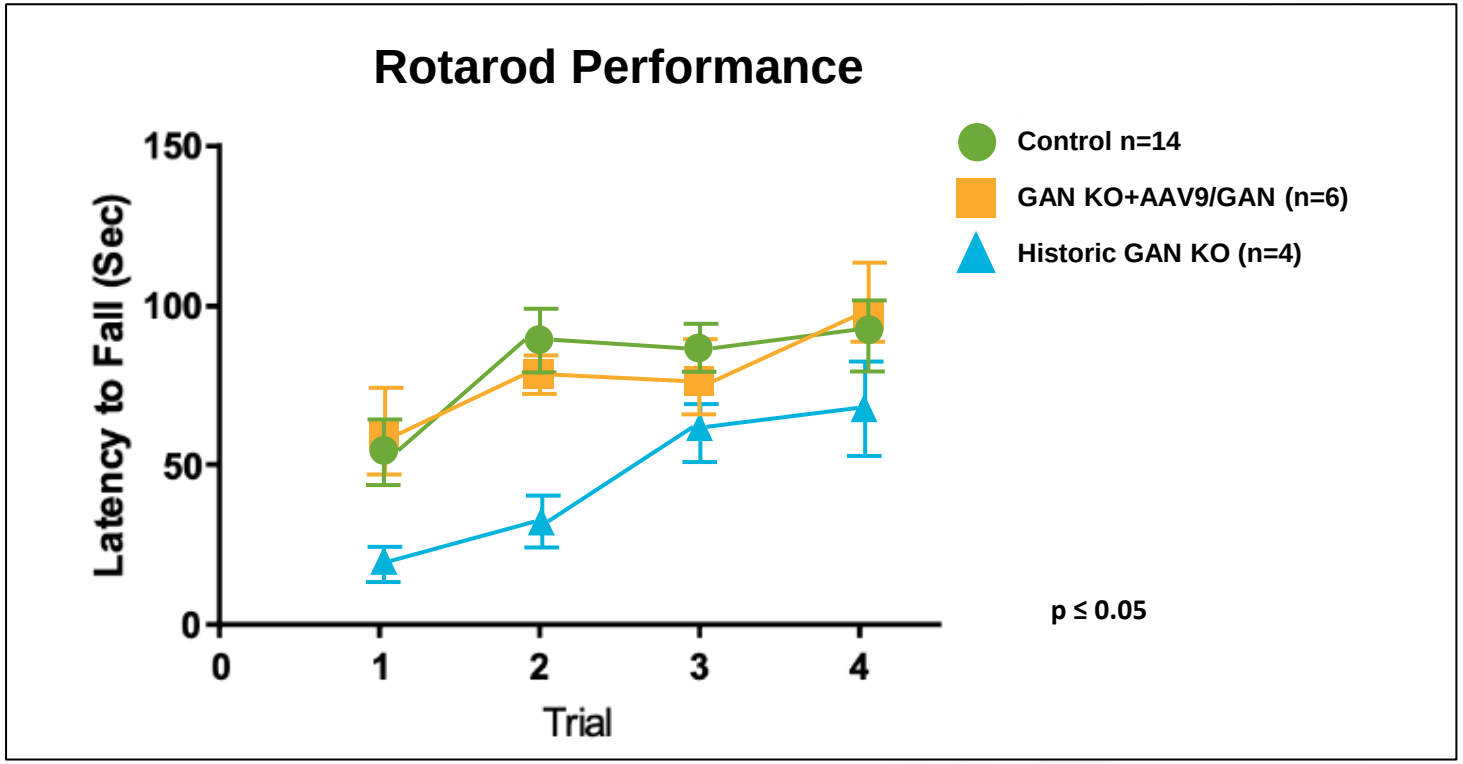
ORIGINAL ARTICLE

Robust spinal motor neuron transduction following intrathecal delivery of AAV9 in pigs

T Federici[1], JS Taub[1], GR Baum[1], SJ Gray[2], JC Grieger[2], KA Matthews[1], CR Handy[1], MA Passini[3], RJ Samulski[2] and NM Boulis[1]

TSHA-120 normalized performance of 18-month-old GAN rodent knockout model

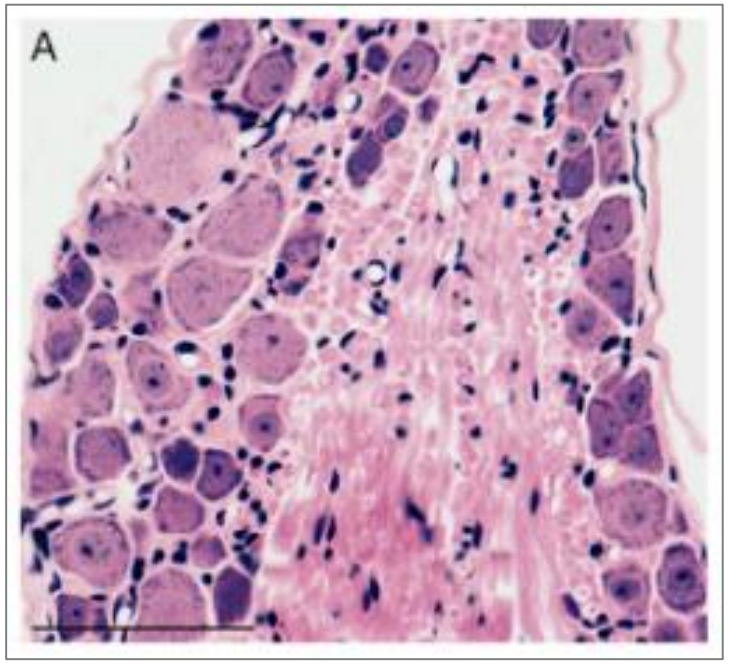
- Untreated GAN rodents performed significantly worse than heterozygous controls
- GAN rodents treated at 16 months old performed significantly better than untreated GAN rodents at 18 months old
- GAN rodents treated at 16 months old performed equivalently to heterozygous controls



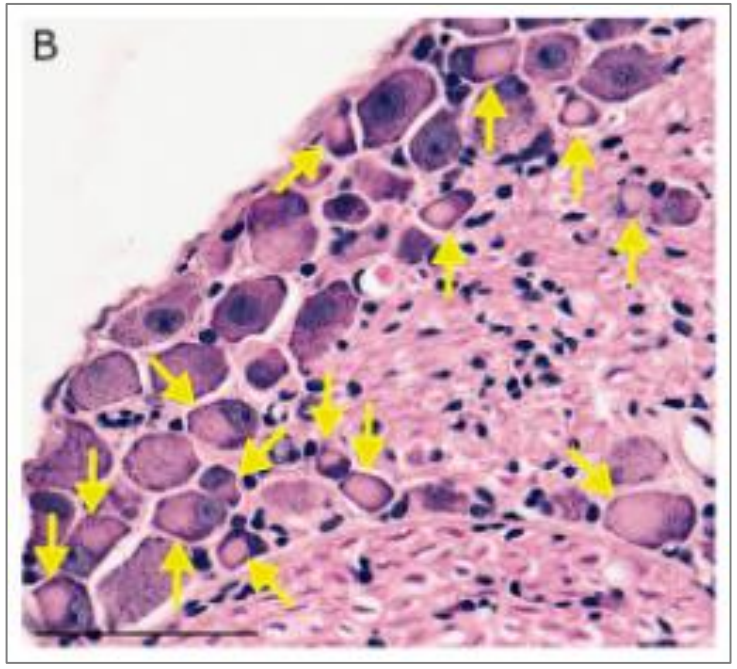
Gray, S.J., unpublished

TSHA-120 improved pathology of the DRG in the GAN KO mice

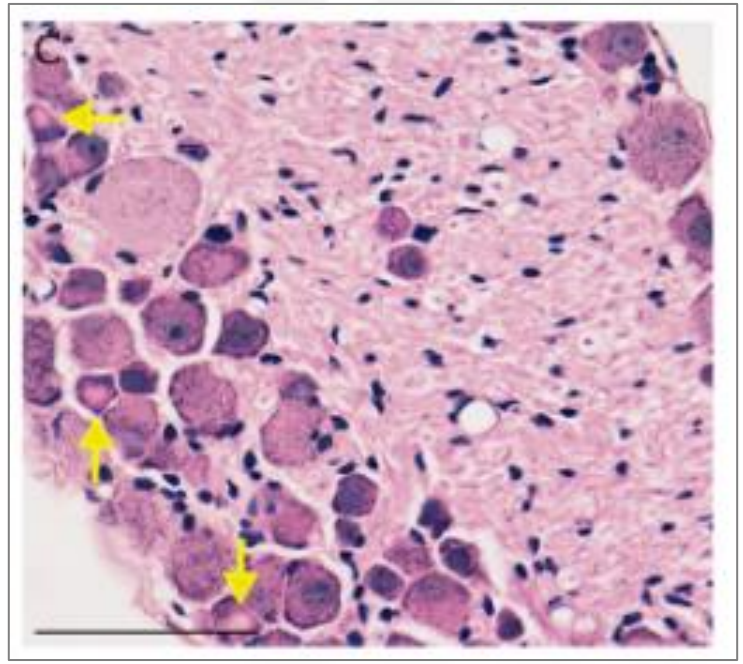
TSHA-120
GAN



Normal control



GAN KO – vehicle injected

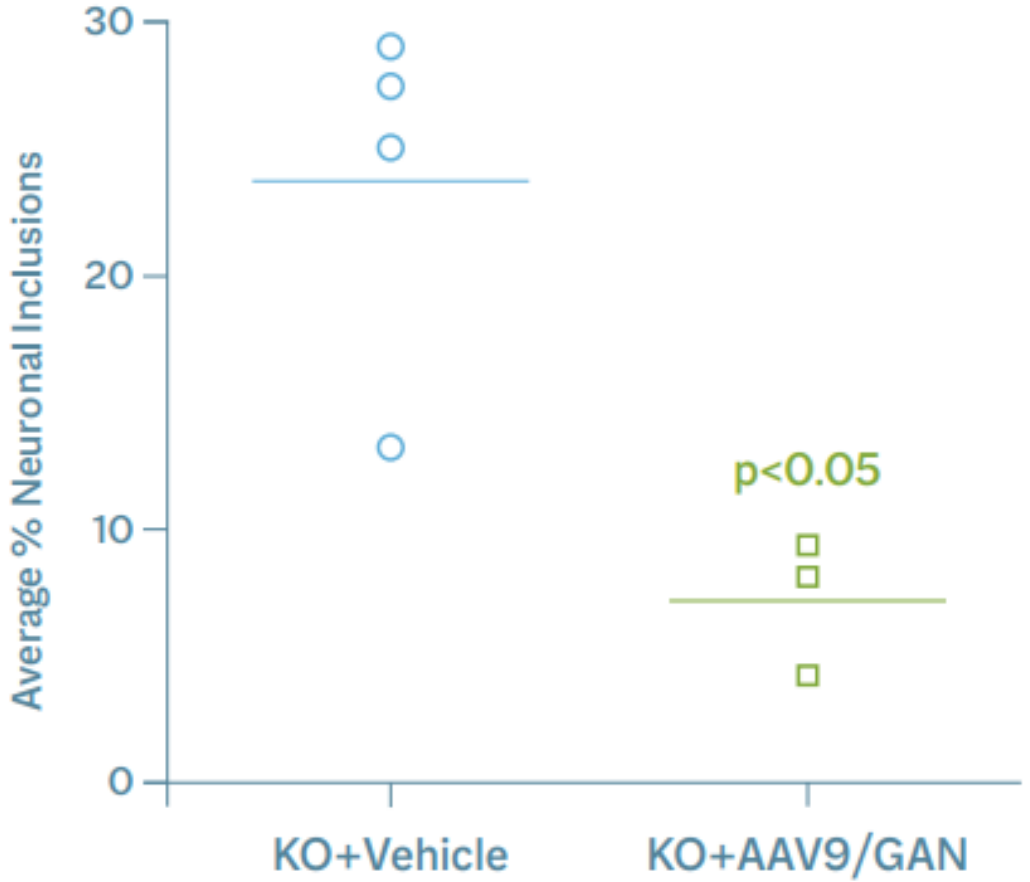


GAN KO – AAV9-GAN

Bailey, R. et al, 2018, MTMCD

TSHA-120 improved pathology of the DRG in the GAN KO mice

Significant reduction in % neuronal inclusions



Bailey, R. et al, 2018, MTMCD

Groundbreaking, historic dose escalation clinical trial – First intrathecally-dosed gene therapy

TSHA-120
GAN

Goals and Targets of Trial

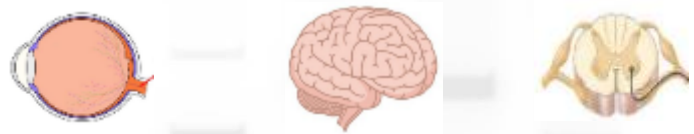
Goals

- **Primary** – Safety: clinical and laboratory assessments
- **Secondary** – Efficacy: pathologic, physiologic, functional and clinical markers

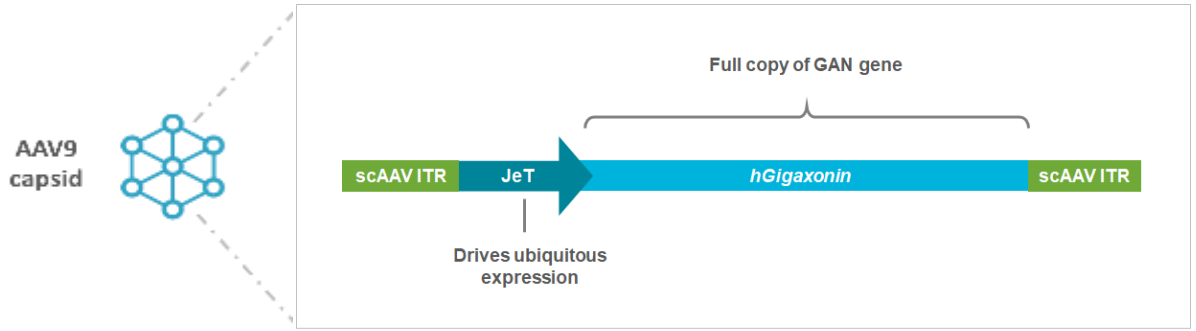
Target Recruitment

- 14 subjects injected
- > 5 years old

Target Areas to Transduce



Product Details and Dose Cohorts



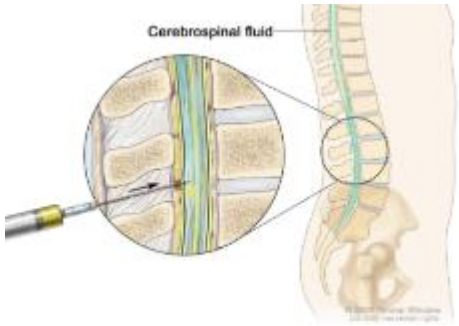
Dose Cohorts*

1x	3.5 x 10^{13} total vg **(N=2)**
3.3x	1.2 x 10^{14} total vg **(N=4)**
5x	1.8 x 10^{14} total vg **(N=5)**
10x	3.5 x 10^{14} total vg **(N=3)**

Route and Method of Administration

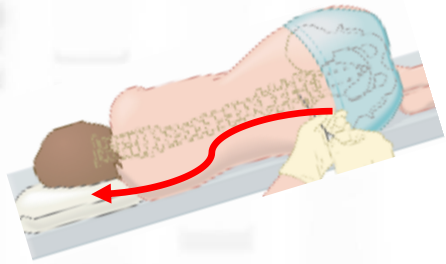
Administration

- Lumbar Intrathecal Infusion (IT)
- Amount and Rate: 10.5 ml; 1 mL/minute
- Immunosuppression regimen of prednisolone and rapamycin



Technique to Improve transduction

- Trendelenburg position (15°)
- During infusion & 1 hour post infusion



*Doses calculated by qPCR
NOTE: Subsequent slides only show data from 1.2 x 10^{14} vg and 1.8 x 10^{14} vg doses

Clinical Trial: NCT02362438

TSHA-120 achieved sustained improvement in primary efficacy endpoint and was well tolerated at multiple doses

TSHA-120
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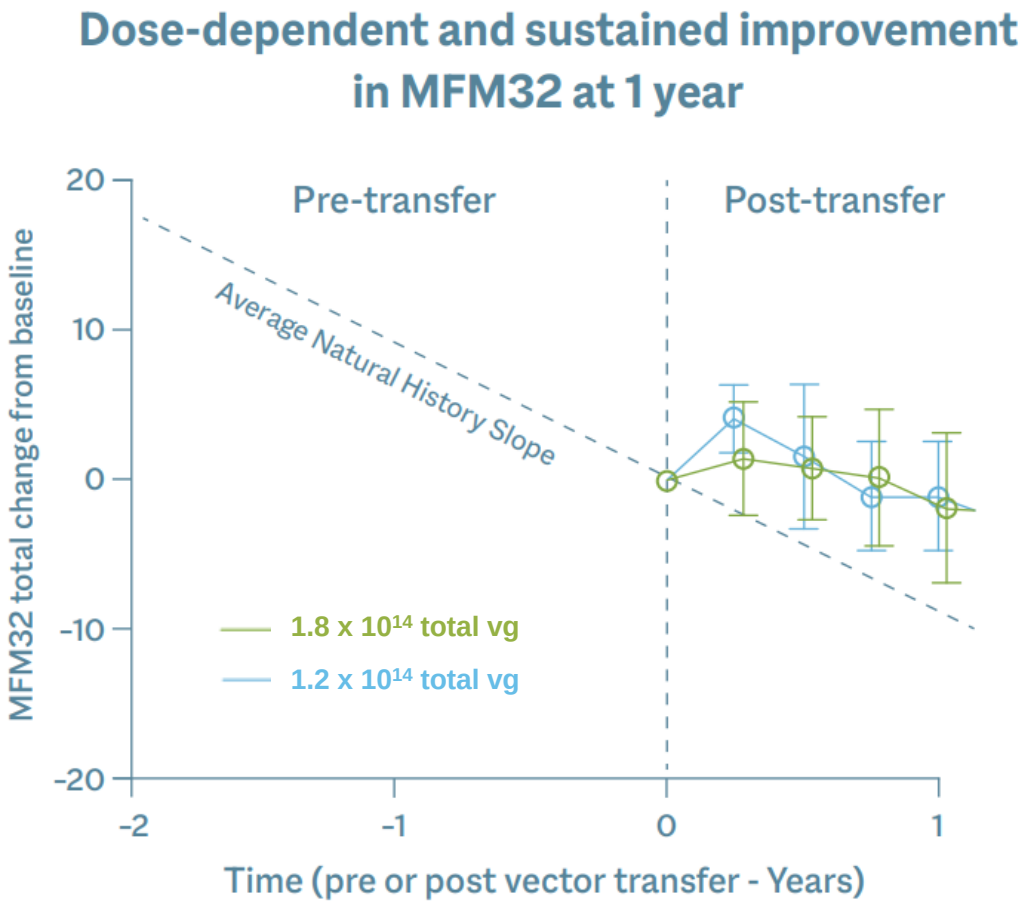
- First successful in-human intrathecal gene transfer
- 14 patients dosed
- Positive efficacy results support a dose-response relationship with TSHA-120
  - $1.8x10^{14}$ total vg dose and $1.2x10^{14}$ total vg cohorts demonstrated statistically significantly slowing of disease progression
  - Data only recently publicly presented
- Treatment with TSHA-120 was well tolerated
  - No signs of significant acute or subacute inflammation
  - No sudden sensory changes
  - No drug-related or persistent elevation of transaminases
- 6 patients beyond 3+ years initial treatment



Bönnemann, C. et al; 2020

Treatment with TSHA-120 resulted in a clear arrest of disease progression at therapeutic doses and long-term durability

TSHA-120
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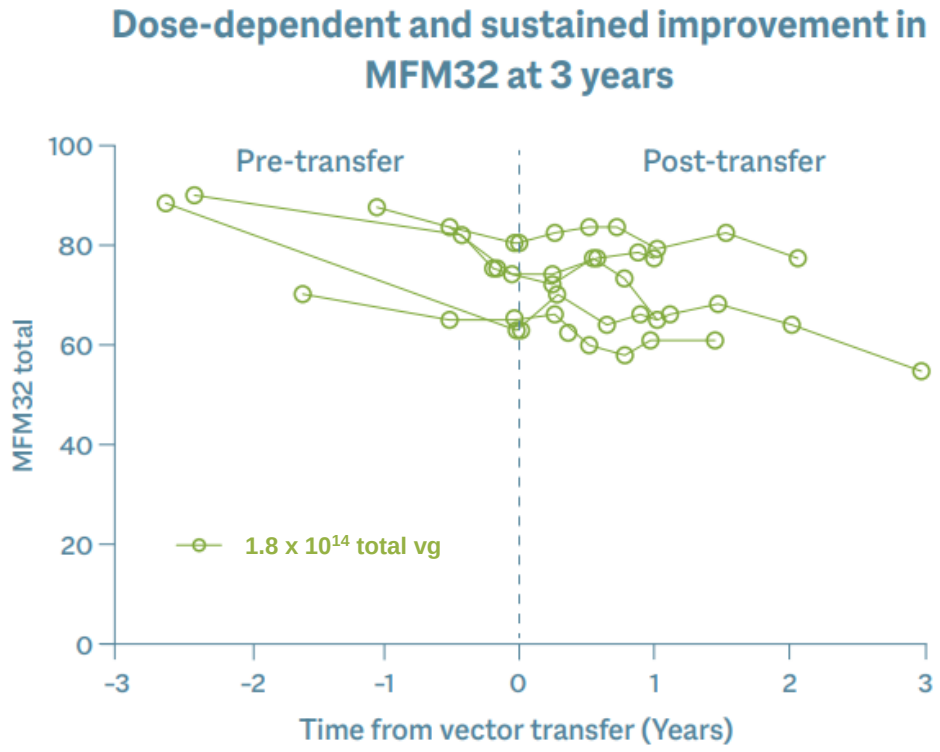

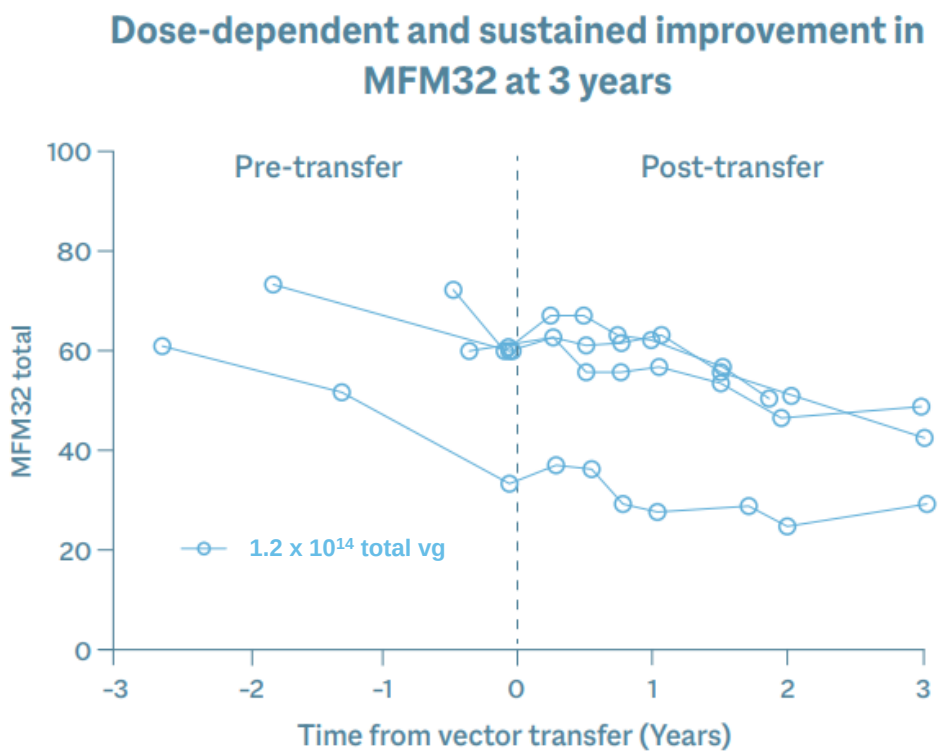

- Arrest of disease progression at therapeutic doses
- TSHA-120 was well tolerated at multiple doses

- 6 patients treated for 3+ years supporting long-term durability
- Plan to engage with agencies in US, EU and Japan to discuss regulatory pathway as soon as possible

Bönnemann, C. et al; 2020

Additional analysis using Bayesian methodology confirmed arrest of disease progression

TSHA-120
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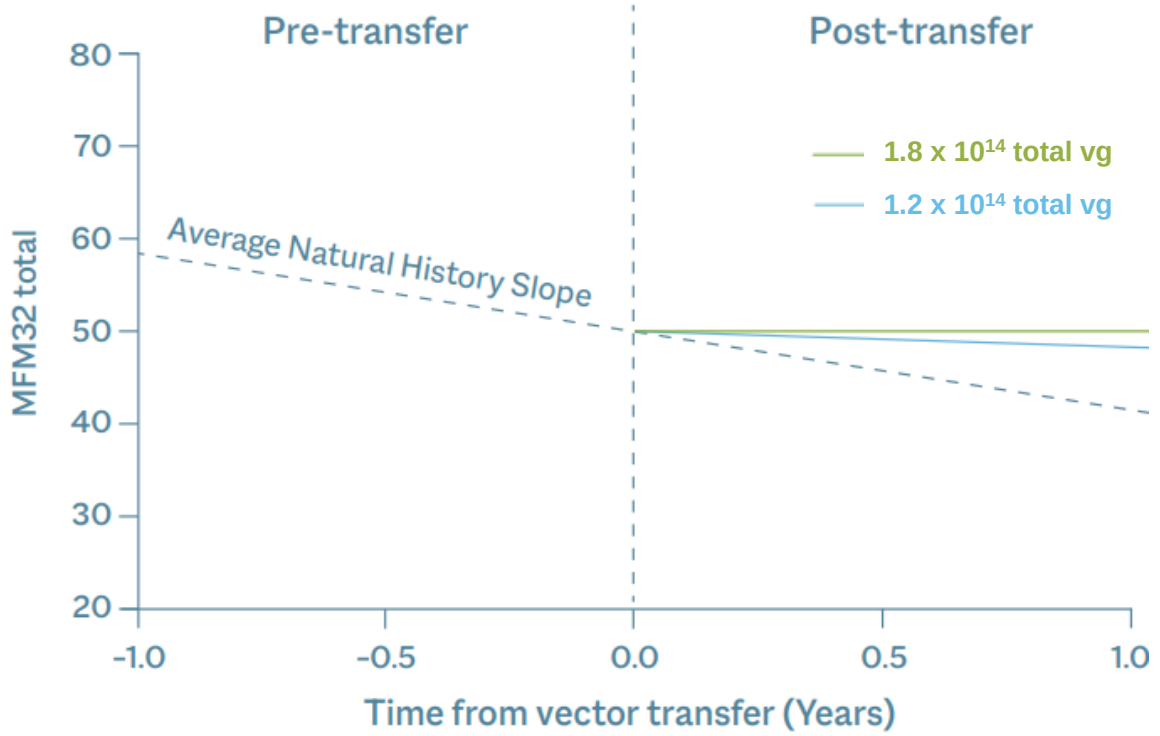
- Bayesian analysis
  - Enables direct probability statements about any unknown quantity of interest
  - Enables immediate incorporation of data gathered as the trial progresses
  - Useful and accepted by regulatory agencies when treating rare diseases and small patient populations
  - Can be used as a sensitivity analysis to support the more commonly accepted frequentist approach
  - Can be used as a way of statistically increasing the power of a clinical trial in a small patient population when used to incorporate auxiliary information
- Confirmed documented natural history data of an 8-point decline in the MFM32 total % score per year
  - 4-point decline in the MFM32 is clinically meaningful
- TSHA-120 dose of 1.8x10^{14} total vg resulted in an arrest of disease progression that was statistically significant



	Bayesian Analysis		Frequentist Analysis		
	Mean	Std Dev	Estimate	Std Error	p-Value
Post infusion: 1.8x10^{14} total vg	7.78	1.94	7.78	1.89	<0.001
Post infusion: 1.2x10^{14} total vg	6.09	2.11	6.07	2.05	0.004
Natural history decline	-8.19	0.74	-8.18	0.72	<0.001

Bönnemann, C. et al; 2020

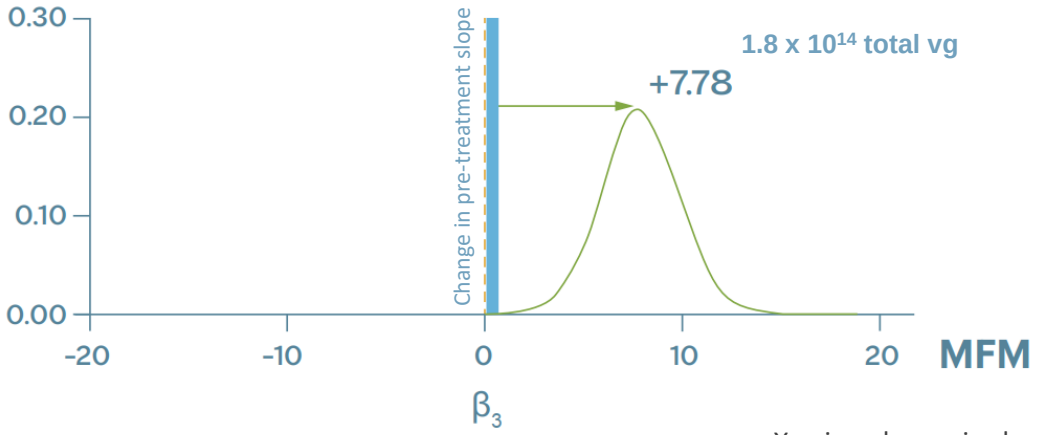
TSHA-120 halted patient pre-treatment rate of decline at 1.8x10^{14} total vg dose

TSHA-120
GAN

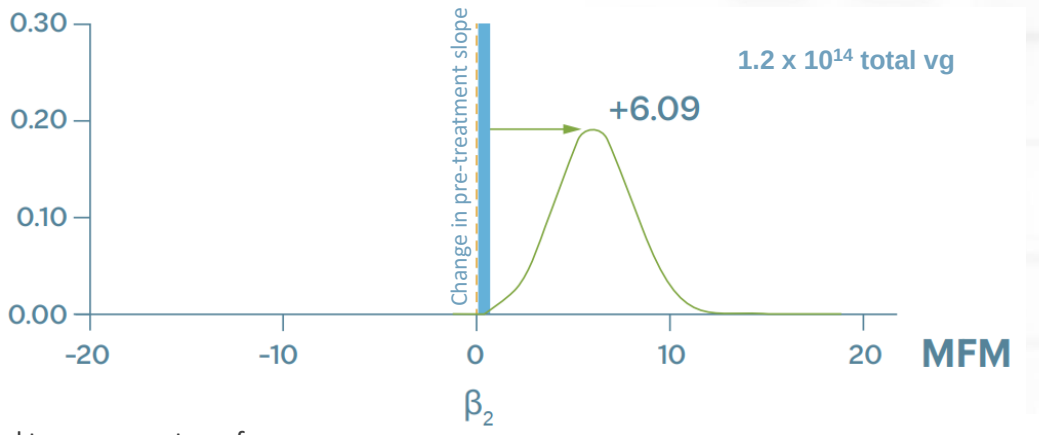
Bayesian Efficacy Analysis

Compared to individual historical data

Posterior distribution of β_3 (1.8 x 10^{14} total vg dose, noninformative prior)



Posterior distribution of β_2 (1.2 x 10^{14} total vg dose, noninformative prior)



X-axis = change in slope compared to pre-gene transfer
Blue line = pre-treatment change in slope = 0

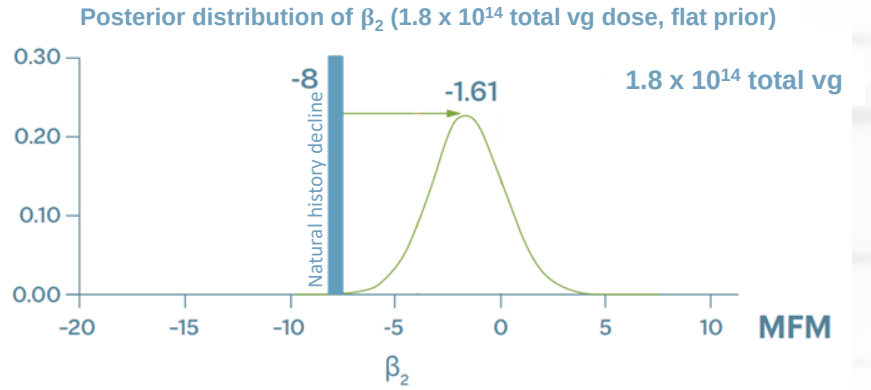
- Graphs depict treated population average annual post-treatment decline for both the 1.8x10^{14} total vg cohort and the 1.2x10^{14} total vg cohort
- 1.8x10^{14} vg halted patient pre-treatment rate of decline, avg annual slope improvement of 7.78 points
- 1.2x10^{14} vg resulted in clinically meaningful slowing of disease progression confirming dose response, avg annual slope improvement of 6.09 points
- Both doses showed superior result compared to natural decline of GAN patients

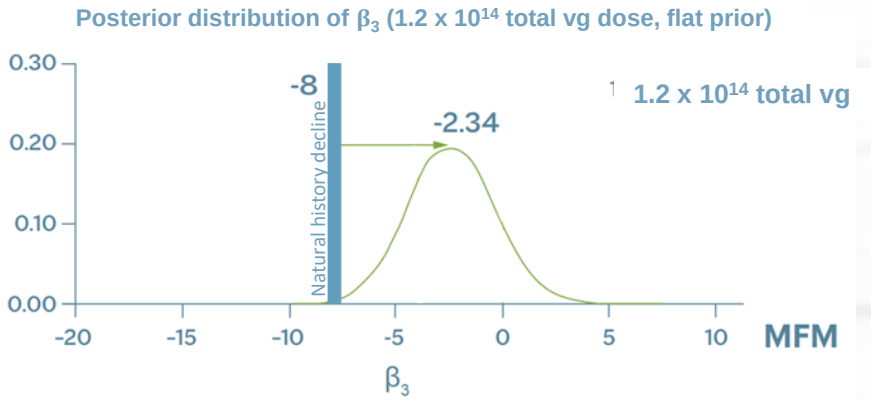
Bönnemann, C. et al; 2020

Further analyses confirmed nearly 100% probability of clinically meaningful slowing of disease compared to natural history

TSHA-120
GAN

- Further analyses were conducted to assess the probability of clinically meaningful slowing of disease as compared to natural history
- A 4-point decline in the MFM32 is considered clinically meaningful
- Graphs depict treated population annual decline for both the $1.8x10^{14}$ total vg cohort and the $1.2x10^{14}$ total vg cohort as compared to natural history
  - $1.8x10^{14}$ total vg dose confirmed nearly 100% probability of clinically meaningful slowing of disease compared to natural history decline of GAN patients
  - $1.2x10^{14}$ total vg dose confirmed approximately 85% probability of clinically meaningful slowing of disease and 100% probability of any slowing of disease





X-axis = annual decline in MFM32 total % score
Blue line = natural history decline (-8 points per year)

	Values = % Probability	
Change in disease progression	**$1.8x10^{14}$ total vg**	**$1.2x10^{14}$ total vg**
Any Slowing	99.9	99.8
Clinically meaningful slowing 50% or more	98.3	84.9

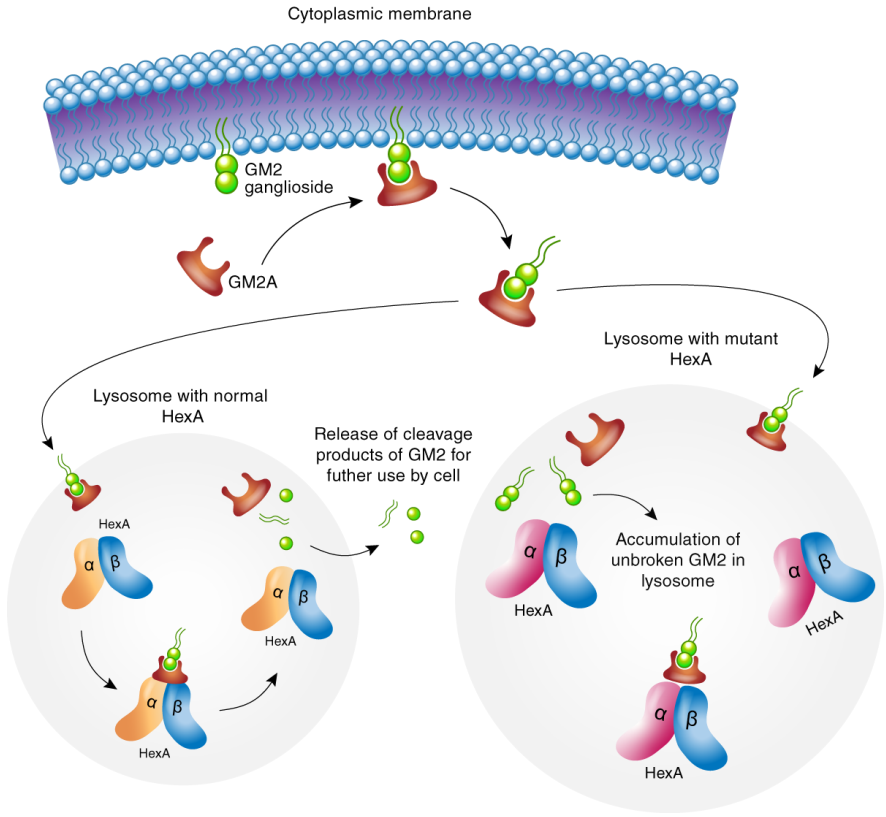
Bönnemann, C. et al; 2020

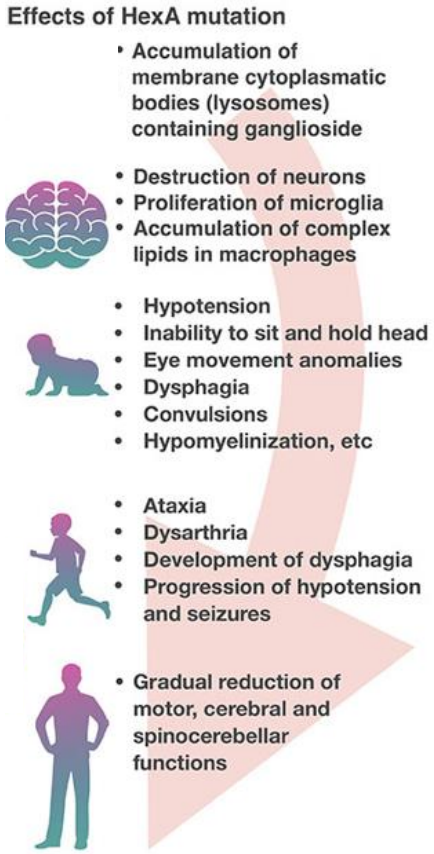
Anticipated next steps for TSHA-120 by the end of 2021

- Complete transfer data from the NIH
- Initiate manufacturing of commercial-grade GMP material
- Request an end-of-Phase meeting; discuss the regulatory pathway for TSHA-120
- Request regulatory guidance from EMA and PMDA
- Initiate new clinical sites in US and EU
- Update on regulatory interactions and current clinical program, including $3.5x10^{14}$ total vg cohort

GM2 gangliosidosis is a severe neurodegenerative disease

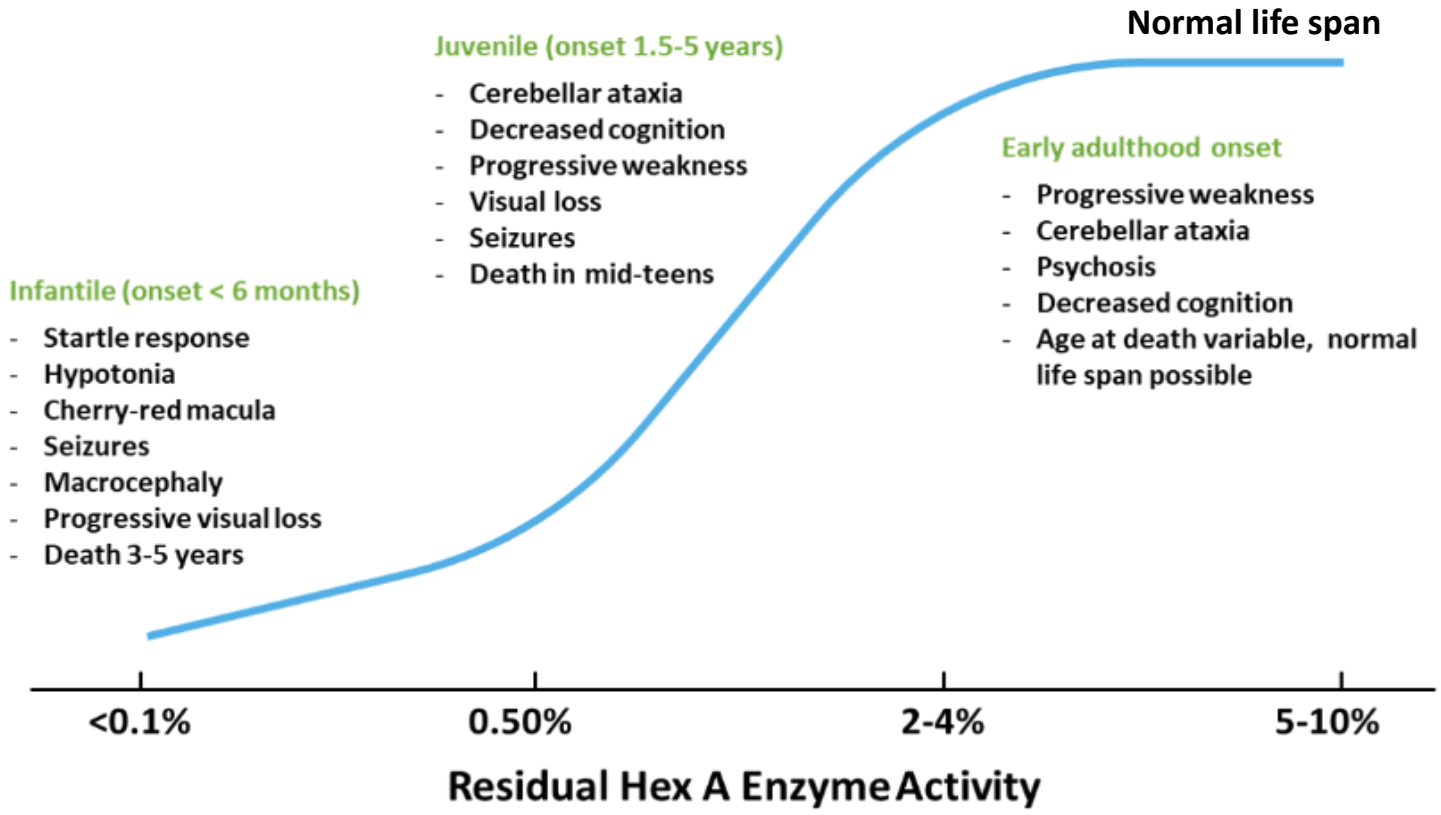
- GM2 gangliosidosis results from a deficiency in the β-hexosaminidase A (Hex A) enzyme
- Hex A is comprised of 2 subunits encoded by the alpha-subunit, *HEXA,* coded for by the *HEXA* gene, and the beta-subunit, *HEXB*, coded for the *HEXB* gene
- Mutations of the *HEXA* gene cause Tay-Sachs disease (TSD) while mutations of the *HEXB* gene cause Sandhoff disease (SD)
- The estimated prevalence is 500 patients (US+EU)
- Preliminary Phase 1/2 safety & biomarker data (Queen's University) expected in 2H 2021
- IND filing and initiation of US Phase 1/2 trial expected in 2H 2021
- Preliminary Phase 1/2 clinical data (Queen's University) expected by the end of 2021





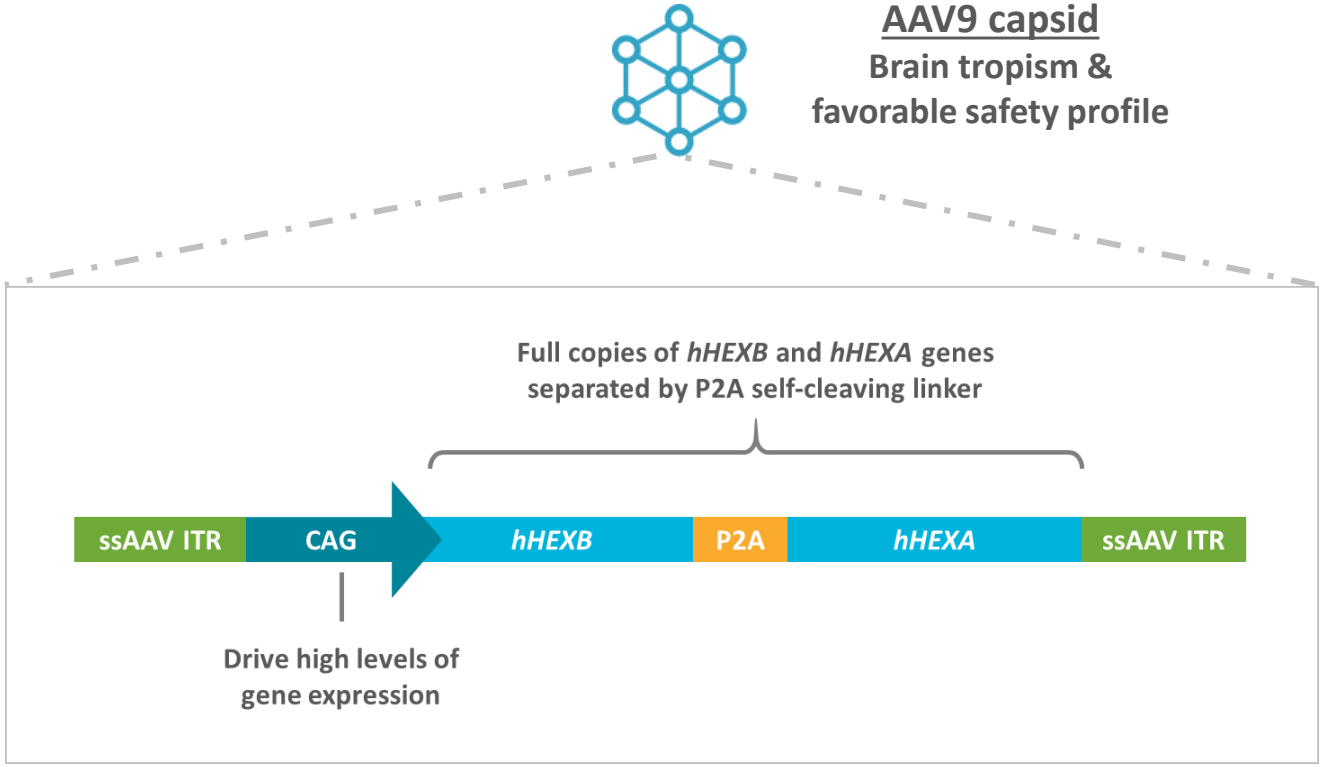
Residual Hex A activity determines the severity of GM2

- Small increases in Hex A activity may lead to significant improvements in clinical outcomes and quality of life
- Infantile onset is the most severe form of GM2
- Infantile forms may die within the first 4 years of life, and juvenile onset patients rarely survive beyond mid-teens

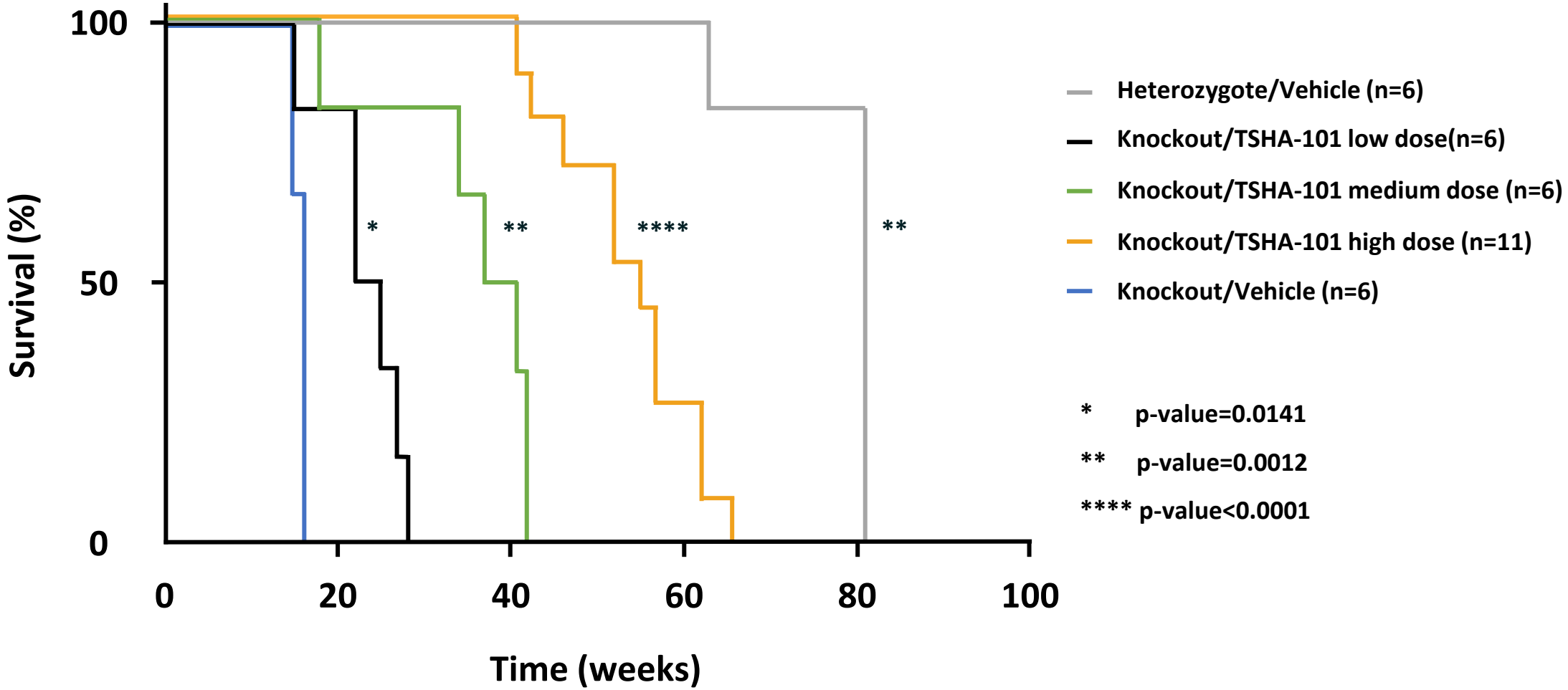


Novel bicistronic vector design allows consistent expression of *HEXA* and *HEXB* genes

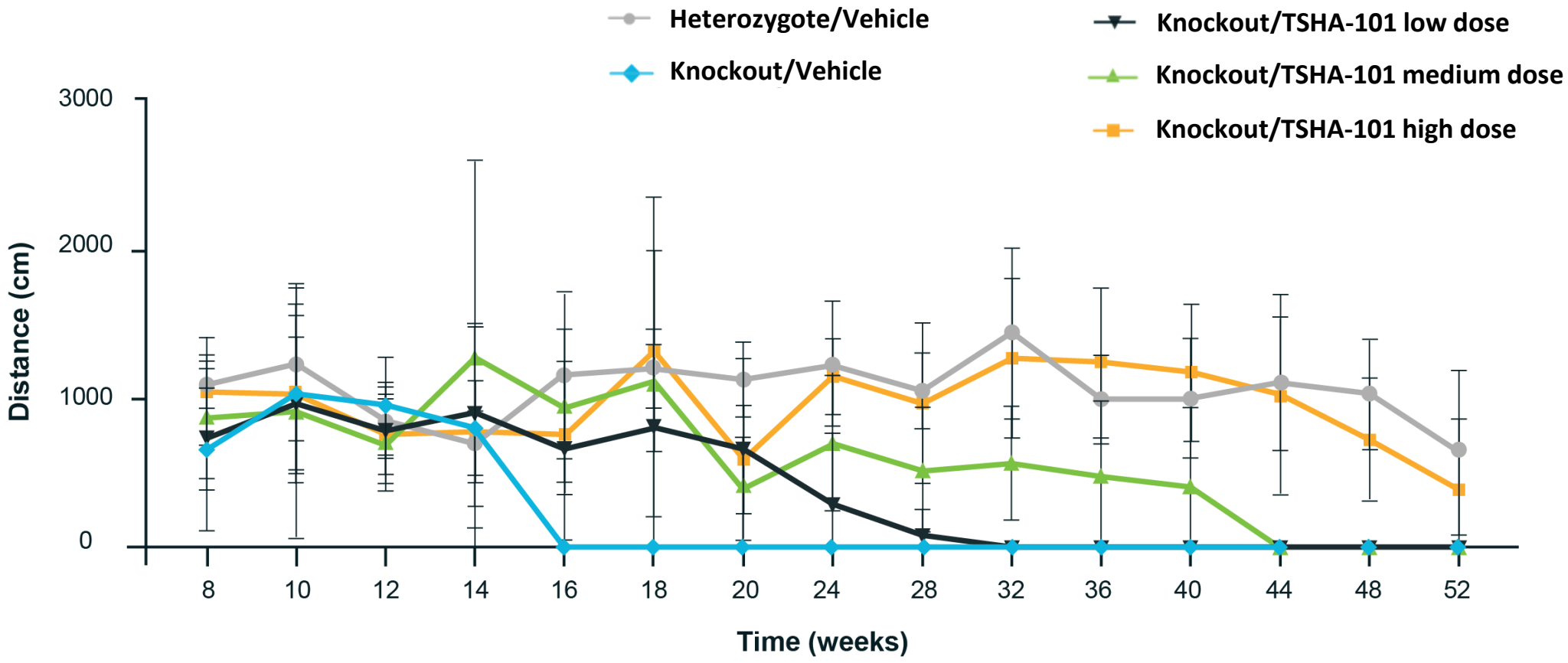
- *HEXA* and *HEXB* genes are required to produce the subunits of the beta-hexosaminidase A enzyme
- The novel bicistronic vector design enables 1:1 expression of the alpha-subunit, *HEXA,* and the beta-subunit, *HEXB,* under the control of a single promoter with a P2A-self-cleaving linker
- SD mice received vehicle or varying doses of TSHA-101 after 6 weeks:
  - High dose ($2.5x10^{11}$ vg/mouse)
  - Medium dose ($1.25x10^{11}$ vg/mouse)
  - Low dose ($0.625x10^{11}$ vg/mouse)
  - Vehicle controls



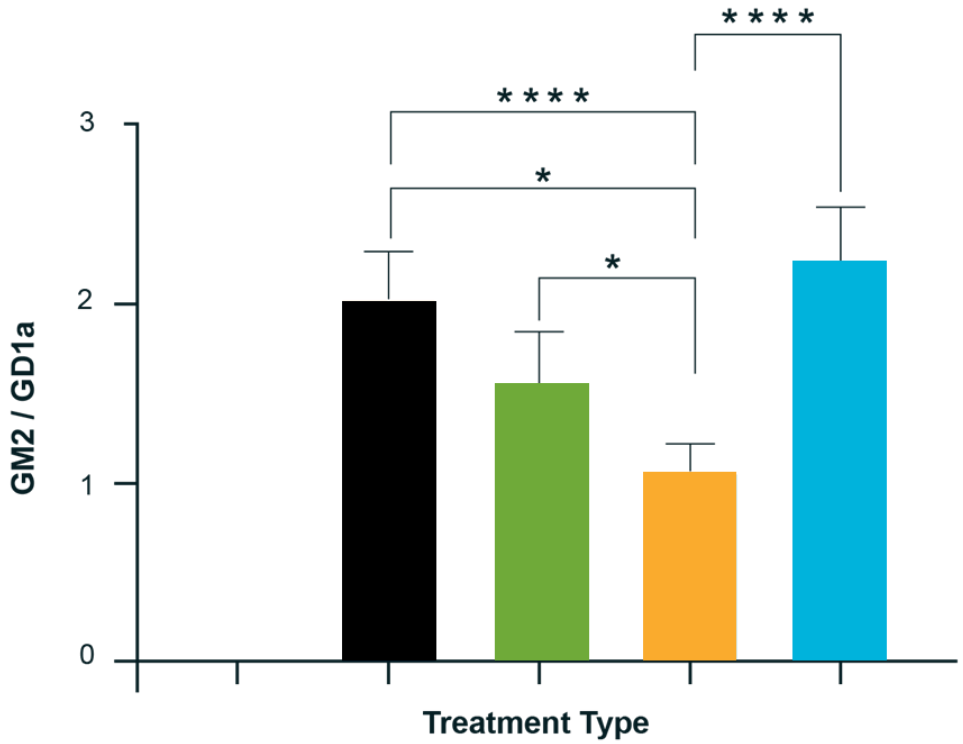
Significant, dose-dependent improvement in survival observed in mice treated with TSHA-101



Dose-dependent improvements observed in rotarod assessments in mice treated with TSHA-101



GM2 accumulation was significantly reduced in the mid-section of the brain following treatment with TSHA-101 after 16 weeks



Heterozygote/Vehicle (n=6)

Knockout/TSHA-101 low dose (n=6)

Knockout/TSHA-101 medium dose (n=6)

Knockout/TSHA-101 high dose (n=11)

Knockout/Vehicle (n=6)

**** p-value<0.0001

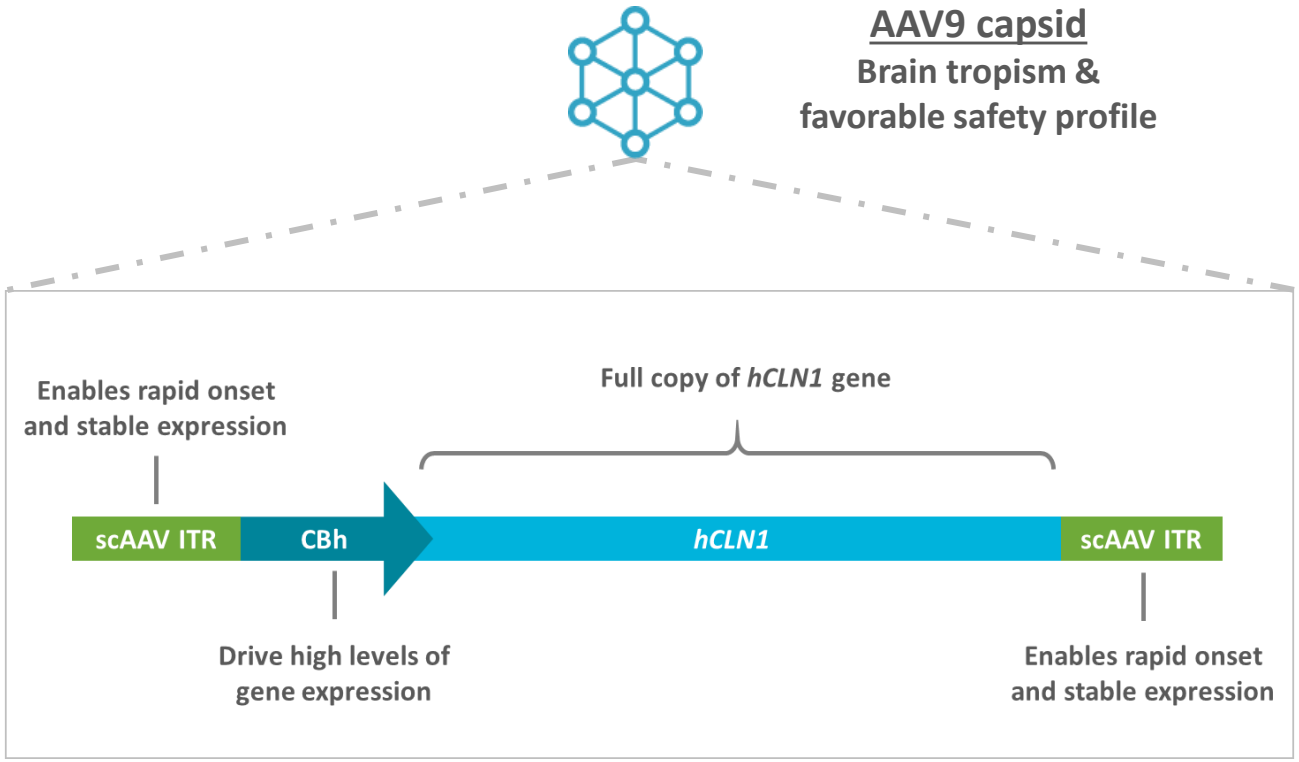
* p-value = 0.0179, 0.0295

Phase 1/2 adaptive trial for TSHA-101 in GM2 gangliosidosis

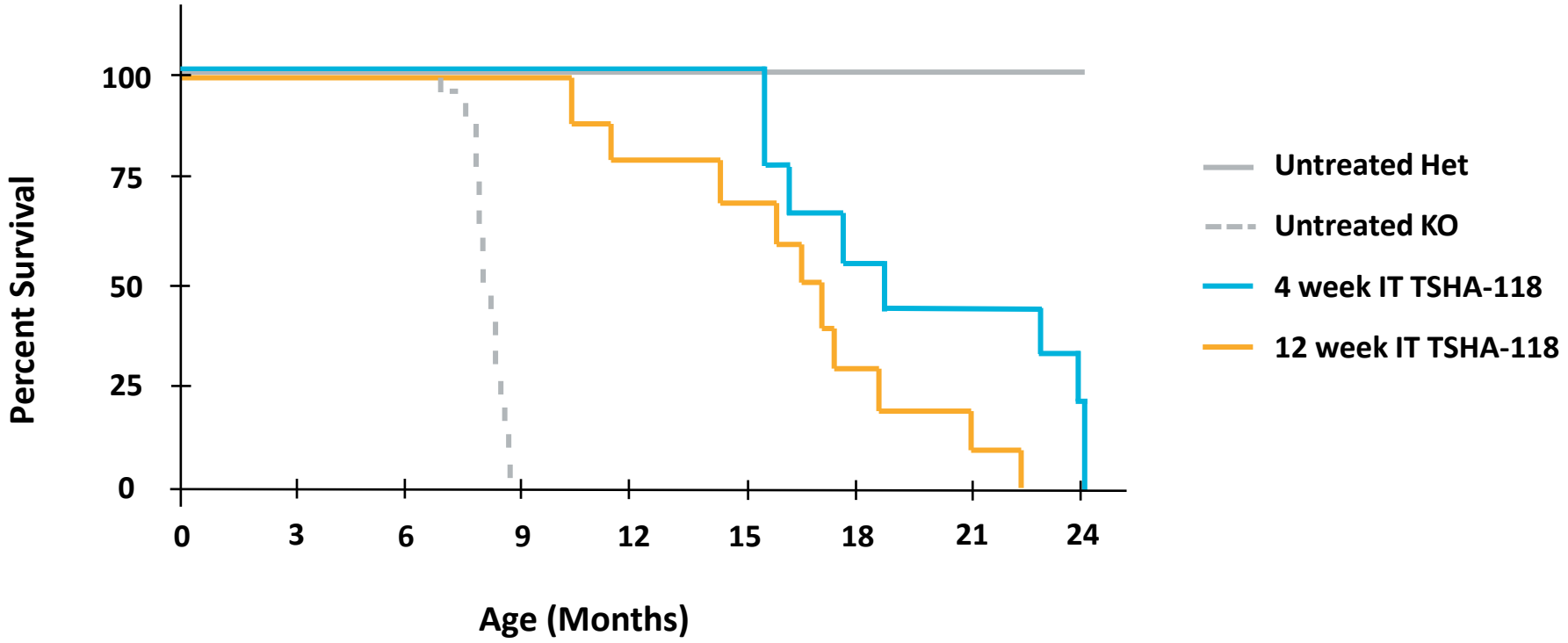
Study design and duration	• Open-label, single center, Phase 1/2 trial • Patients evaluated for one year, followed by longer-term extension
Patient cohort (n=4)	• Age younger than 1 year • Pathogenic confirmation of mutation in *HEXA* or *HEXB* gene • Patients not on ventilator support
Intervention	• Single total dose of $5x10^{14}$ vg of TSHA-101 (AAV9/*HEXB*-P2A-*HEXA)* • Delivered intrathecally
Key clinical assessments	• Safety and tolerability • Gross motor and fine motor milestones • Bayley score, CHOP-INTEND • Bulbar function/vocalization • Respiratory function • Seizure frequency/medications • Ophthalmological assessments • QOL and caretaker burden assessments
Key biomarker assessments	• Hex A enzyme in CSF and serum • GM2 accumulation in CSF • MRI changes

CLN1 disease is a severe neurodegenerative lysosomal storage disease

- Severe, progressive, neurodegenerative lysosomal storage disease, with no approved treatment
- Caused by mutations in the *CLN1* gene, encoding the soluble lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1)
- The absence of PPT1 leads to the accumulation of palmitoylated substrate within the lysosome
- Disease onset is typically within 6-24 months, with progression visual failure, cognitive decline, loss of fine and gross motor skills, seizures, and death usually occurring by 7 years of age
- The estimated prevalence of CLN1 disease is 900 patients (US+EU)
- Currently an open IND for this program
- Initiation of Phase 1/2 trial expected in 2H 2021

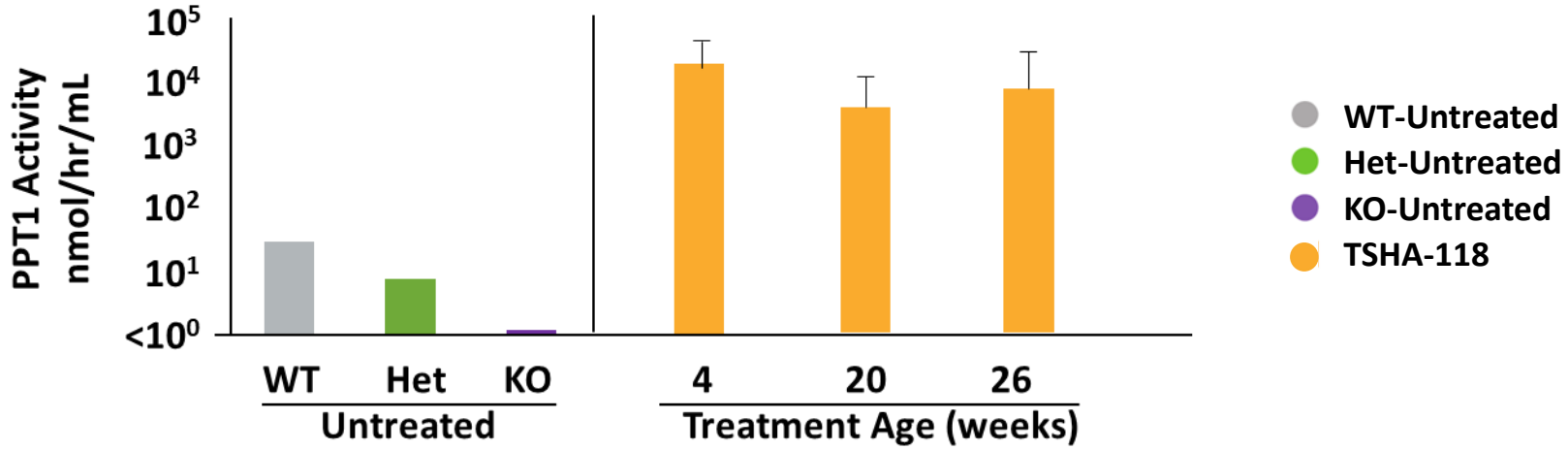


TSHA-118-treated CLN1 KO mice had improved survival rates



IT administration of TSHA-118 significantly extended survival of *PPT1* KO mice for all ages and at all dose levels

TSHA-118-treated CLN1 mice had increased and sustained plasma PPT1 activity



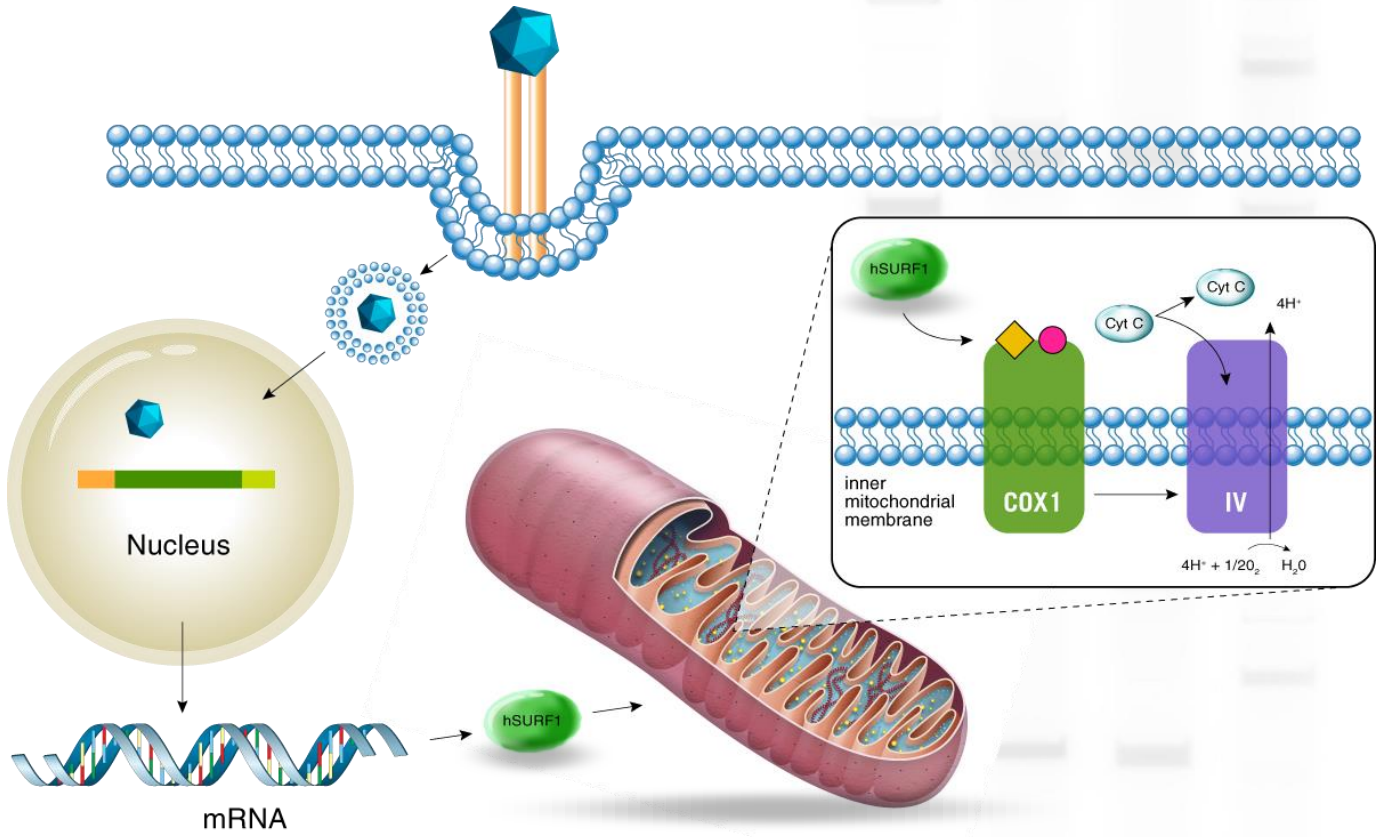
- Supraphysiological levels of active PPT1 were observed in all TSHA-118 treated mice and persisted through the study endpoint
- Persistence of effect after animal sacrificed up to 8.5 months post-treatment

Phase 1/2 adaptive trial for TSHA-118 in CLN1 disease

Study design and duration	• Open-label, dose finding, adaptive design trial • Patients evaluated for one year, followed by longer-term extension
Patient cohort (n=18)	• Infantile and juvenile patients • Pathogenic confirmation of mutation in *CLN1* gene • Patients not on ventilator support
Intervention	• TSHA-118 • Starting dose $5x10^{14}$ total vg IT
Key clinical assessments	• Safety and tolerability • Gross motor and fine motor milestones • UBDRS and Hamburg Battens scale • Bayley score, Vineland scale • Bulbar function/vocalization • Visual loss • Seizure frequency/medications • QOL and caretaker burden assessments
Key biomarker assessments	• PPT1 enzyme in CSF and serum • Accumulation of palmitoylated substrate in CSF • MRI changes

SURF1 deficiency is the most common cause of Leigh syndrome

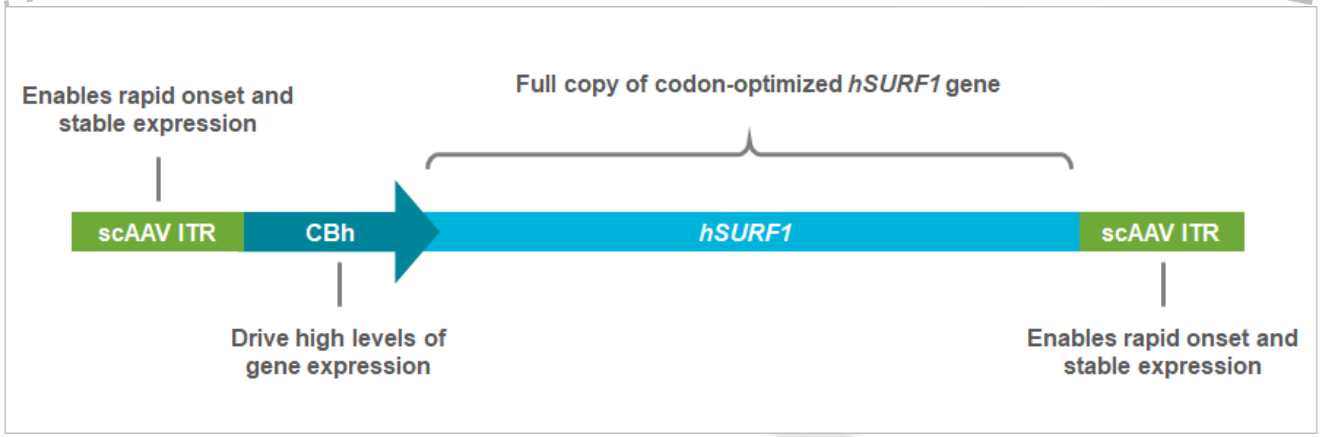
- A monogenic mitochondrial disorder
- Most common cause of cytochrome c oxidase deficient Leigh syndrome
- Leigh syndrome – severe neurological disorder that presents in the first year of life
  - Initially often presents with gastrointestinal symptoms
  - Progressive loss of mental and movement abilities, often regression is episodic in nature
  - Can result in death within two to three years
  - ~10-15% have SURF1 mutation
- No approved therapies
- Estimated prevalence of SURF1 deficiency is 300 to 400 patients (US+EU)



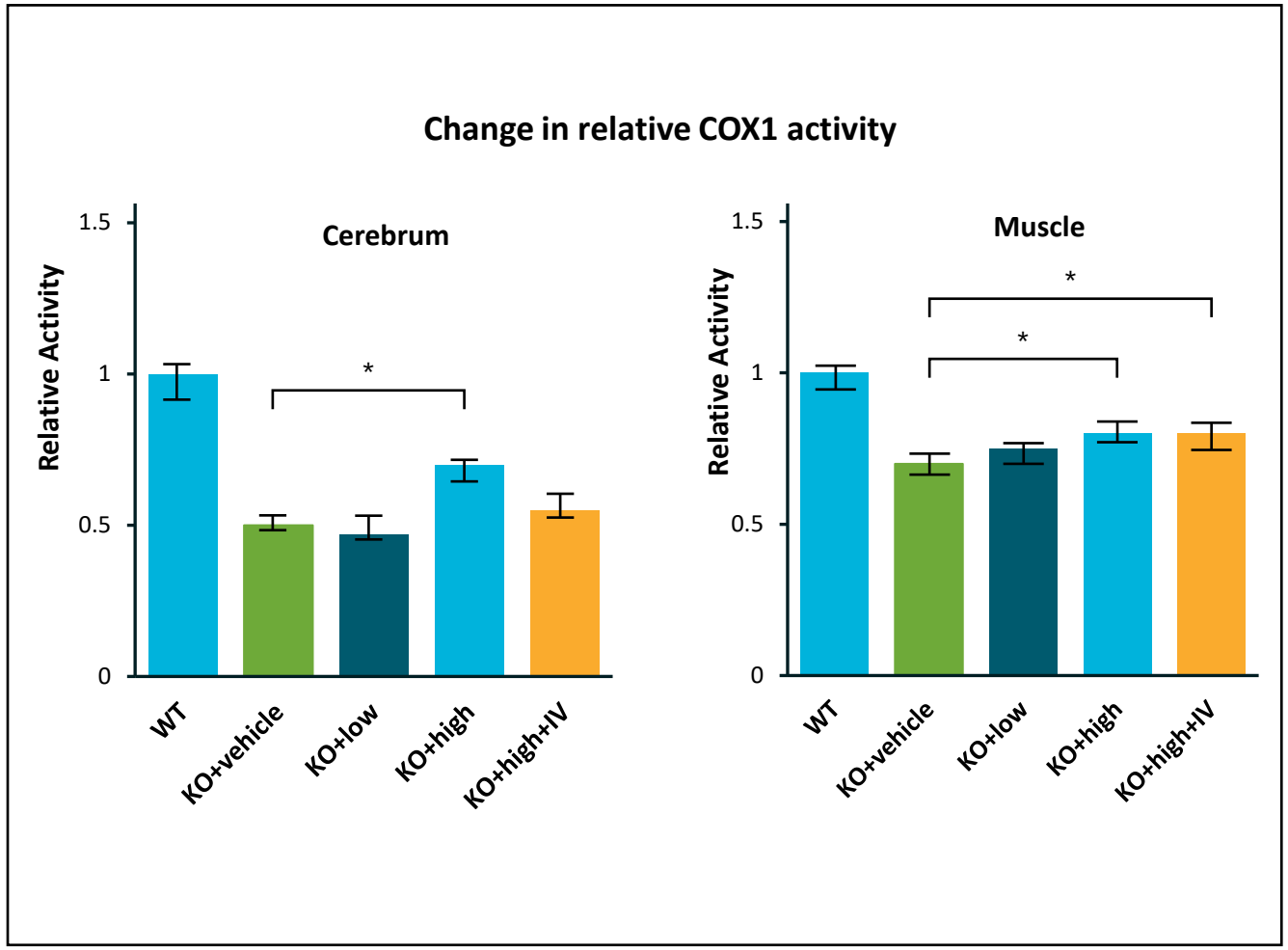
TSHA-104 IND or CTA filing expected in 2H 2021

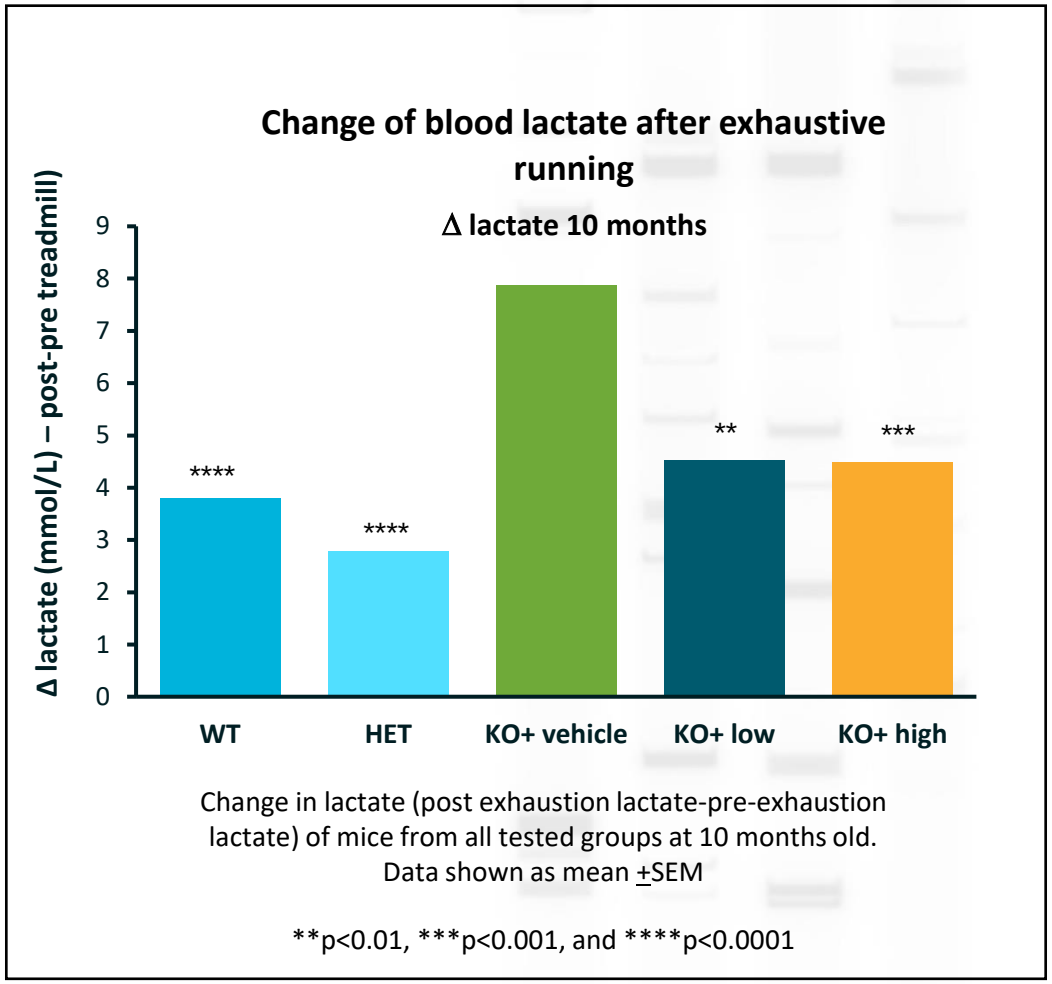
- Recombinant AAV9 viral vector with engineered transgene encoding the human SURF1 protein
- Designed to deliver a functional copy of the *SURF1* gene
- Received orphan drug and rare pediatric disease designations
- IND/CTA filing expected in 2H 2021
- Initiation of Phase 1/2 trial expected by the end of 2021

AAV9 capsid
Brain tropism & favorable safety profile



TSHA-104 increased COX1 activity in brain and muscle and restored elevation of blood lactate on exhaustive exercise in dose-dependent manner in SURF1 KO mice



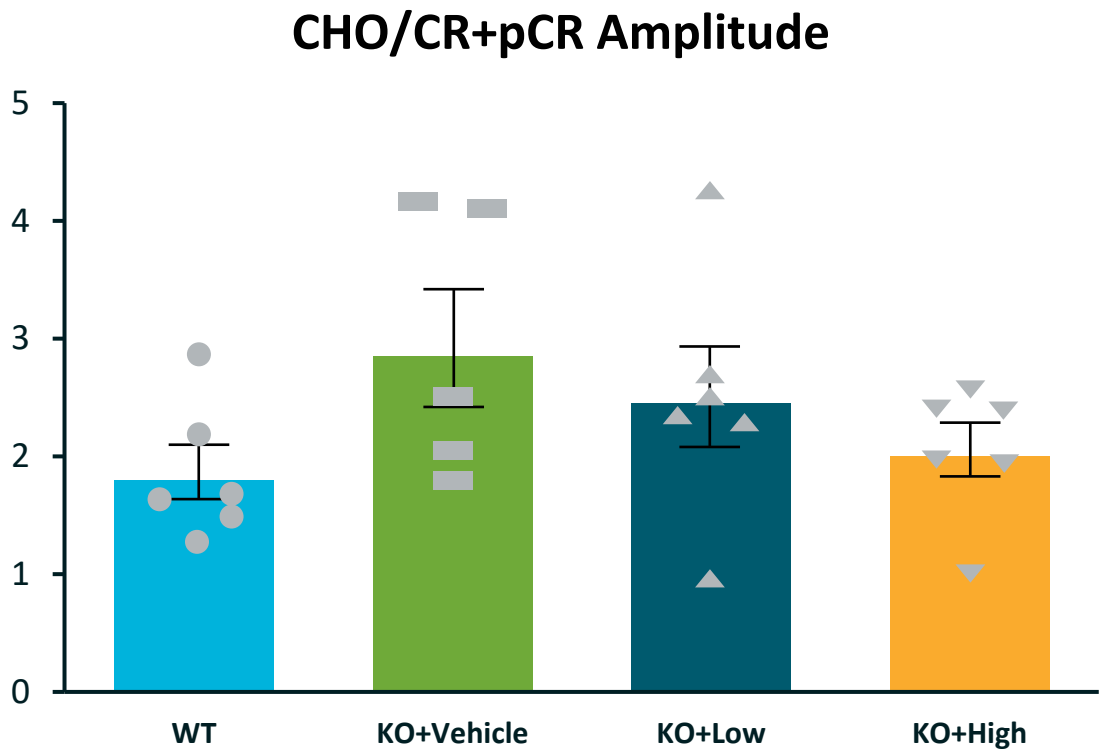


Change in lactate (post exhaustion lactate-pre-exhaustion lactate) of mice from all tested groups at 10 months old.
Data shown as mean ±SEM

**p<0.01, ***p<0.001, and ****p<0.0001

Ling, Q. et al. Gene Therapy for SURF1-Related Leigh Syndrome. ASGCT 2020.

TSHA-104 MR spectroscopy analysis – Reduction in choline levels reflective of reduction in brain inflammation

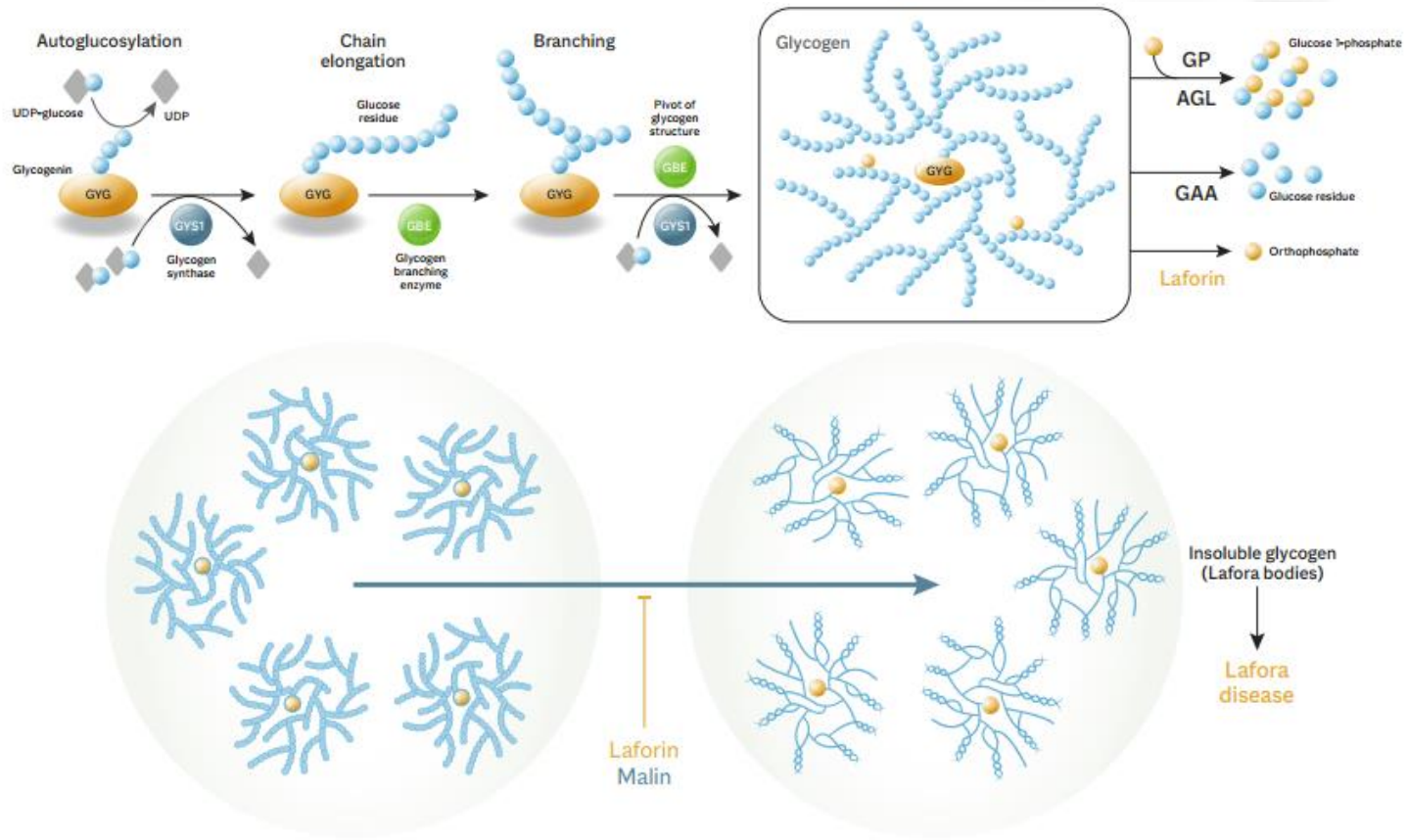


Phase 1/2 trial for TSHA-104 in SURF1 deficiency

Study design and duration	• Open-label, single center, Phase 1/2 trial • Patients evaluated for one year, followed by longer-term extension
Patient cohort (n=4)	• Pathogenic confirmation of mutation in *SURF1* gene • Patients not on ventilator support
Intervention	• Single total dose of $5x10^{14}$ total vg of TSHA-104 • Delivered intrathecally
Key clinical assessments	• Safety and tolerability • Gross motor and fine motor milestones • Bayley score, CHOP-INTEND, GMFM and vineland • Bulbar function/vocalization • Respiratory function • Seizure frequency/medications/EEG • QOL and caretaker burden assessments
Key biomarker assessments	• Lactate and pyruvate in serum and CSF • COX1 activity • MRI and MRS Spectroscopy

Lafora disease is a progressive and fatal neurodegenerative disorder

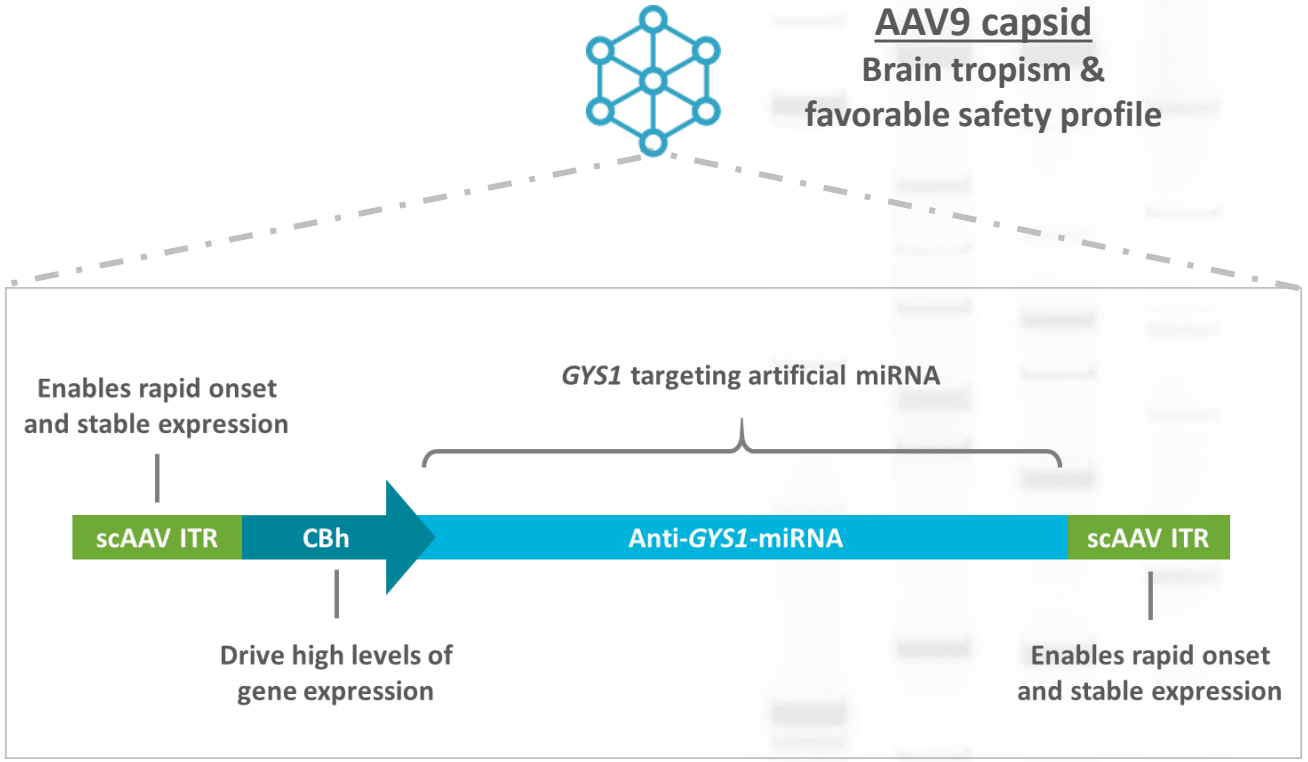
- Inherited, severe form of progressive myoclonus epilepsy
- Caused by loss of function mutations in the *EPM2A* (laforin) or *EPM2B* (malin) genes responsible for glycogen metabolism
- Absence of laforin or malin results in aggregates of polyglucosans or abnormally shaped glycogen molecules known as Lafora bodies
- Signs and symptoms include recurrent epileptic seizures in late childhood or adolescence, difficulty walking, muscle spasms and dementia
- Fatal within 10 years of onset
- No approved therapies
- Estimated prevalence of Lafora disease is 700 patients (US+EU)



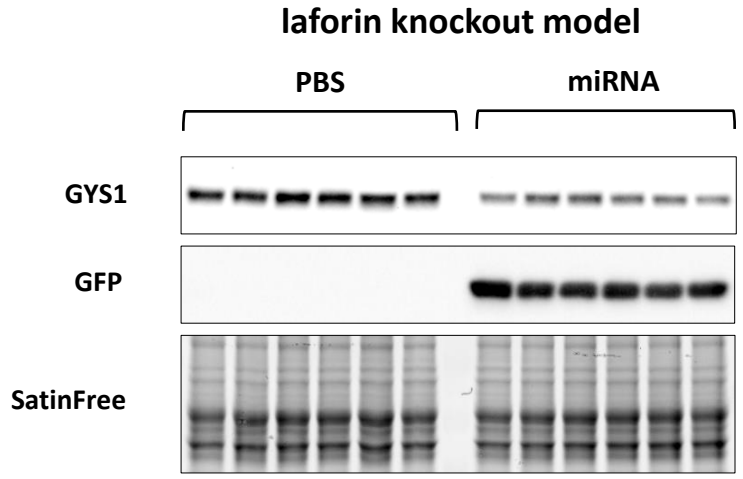
TSHA-111-LAFORIN and TSHA-111-MALIN, miRNA approaches

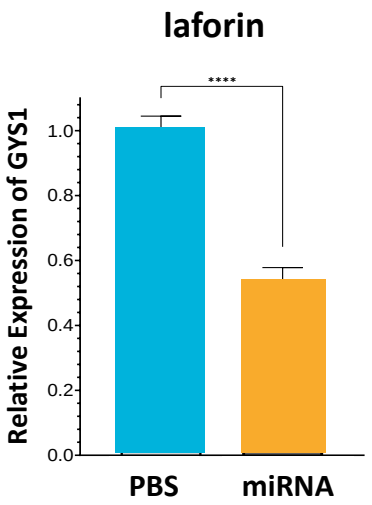
TSHA-111
Lafora disease

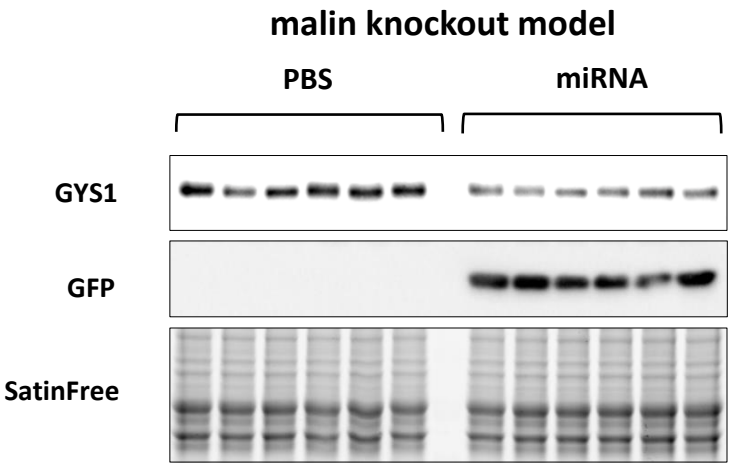
- Recombinant AAV9 viral vector designed for miRNA-mediated knockdown of the *GYS1* gene
- GYS1 knockdown designed to reduce Lafora bodies and improve clinical condition
- Self-complementary AAV capsid (scAAV) for rapid activation and stable expression
- CBh promoter drives high levels of expression
- Currently in IND/CTA-enabling studies

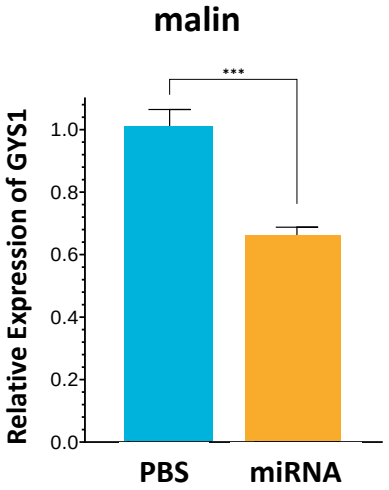


TSHA-111-LAFORIN and TSHA-111-MALIN reduced GYS1 expression in the laforin and malin KO models

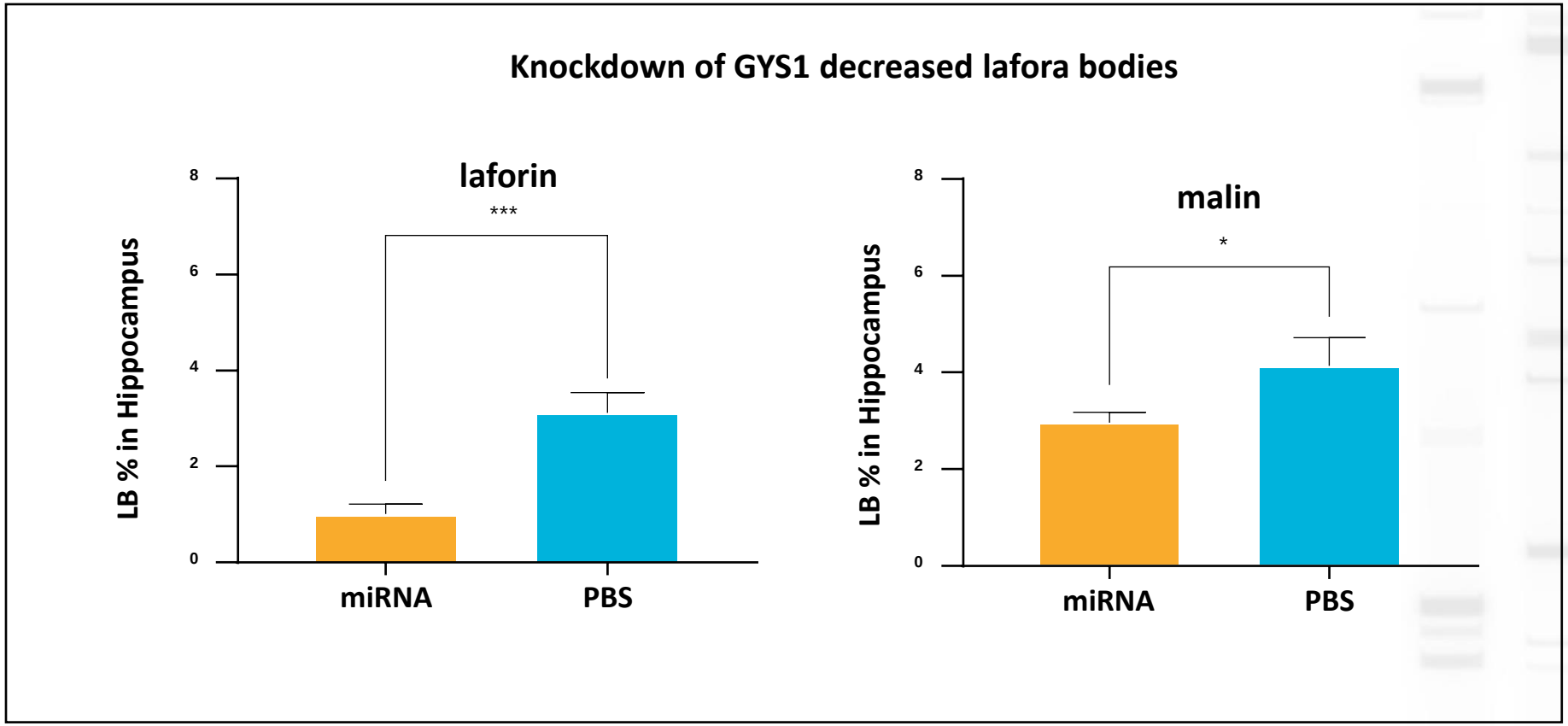






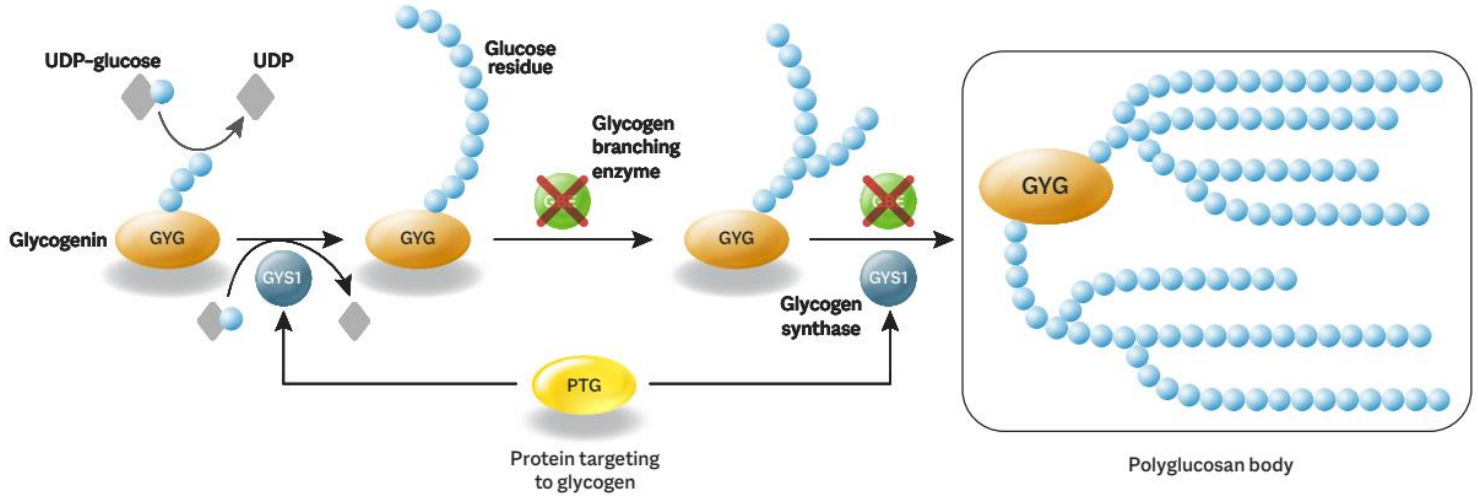


TSHA-111-LAFORIN and TSHA-111-MALIN decreased Lafora body formation in mice brain



Adult polyglycosan body disease (APBD)

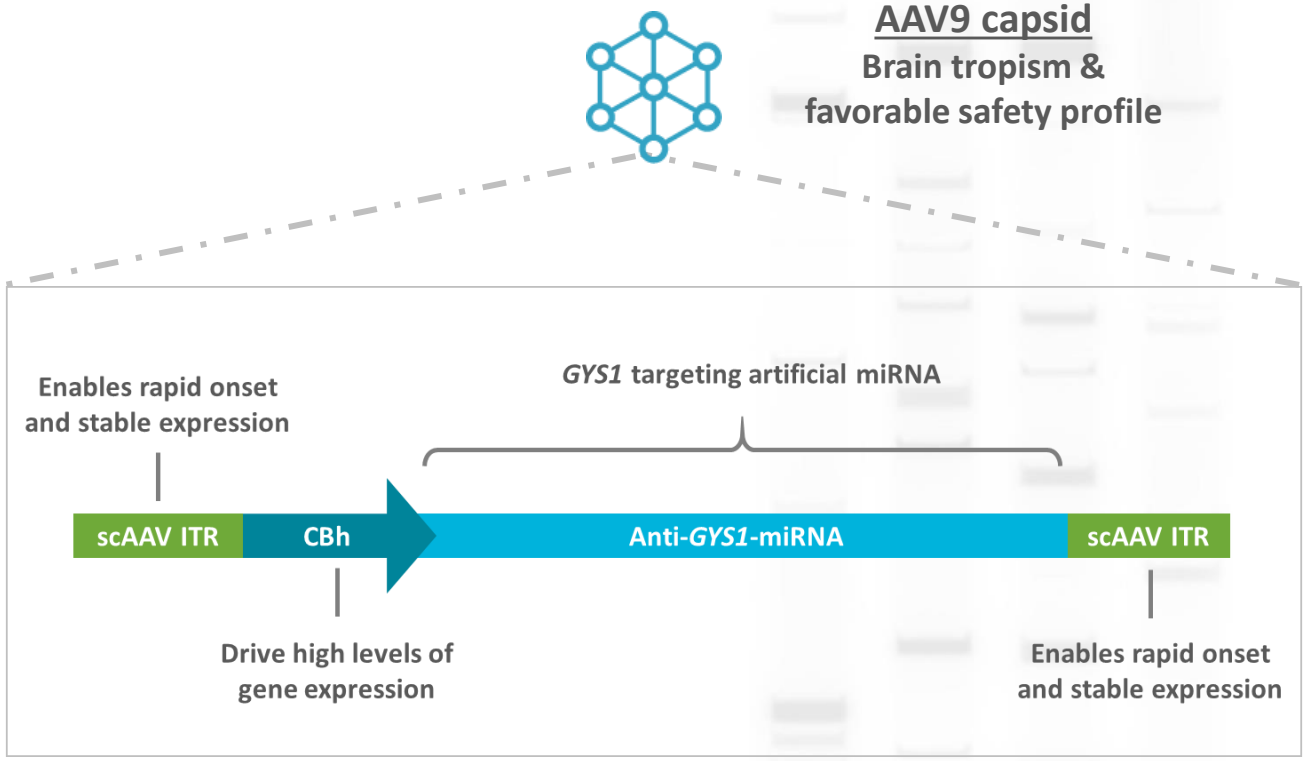
- Caused by a mutation in the *GBE1* gene, responsible for the creation of branches during glycogen synthesis
- Reduction in glycogen synthesis yields elongated glycogen changes that form poorly soluble aggregates in the liver, muscle and CNS
- Prime of life disease, with onset between 40-50 years
- Signs and symptoms include sensory loss in the legs, progressive muscle weakness, gait disturbances, mild cognitive impairment and urinary difficulties
- Often misdiagnosed as multiple sclerosis
- No approved therapies
- Estimated prevalence of APBD is 10,000 patients (US+EU)



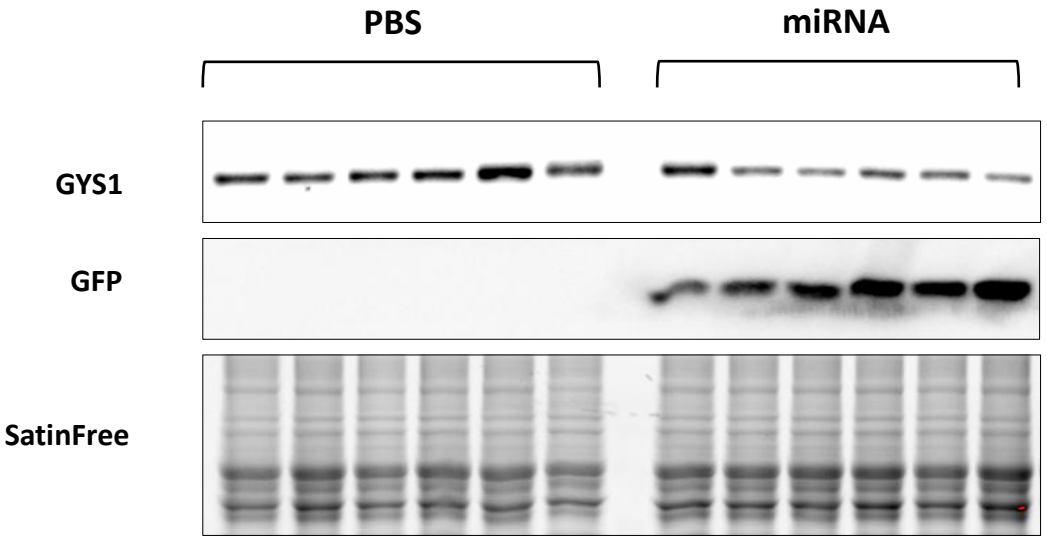
TSHA-112 expected to advance in IND/CTA-enabling studies in 2021

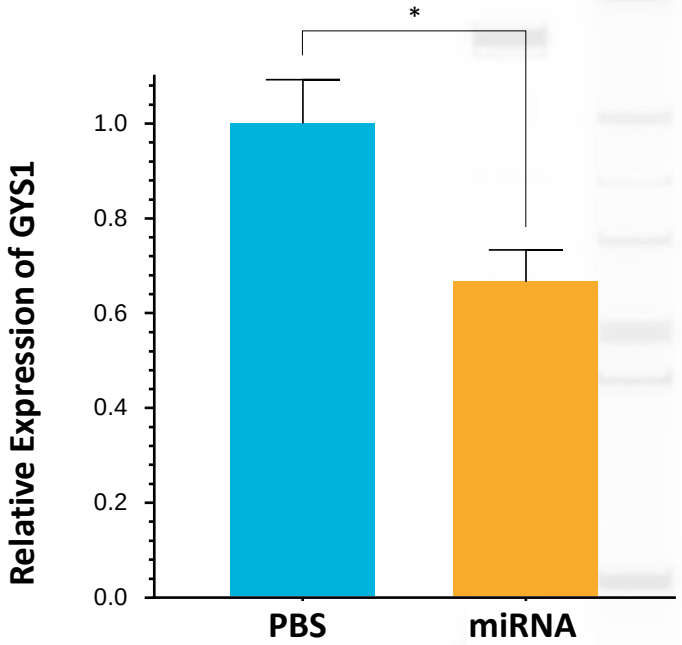
TSHA-112
APBD

- Recombinant AAV9 viral vector designed for miRNA-mediated knockdown of the *GYS1* gene to treat APBD
- Self-complementary AAV capsid (scAAV) for rapid activation and stable expression
- CBh promoter drives high levels of expression
- Currently in IND/CTA-enabling study



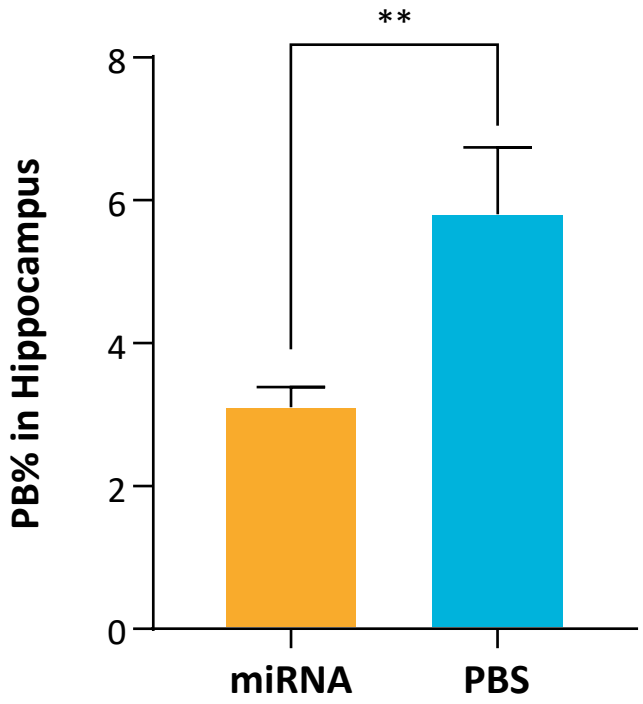
TSHA-112 reduced GYS1 expression in the APBD KO model





Gumusgoz, E. 2020

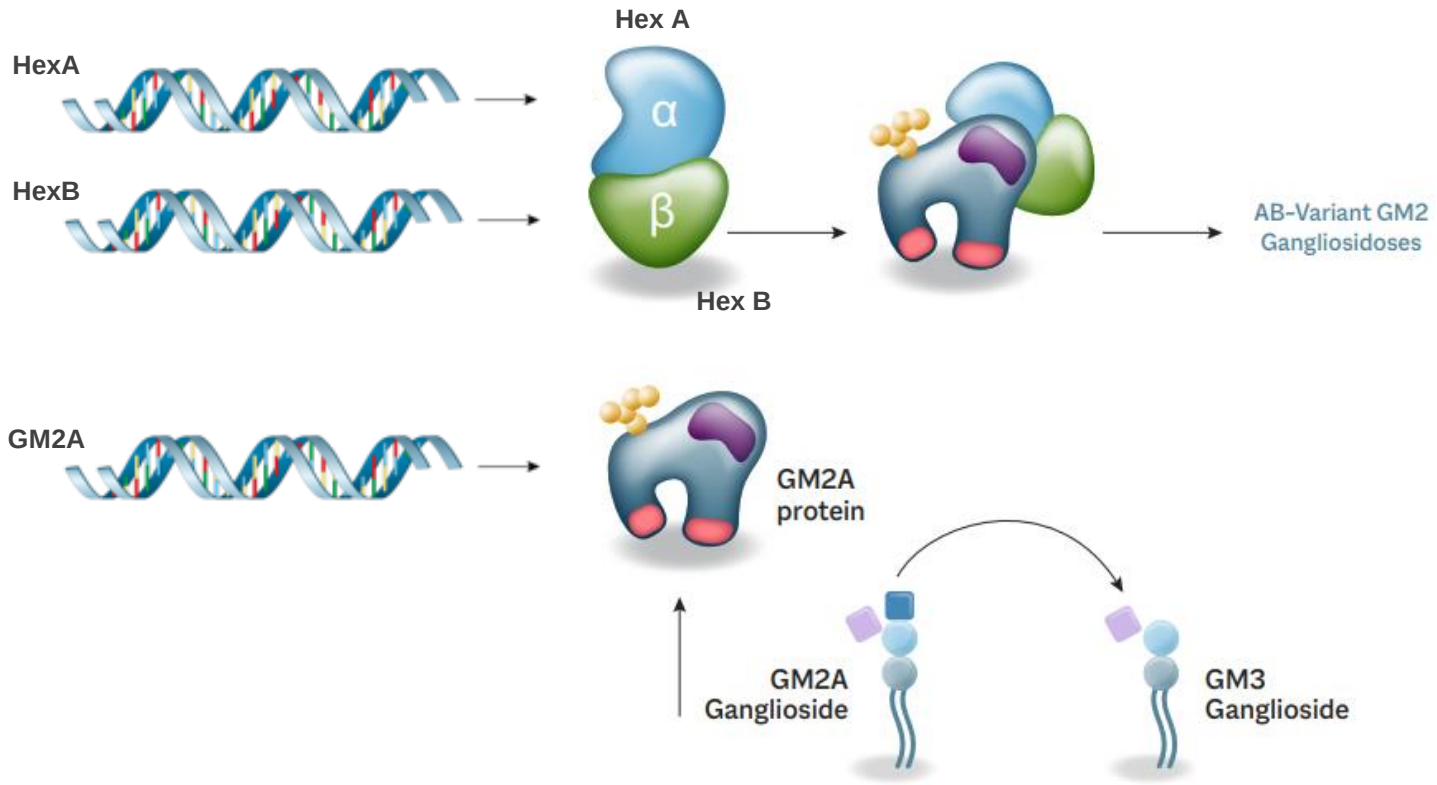
TSHA-112 decreased polyglucosan body formation in mice hippocampus



TSHA-112 decreased polyglucosan body formation in the hippocampus

GM2 gangliosidosis, AB variant

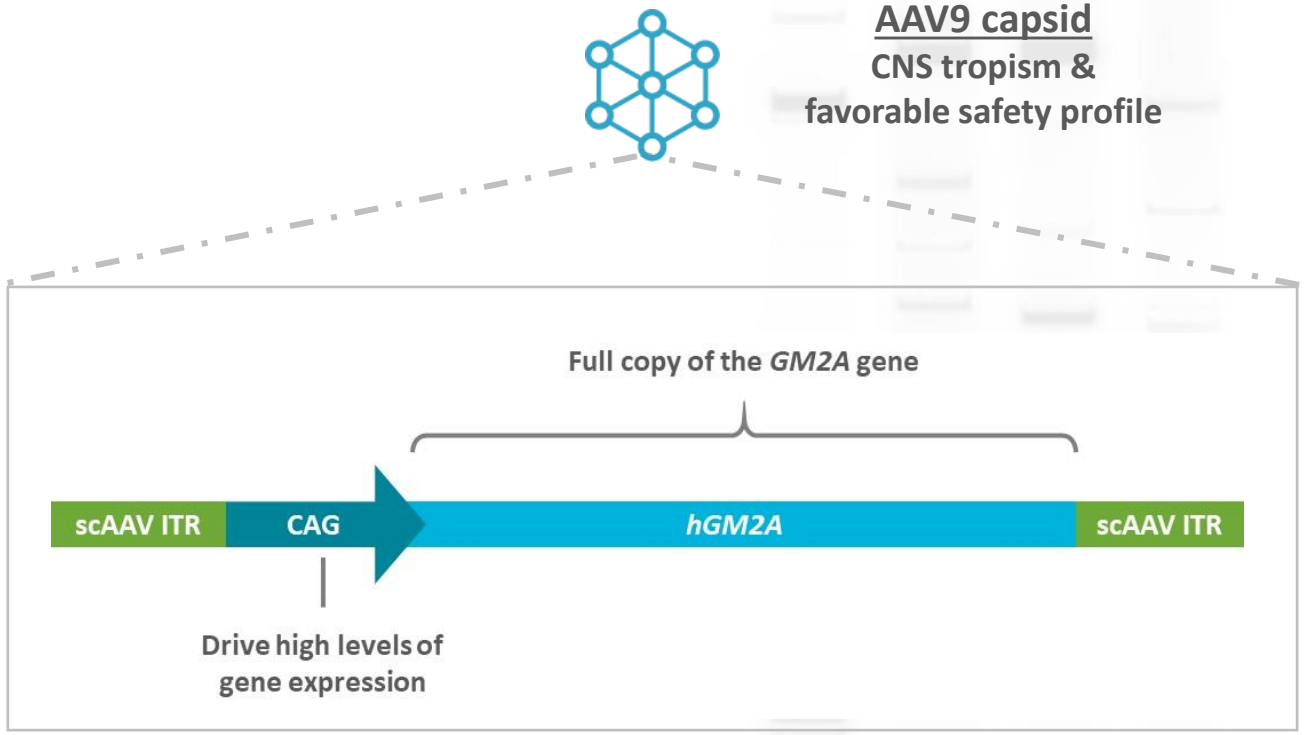
- Characterized by a mutation in the *GM2A* gene, leading to a deficiency of the GM2-activator protein (GM2AP), a required co-factor for the breakdown of GM2-gangliosides by the protein Hex A
- Loss-of-function mutations result in a deficiency of GM2AP causing intra-lysosomal accumulation of GM2 and other glycolipids in neuronal cells ultimately resulting in cell death.
- Signs, symptoms and progression mirror that of infantile GM2, and include seizures, vision and hearing loss, intellectual disability and paralysis and early death
- No approved therapies



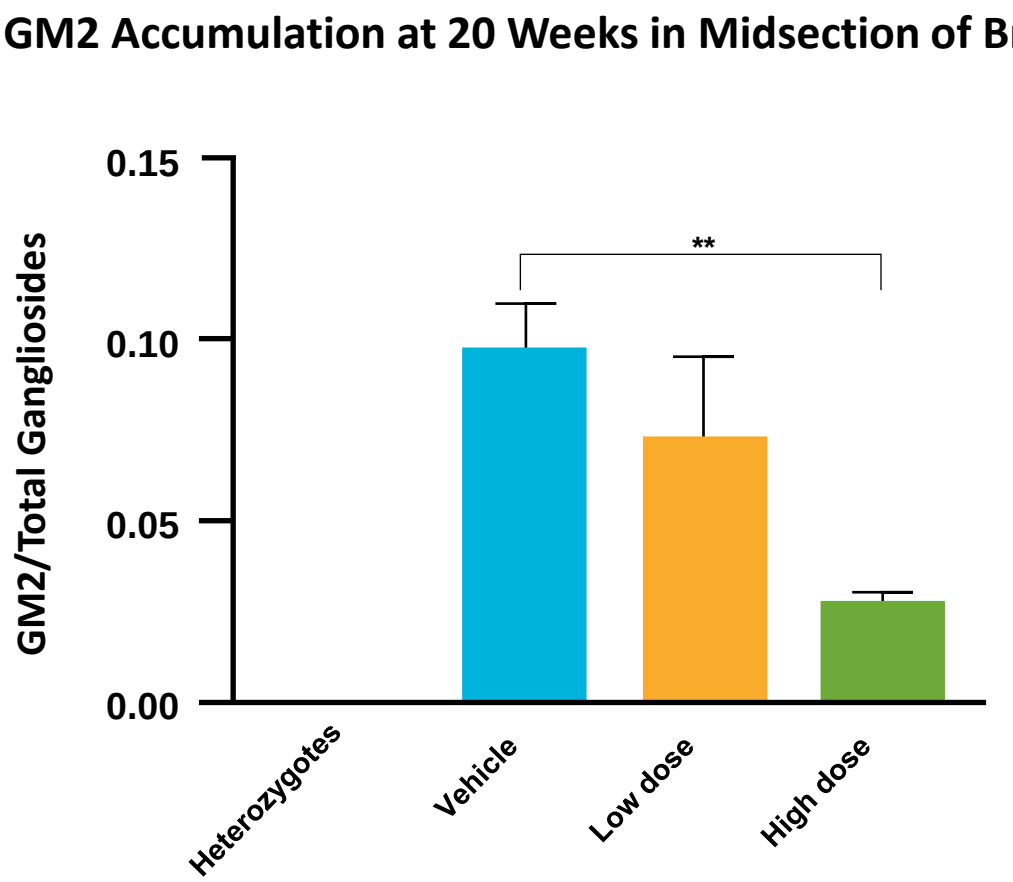
TSHA-119 in preclinical development

TSHA-119
GM2 AB Variant

- Self-complementary AAV9 viral vector for rapid activation and stable expression
- Designed to deliver a functional copy of the *GM2A* gene
- CAG promoter drives high levels of expression
- Proof-of-concept demonstrated in GM2A KO mouse model
- Currently in IND/CTA-enabling studies

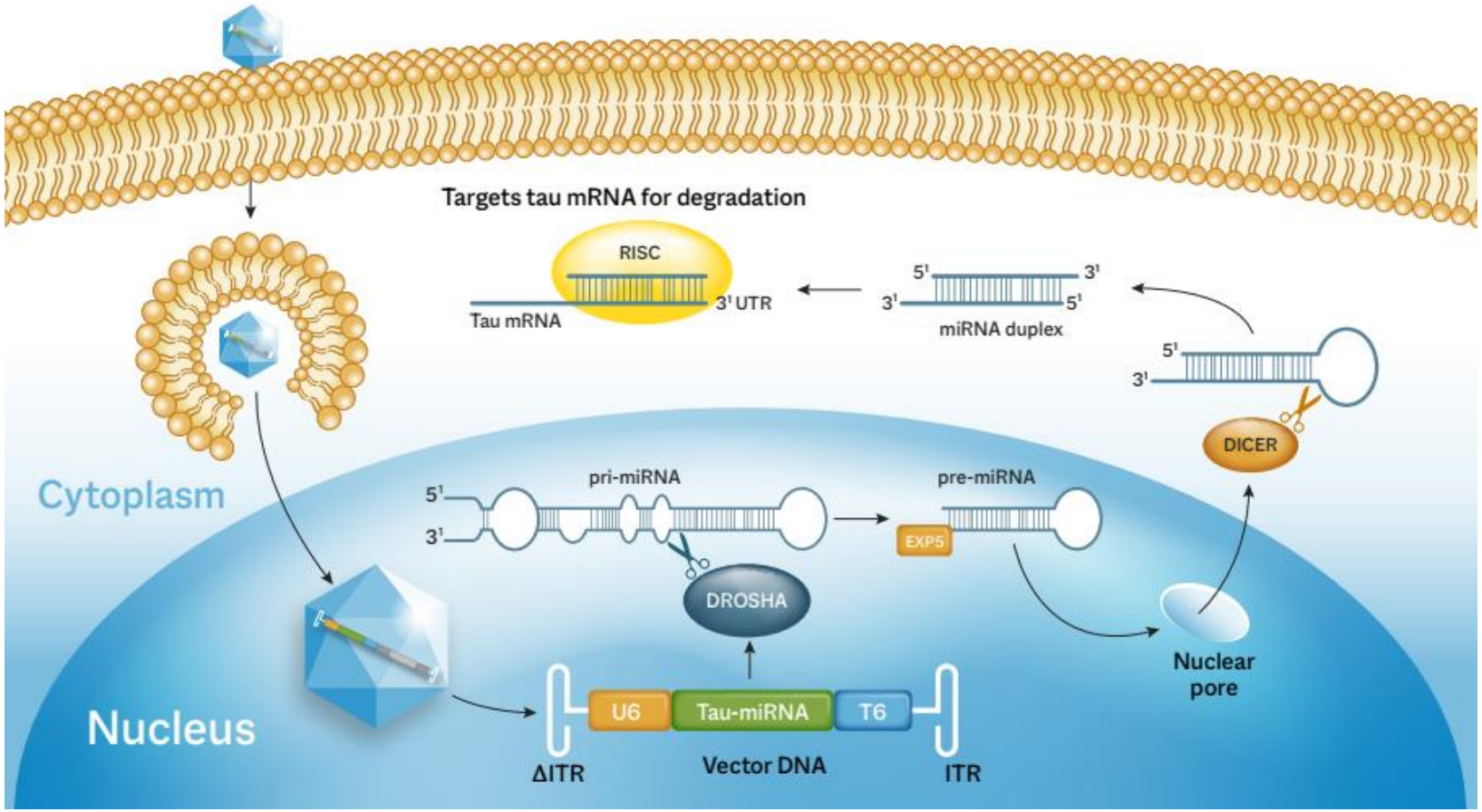


TSHA-119 caused a dose-dependent reduction of GM2 accumulation in mice



Tauopathies – Microtubule associated Protein Tau (MAPT)

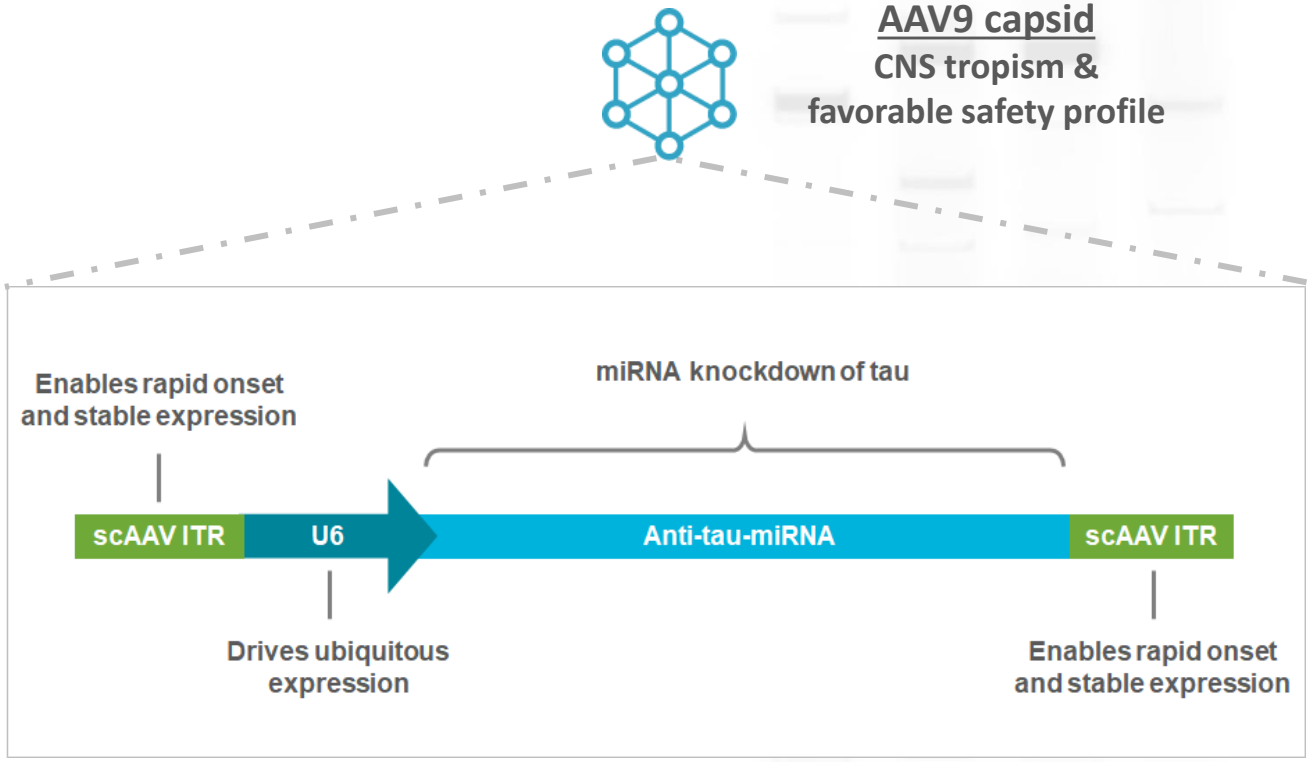
- Tauopathies are characterized by the accumulation of toxic tau protein in the brain that results in widespread neuronal dysfunction and loss
- Tau accumulation is thought to underpin several neurodegenerative diseases, including Alzheimer's, frontotemporal dementia (FTD), progressive supranuclear palsy, corticobasal degeneration, chronic traumatic encephalopathy and parkinsonism linked to chromosome 17
- Tau isoforms are expressed in the central and peripheral nervous systems
- We are employing tau-specific miRNA shuttles that have been designed to target mRNA for all six isoforms of tau found in the human brain and/or mouse brain
- Estimated prevalence of 13,000 patients with MAPT-FTD, PSP, CBD in the US and EU
- Estimated 6.2 million Americans and 7.8 million Europeans are living with Alzheimer's disease



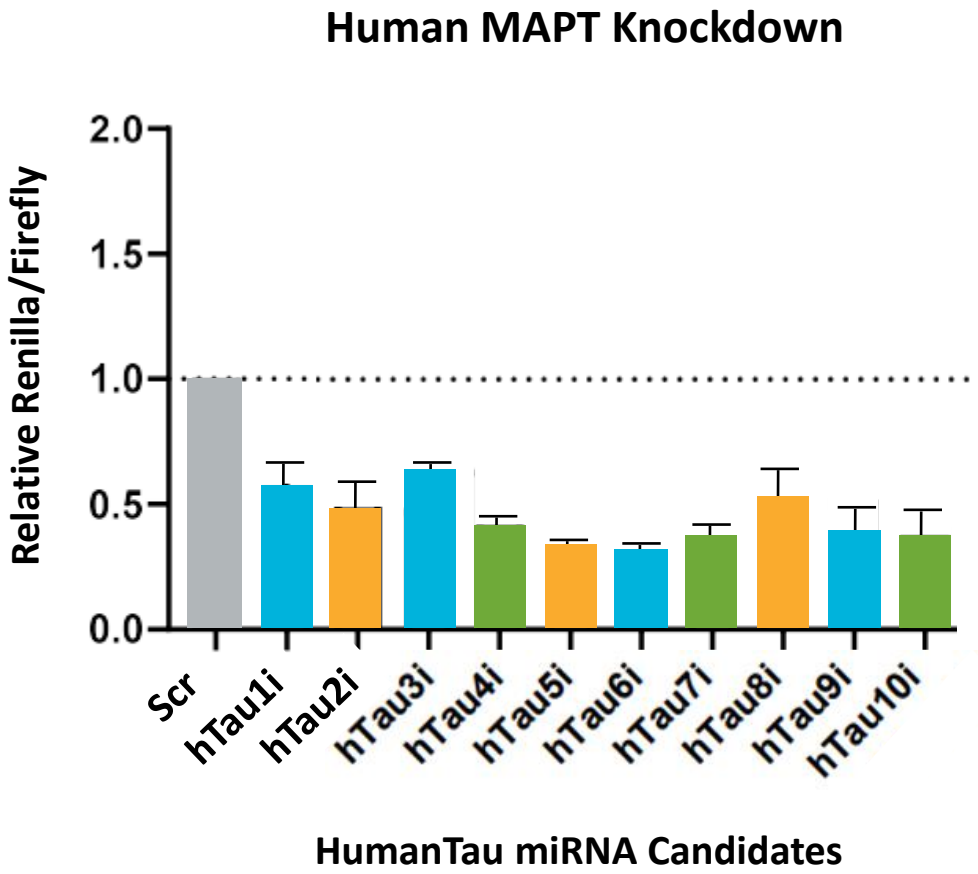
FTD – frontotemporal dementia; PSP – progressive supranuclear palsy; CBD – corticobasal degeneration

TSHA-113 in preclinical development

- Self-complementary AAV9 viral vector for rapid activation and stable expression
- Utilizes AAV-mediated gene silencing to deliver life-long reduction of tau protein levels in neurons following administration of a single dose
- U6 promoter drives ubiquitous expression
- Currently in preclinical development



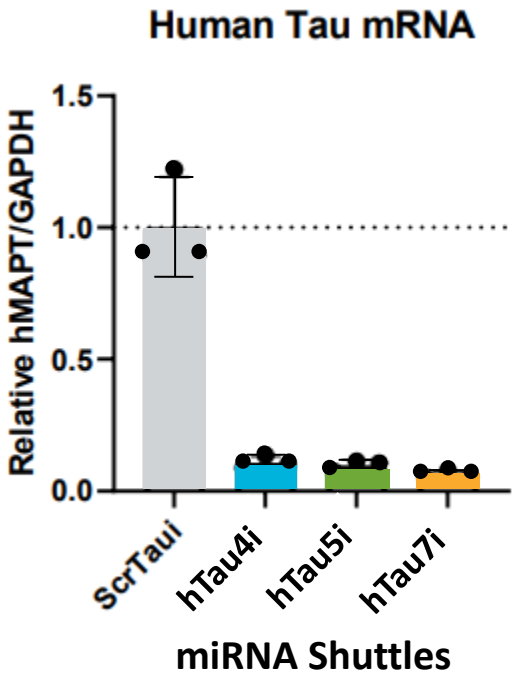
Primary screen of human tau miRNA candidates

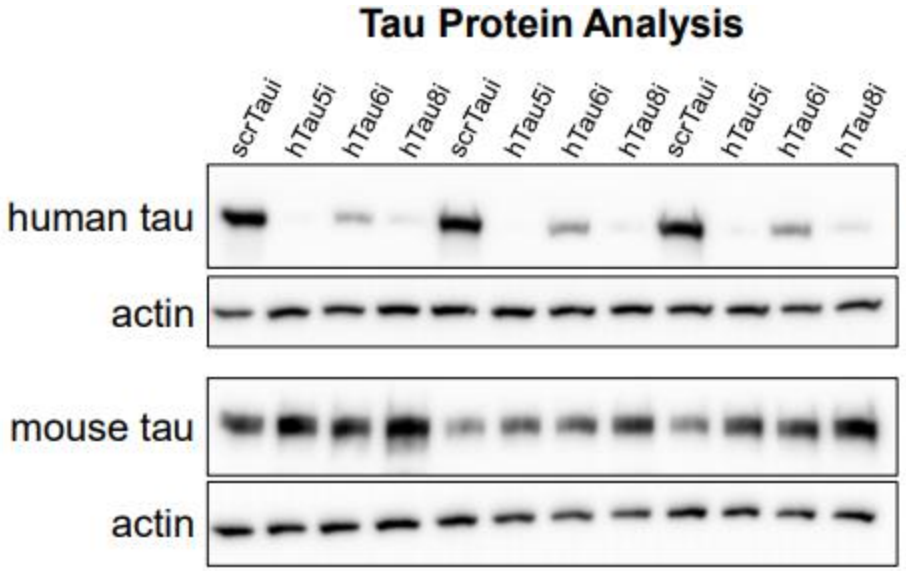


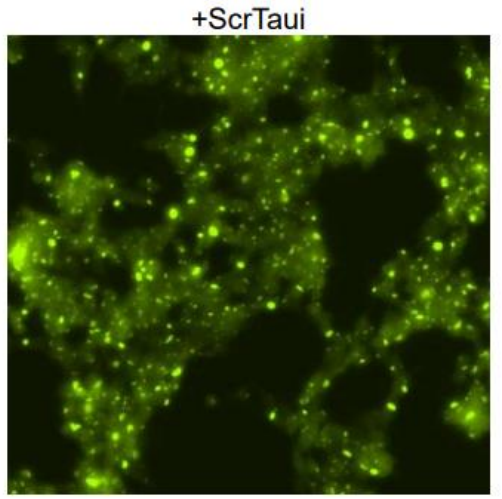
Secondary screening of top candidates: hTau4i, hTau5i, and hTau7i

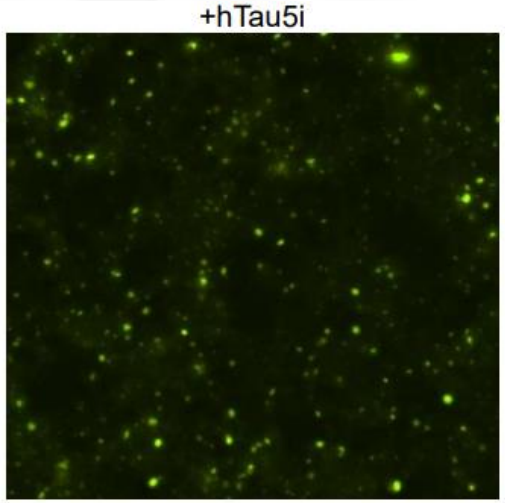
Scr = scrambled tau miRNA
hTau = human-specific tau miRNA

TSHA-113 reduced K18 tau expression

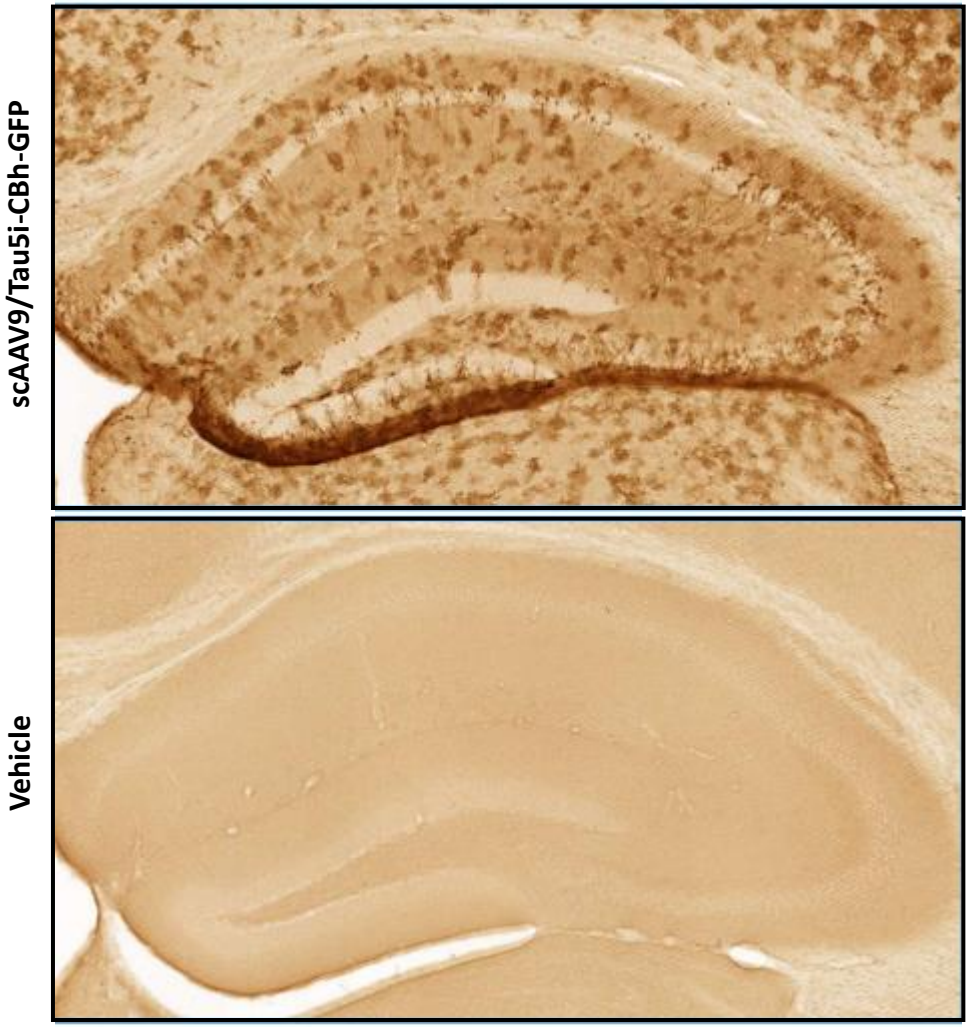


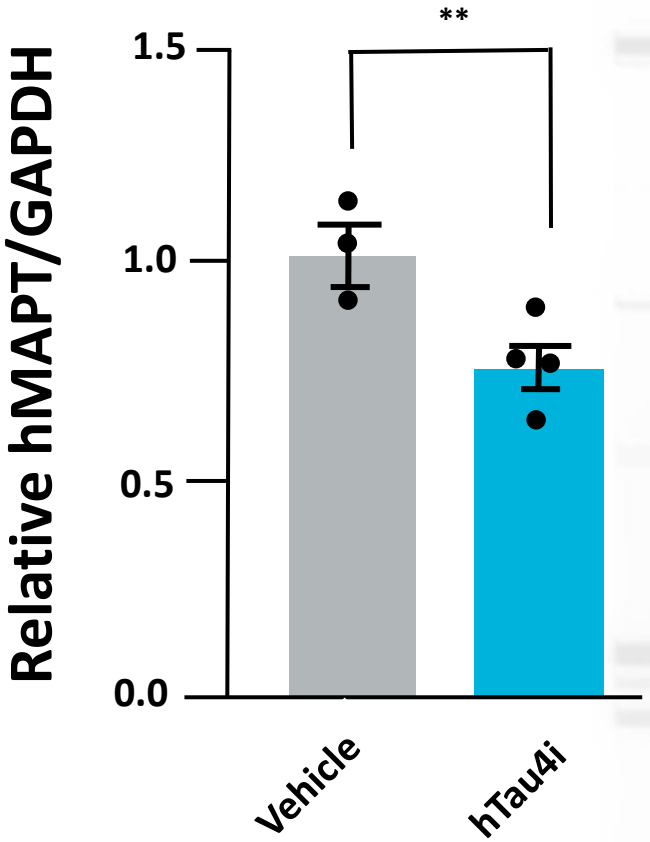






Mice dosed with TSHA-113 demonstrated widespread function and GFP expression in neurons and glia





Additional candidates targeting neurodegenerative diseases

TSHA-115 *miRNA*
GSDs
Preclinical

- miRNA targeting *GYS1* to inhibit glycogen synthase in the brain to decrease abnormal glycogen formation
- This approach may enable the treatment of several glycogen storage disorders
- Identical construct as TSHA-111-LAFORIN and TSHA-111-MALIN for Lafora disease and TSHA-112 for APBD
- Estimated prevalence of 20,000 patients in the US and EU

Neurodevelopmental Disorder Franchise

Rett syndrome is one of the most common genetic causes of intellectual disabilities in women

TSHA-102
Rett Syndrome

- Rett Syndrome is caused by mutations in the X-linked *MECP2* gene
- *MeCP2* regulates the expression of many genes involved in normal brain function
- A brief period of normal development is followed by a devastating loss of speech and purposeful hand use along with the emergence breathing abnormalities
- Disease reversibility described in animal models as demonstrated by Sir Adrian Bird[1]
- The estimated prevalence of Rett syndrome is 25,000 patients in the US and EU
- IND/CTA filing expected in 2H 2021
- Initiation of Phase 1/2 trial expected by the end of 2021

STAGE I

6-18 months (typical)
≤6 months (early)

Developmental Arrest Symptom Onset

Infants are generally described as having normal development until approximately 6 to 18 months of age

STAGE II

1-4 years

Rapid Deterioration Symptom progression-regression

Hallmark Rett symptoms appear: Hand wringing or squeeze, clapping, rubbing, washing, or hand to mouth movements

STAGE III

4-10 years

Pseudo stationary Symptoms stabilize/improve

After a period of rapid deterioration neurological symptoms stabilize, with some even showing slight improvements

STAGE IV

>10 years

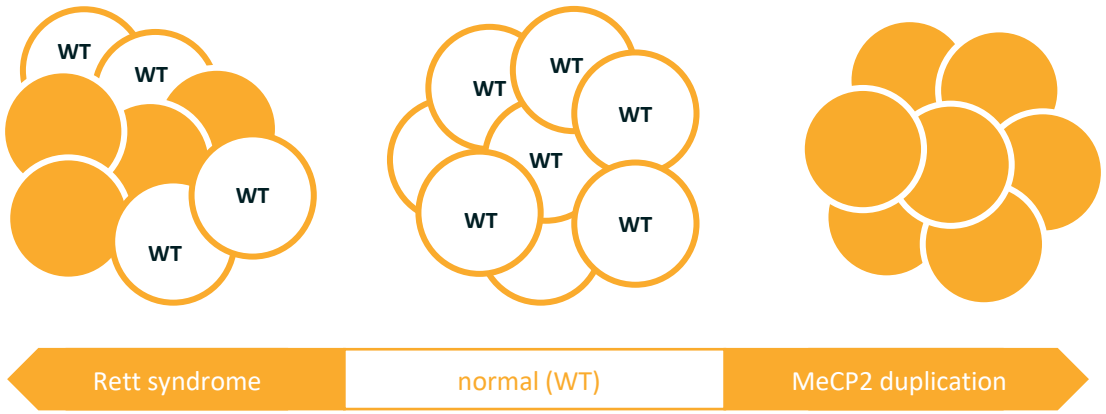
Late Motor Deterioration Muscle wasting with age

85-90% of affected people may **experience growth failure** and **muscle wasting** that worsens with age

1. Guy J et al. Science 2007

Rett syndrome (RTT) is an X-linked neurodevelopmental disorder

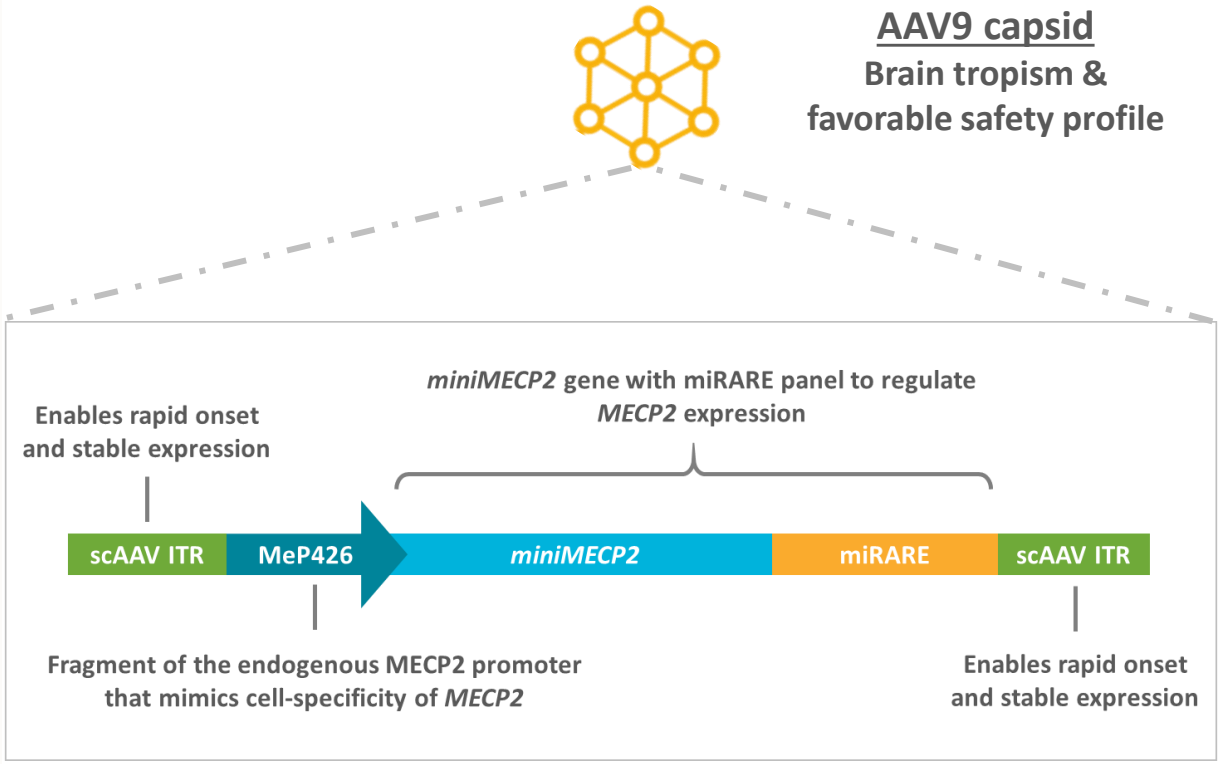
- Characterized by mutations in methyl CpG-binding protein 2 (*MECP2*), a protein that is essential for neuronal and synaptic function in the brain.
- Female heterozygous RTT patients are mosaic carriers of normal and mutated *MECP2*
- RTT falls along a spectrum of *MECP2* activity and toxicity from gene therapies is linked to unregulated expression of *MECP2*
- *MECP2* expression must be regulated to correct the deficiency, while avoiding toxicity associated with overexpression



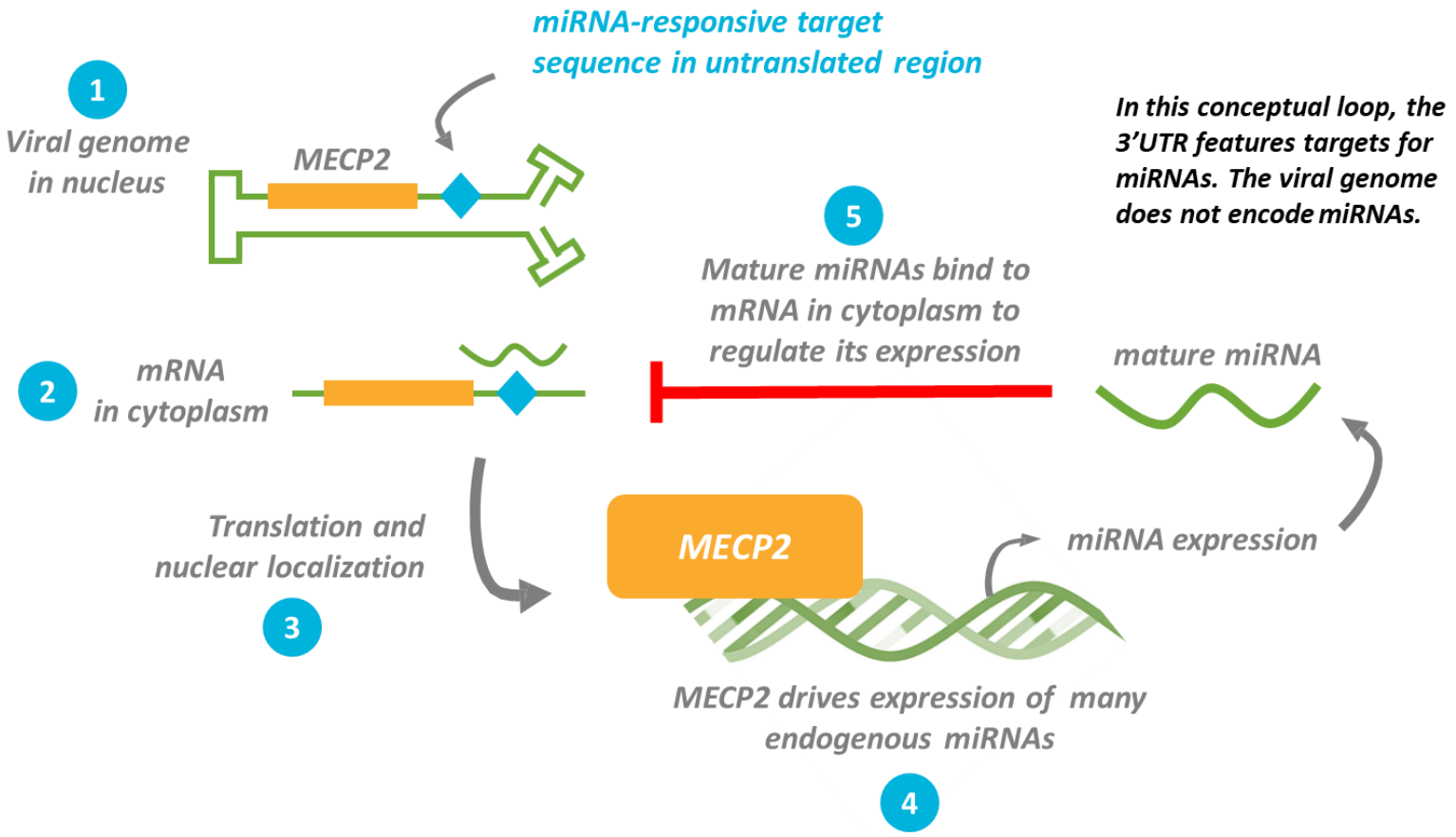
Development of a gene therapy for Rett syndrome requires regulated expression of *MECP2*

TSHA-102
Rett Syndrome

- AAV9/*MECP2* caused dose-dependent side effects after intraCSF administration in WT and KO mice
- We have developed a novel miRNA-responsive target sequence (miRARE) that regulates the expression of the *MECP2* transgene
- Our approach provides a superior therapeutic profile to that of competitor unregulated *MECP2* gene replacement



miRARE is a targeting panel for endogenous miRNAs which regulate MECP2 expression



Preclinical data for TSHA-102 in Rett syndrome recently published in *Brain*

ACCEPTED MANUSCRIPT

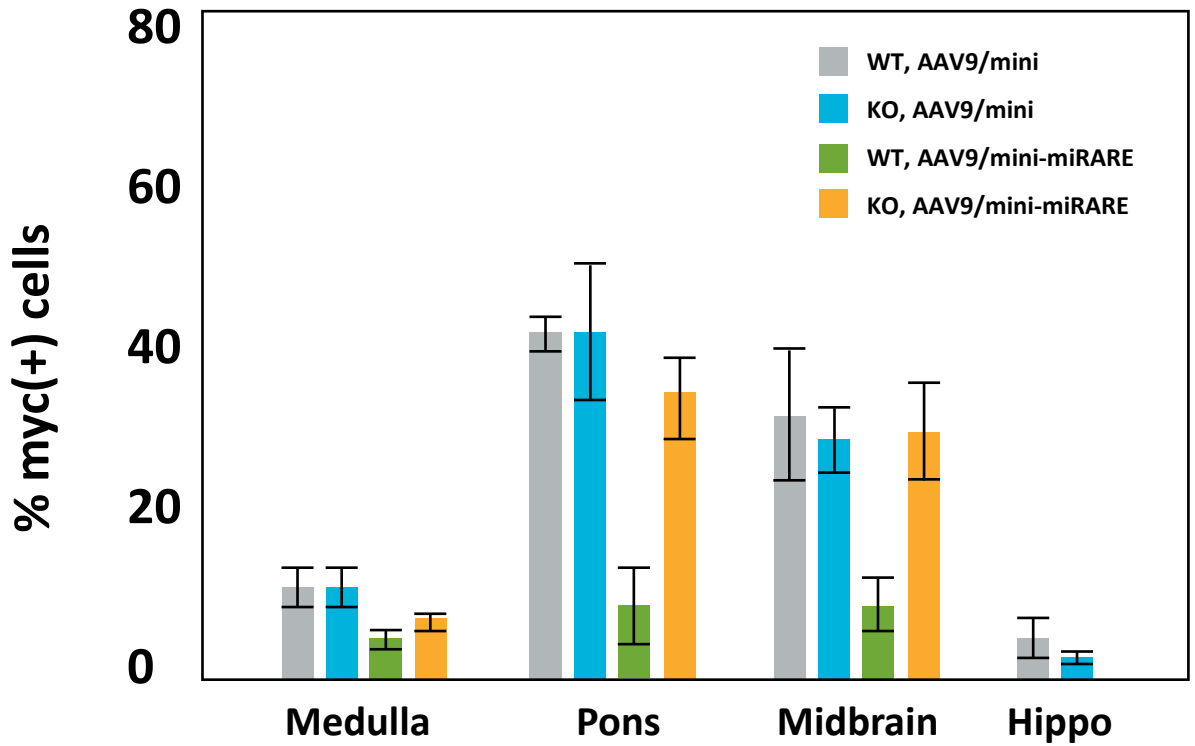
Engineered microRNA-based regulatory element permits safe high-dose mini*MECP2* gene therapy in Rett mice

Sarah E Sinnett, Emily Boyle, Christopher Lyons, Steven J Gray

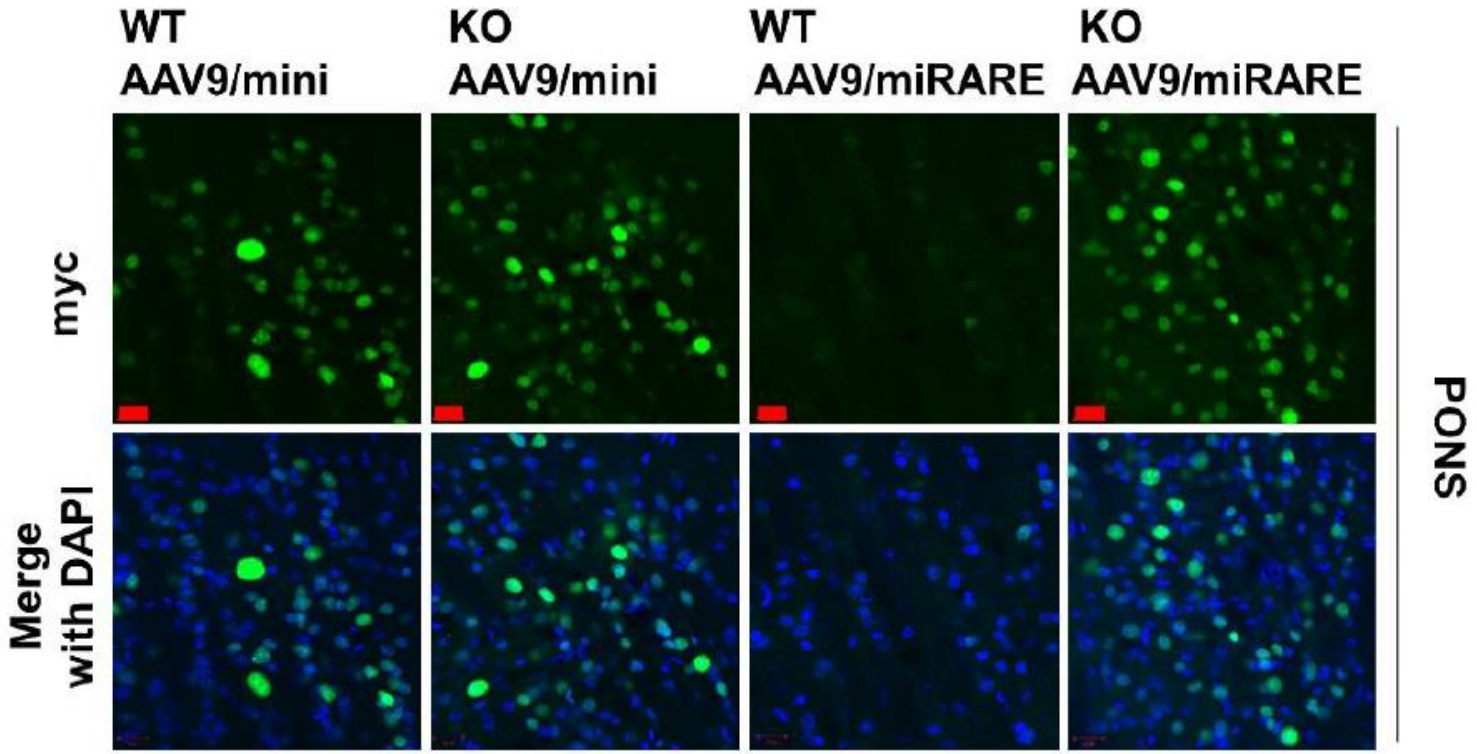
Abstract

MECP2 gene transfer has been shown to extend the survival of *Mecp2*$^{-/y}$ knockout (KO) mice modeling Rett syndrome (RTT), an X-linked neurodevelopmental disorder. However, controlling deleterious overexpression of MeCP2 remains the critical unmet obstacle towards a safe and effective gene therapy approach for RTT. A recently developed truncated mini*MECP2* gene has also been shown to be therapeutic after AAV9-mediated gene transfer in KO neonates. We show that AAV9/mini*MECP2* has a similar dose-dependent

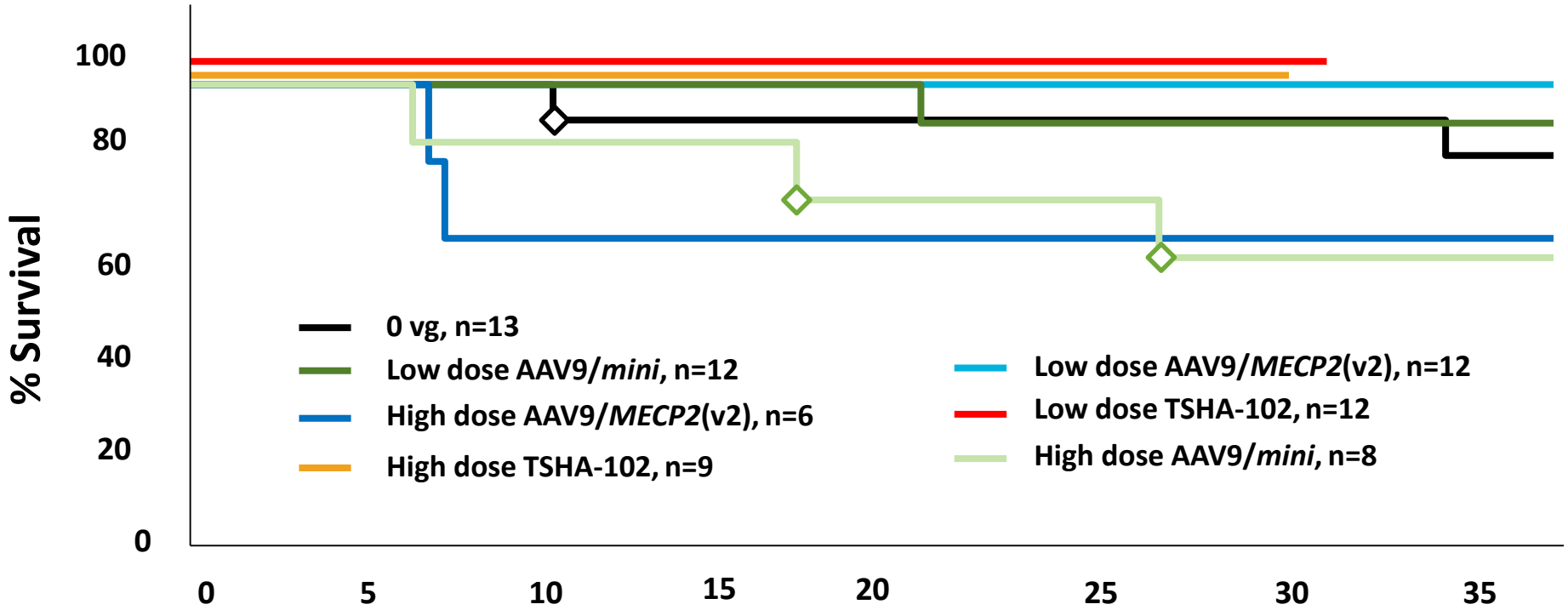
miRARE regulates genotype-dependent MECP2 expression across different brain regions in wild type and knockout Rett mouse models



Significantly fewer cells demonstrated expression in the pons and midbrain in TSHA-102-treated wild type mice compared to knockout mice



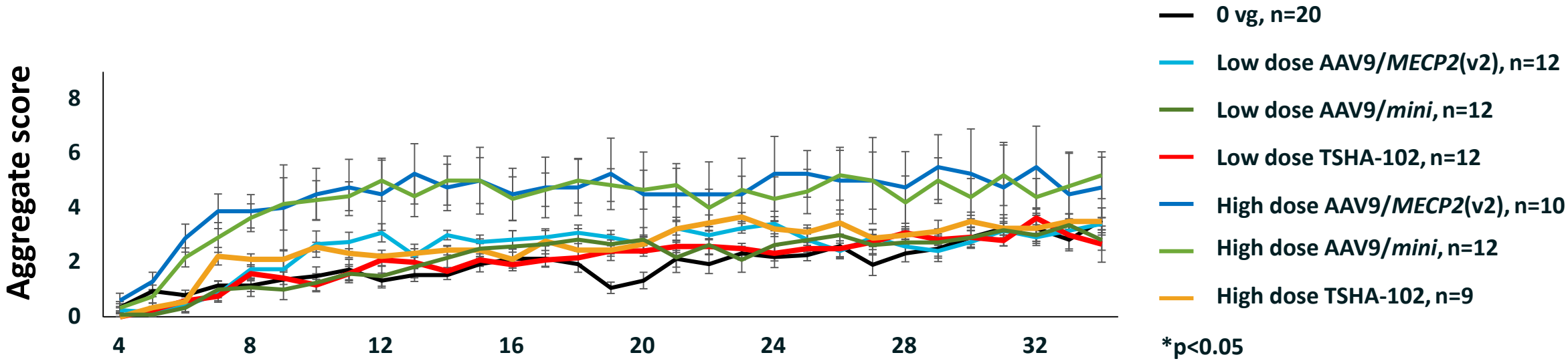
Safety: Intrathecal TSHA-102 was not associated with early death in WT mice



Mice were dosed P28-35

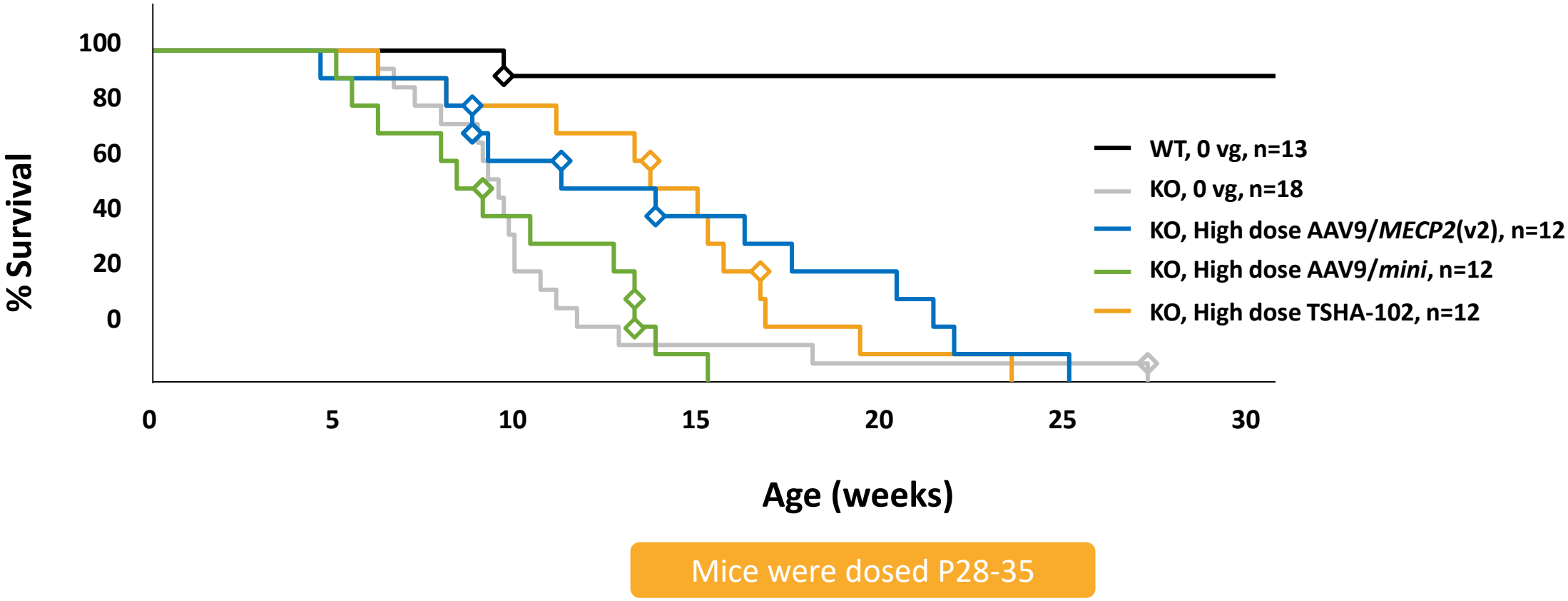
Diamond = vet-requested euthanasia for prolapse or bullying-related injury

Safety: TSHA-102 did not cause adverse behavioral side effects in WT mice



Mice were dosed P28-35

Efficacy: TSHA-102 outperformed unregulated AAV9/mini in MECP2 KO mouse survival study



Mice were dosed P28-35

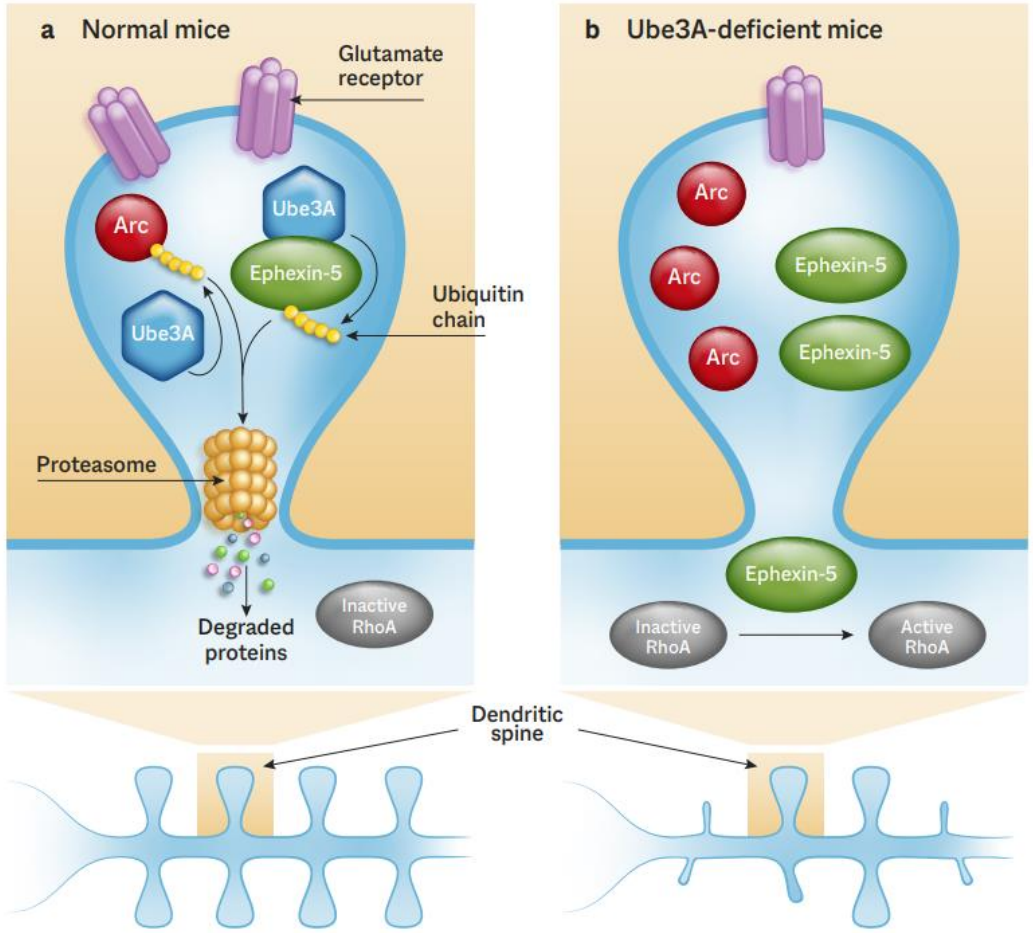
Diamond = vet-requested euthanasia, primarily for lesions. Lesions have been observed with varying frequencies among saline-treated KO mice, virus-treated WT and KO mice, as well as untreated RTT weanlings.

IND/CTA filing for TSHA-102 in Rett syndrome expected in 2H 2021

Study design and duration	• Open-label, dose-ranging, randomized, multi-center Phase 1/2 trial • Safety and preliminary efficacy • Each cohort randomized 3:1 (one patient is a delayed treatment control)
Key inclusion/exclusion criteria	• Adults with pathogenic confirmation of mutation in *MECP2*
Intervention	• First cohort (n=4): single dose of $5x10^{14}$ total vg of TSHA-102 (AAV9/*MECP2*-miRARE) • Second cohort (n=4): single dose of $1x10^{15}$ total vg of TSHA-102 (AAV9/*MECP2*-miRARE) • Delivered intrathecally
Key clinical assessments	**Rett-Specific/Global Assessments** • Motor Behavior Assessment Scale (MBA) • Rett Syndrome Hand Apraxia Scale (RHAS) • Rett Syndrome Behavior Questionnaire (RSBQ) • Functional Mobility Scale in Rett Syndrome (FMS) • Clinical Global Impression **Behavior/Mood Assessments** • Anxiety, Depression, and Mood Scale (ADAMS) • Aberrant Behavior Checklist (ABC) **Seizure Assessments** • EEG and neurophysiology • Seizure diary **Respiratory Assessments** • Respiratory Disturbance Index (RDI) • Sleep apnea, sleep study **Communication Assessments** • Observer Reported Communication Assessment (ORCA) **Quality of Life/Other Assessment** • SF-36 – Quality of life assessment from principal caregiver • RTT-CBI – Caregiver burden inventory **Wearables** • Hexoskin: cardiac, respiratory, sleep & activity

Angelman syndrome is a rare, neurogenic disorder due to genomic imprinting

- Caused by a deletion or loss of function of the maternally inherited allele of the *UBE3A* gene resulting in loss of the UBE3Q protein expression in neurons and abnormal communications between neurons
- Maternal-specific inheritance pattern due to genomic imprinting of *UBE3A* in neurons
- Maternal UBE3Q allele is expressed; paternal allele is silenced by a long non-coding RNA, *UBE3A* antisense transcript, or *UBE3A*-ATS



UPD – Uniparental disomy

Scheiffele, P. et al. Nature. 2010

There are currently no approved treatments for Angelman syndrome

- Signs and symptoms include developmental delay, severe impairments in behavior, motor function, communication and sleep as well as intellectual disability, debilitating seizures and ataxia
- Normal lifespan but unable to live independently
- No currently approved therapies
- The estimated prevalence of Angelman syndrome is 55,000 patients (US+EU)

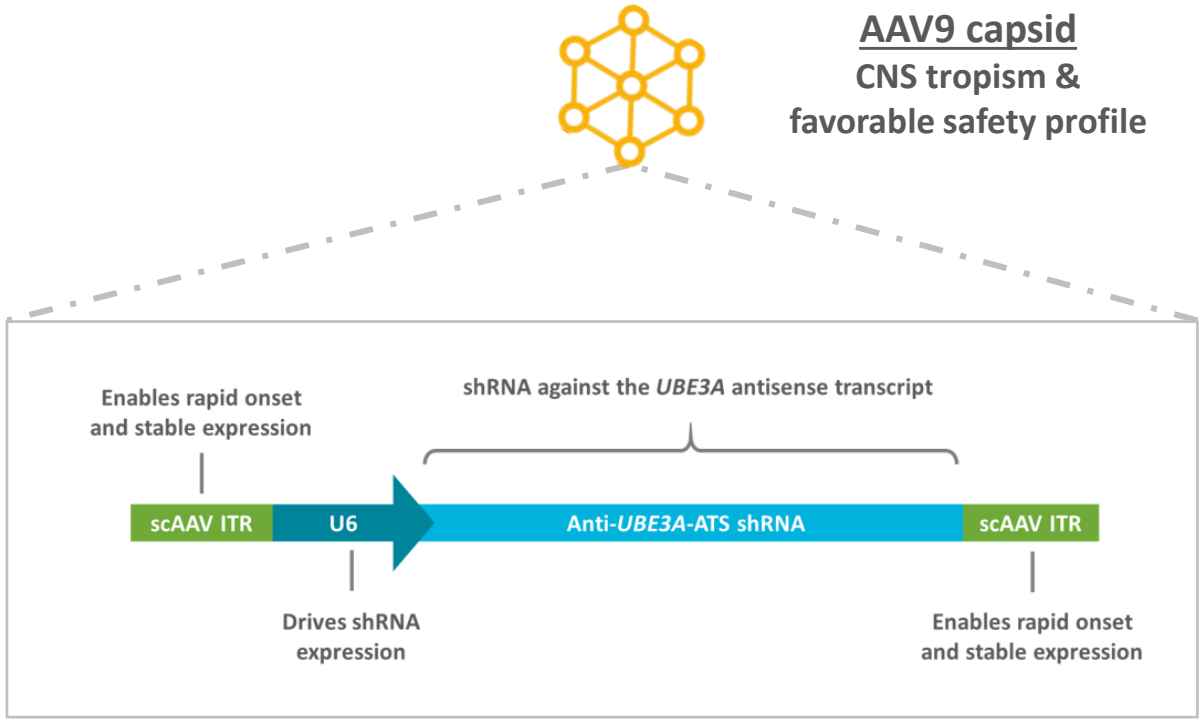
The paternal UBE3A gene is inactive. The maternal UBE3A gene is active but non-functional due to the mutation (or deletion)

The paternal UBE3A gene is activated by the treatment and takes over the function of the mutated UBE3A gene.

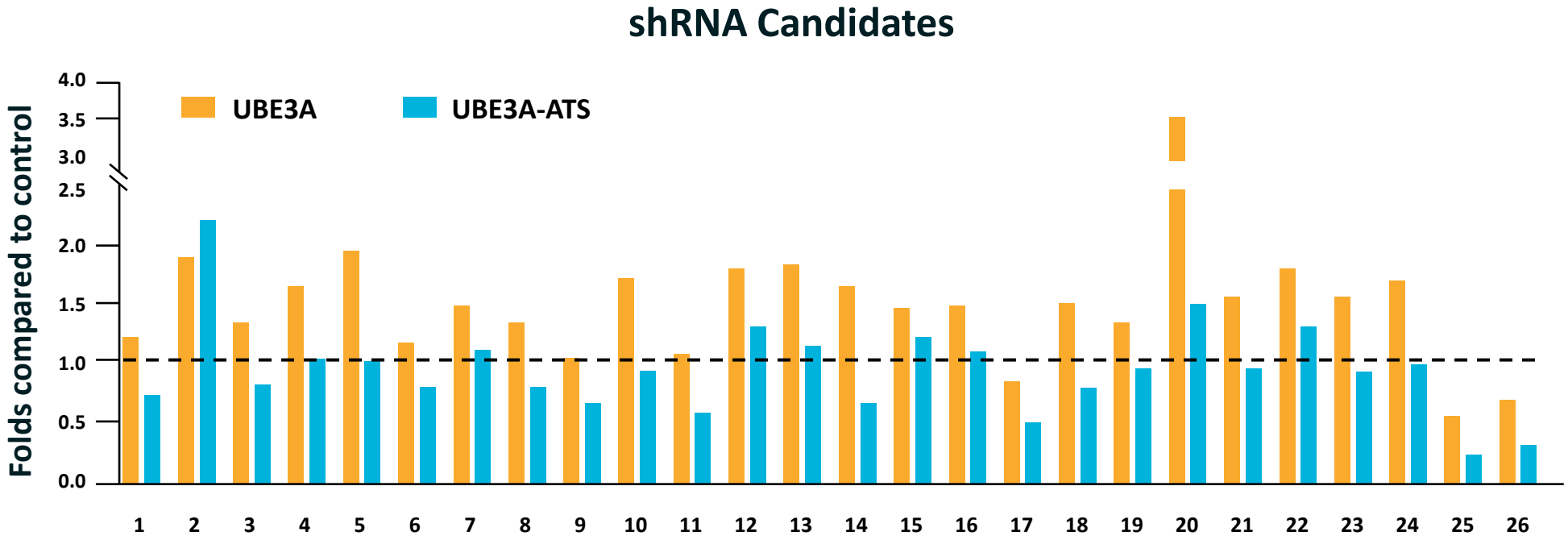
TSHA-106 for Angelman targets *UBE3A-ATS* transcript through shRNA knockdown

TSHA-106
Angelman Syndrome

- AAV9 viral vector designed for shRNA-mediated knockdown of *UBE3A-ATS*, the antisense transcript governing the expression of UBE3A through the paternal allele.
- Using AAV-based strategy to achieve broad distribution of the shRNA expression cassette across the entire CNS
- Single intrathecal dose
- Delivery of an ASO targeting *UBE3A*-ATS has shown promising results in ameliorating Angelman symptoms in transgenic mouse model
- Additional testing in iPSC-derived neurons leading to candidate selection anticipated by mid-2021
- Interim expression and safety data from confirmatory NHP studies expected by the end of 2021



TSHA-106 targets *UBE3A-ATS* transcript through shRNA knockdown



Testing in neuroblast cell line demonstrated consistent knockdown of *UBE3A-ATS* and a subsequent increase in UBE3A expression across 26 distinct shRNA candidates

Additional candidates targeting neurodevelopmental disorders

TSHA-114 GRT
Fragile X syndrome
Preclinical

- FMR1 is the most common single gene cause of autism and cognitive impairment
- Fragile X Syndrome is characterized by anxiety, aggression, hyperactivity, attention deficits, and sleep/communication disruption
- Estimated prevalence of 100,000 patients in the US and EU

TSHA-116 shRNA
Prader-Willi syndrome
Preclinical

- Loss of function of genes along 15q11-q13 chromosome region due to an imprinting defect
- Patients have developmental delay, insatiable eating habits accompanied by obesity and overt diabetes
- Estimated prevalence of 40,000 patients in the US and EU

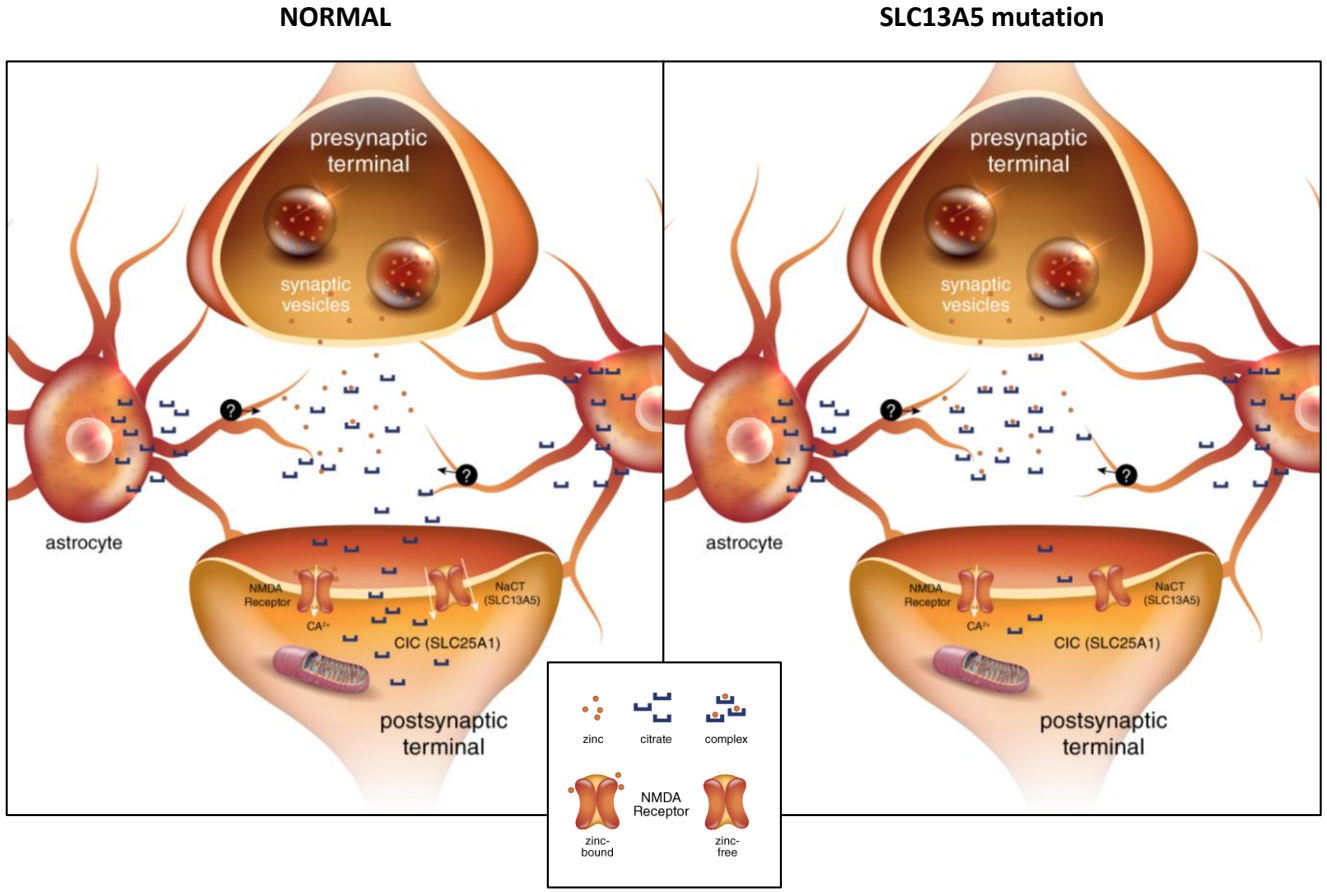
TSHA-117 regulated GRT
FOXG1 syndrome
Preclinical

- Newly discovered gene with prevalence expected to steadily rise as more children as tested with autism spectrum disorder
- Development and intellectual disabilities, growth restriction with microcephaly, epilepsy, and hyperkinetic-dyskinetic movement disorder
- Estimated prevalence of 20,000 patients in the US and EU

Genetic Epilepsy Franchise

SLC13A5 deficiency results in persistent seizures and developmental delays

- Bi-allelic loss of function in the *SLC13A5* gene, resulting in a loss or reduction in citrate transport and aberrant cellular metabolism
- Patients have impaired motor function, speech production and seizures
- Signs and symptoms include seizures within a few days of birth, persisting through life, encephalopathy, delayed speech/language development, developmental regression and abnormalities in tooth enamel
- First-line treatment is anti-seizure medications
- Estimated prevalence of SLC13A5 deficiency is 1,900 patients in the US and EU



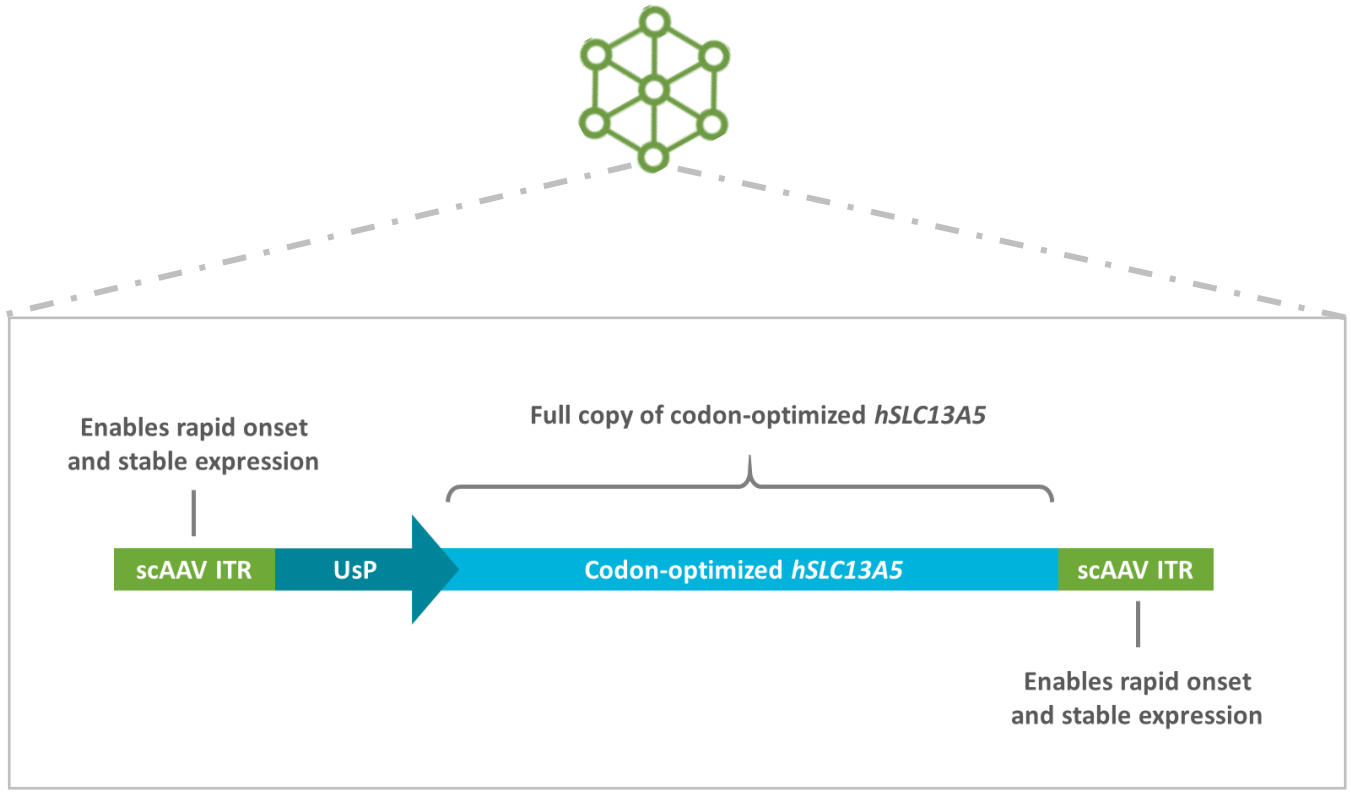
Bhutia, Molecules 2017

TSHA-105 currently in IND/CTA-enabling studies

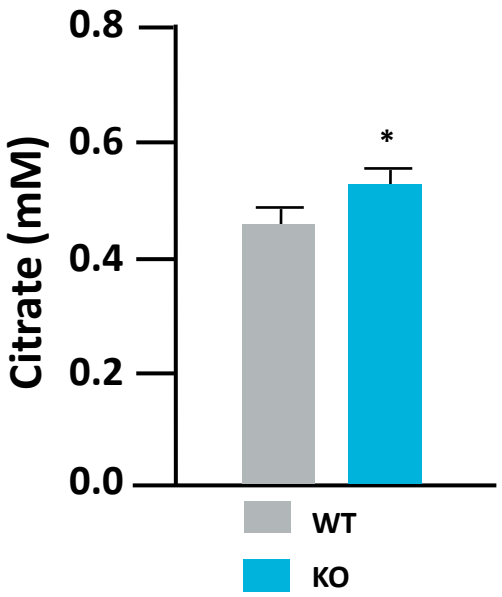
TSHA-105
SLC13A5 deficiency

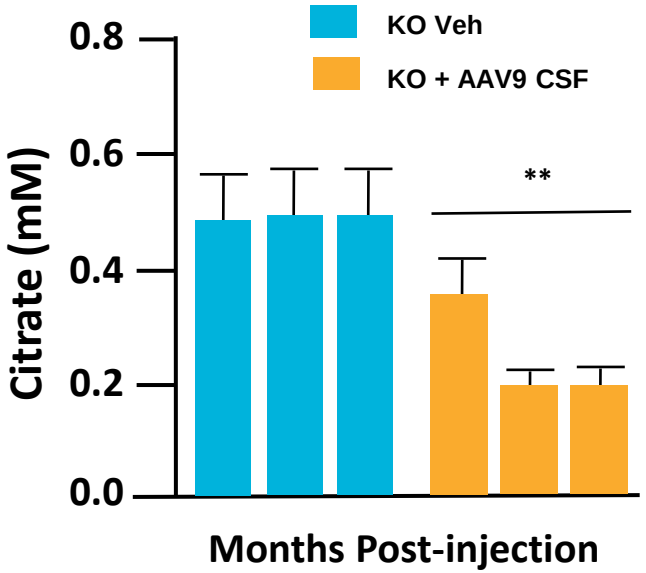
- Self-complementary AAV9 expressing human SLC13A5 protein under the control of a single promoter vector design
- Delivered intrathecally
- Received orphan drug and rare pediatric disease designations
- Currently in IND/CTA-enabling studies

AAV9 capsid
CNS tropism & favorable safety profile



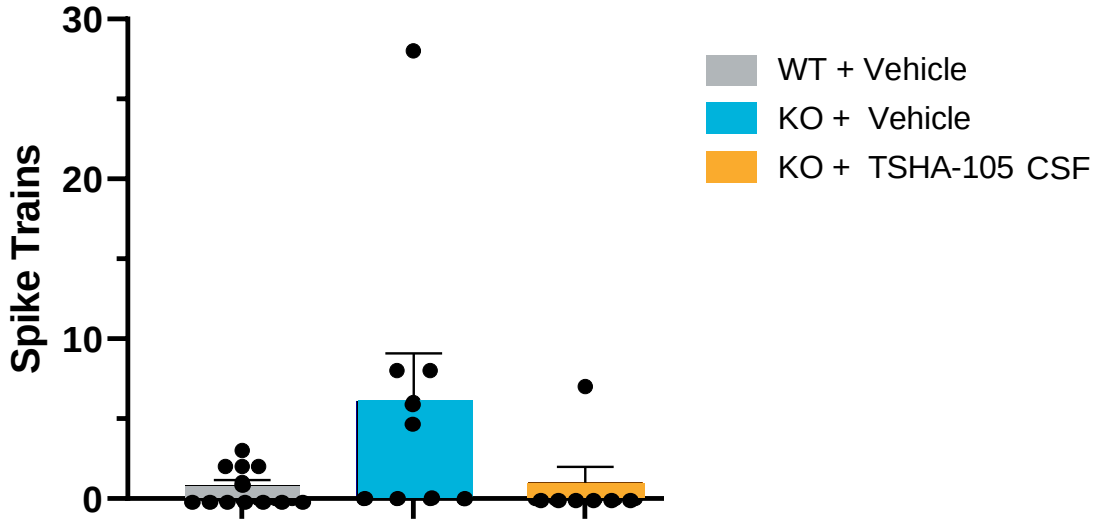
TSHA-105 decreased plasma citrate levels in SLC13A5 KO mice

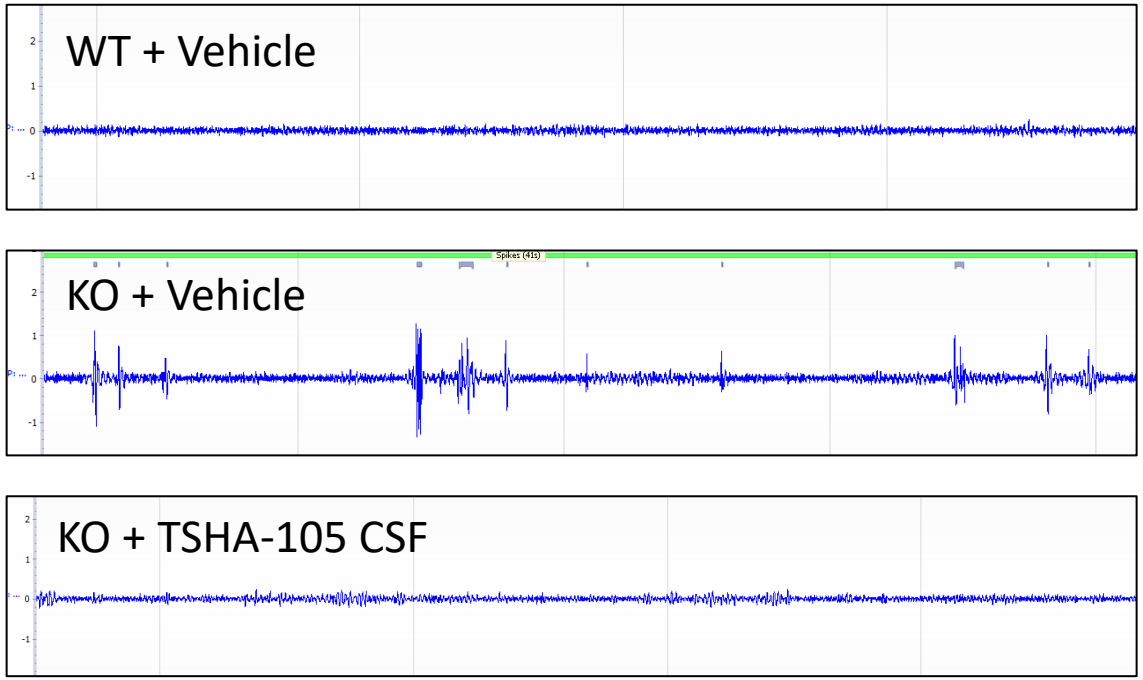




Bailey, R. 2020

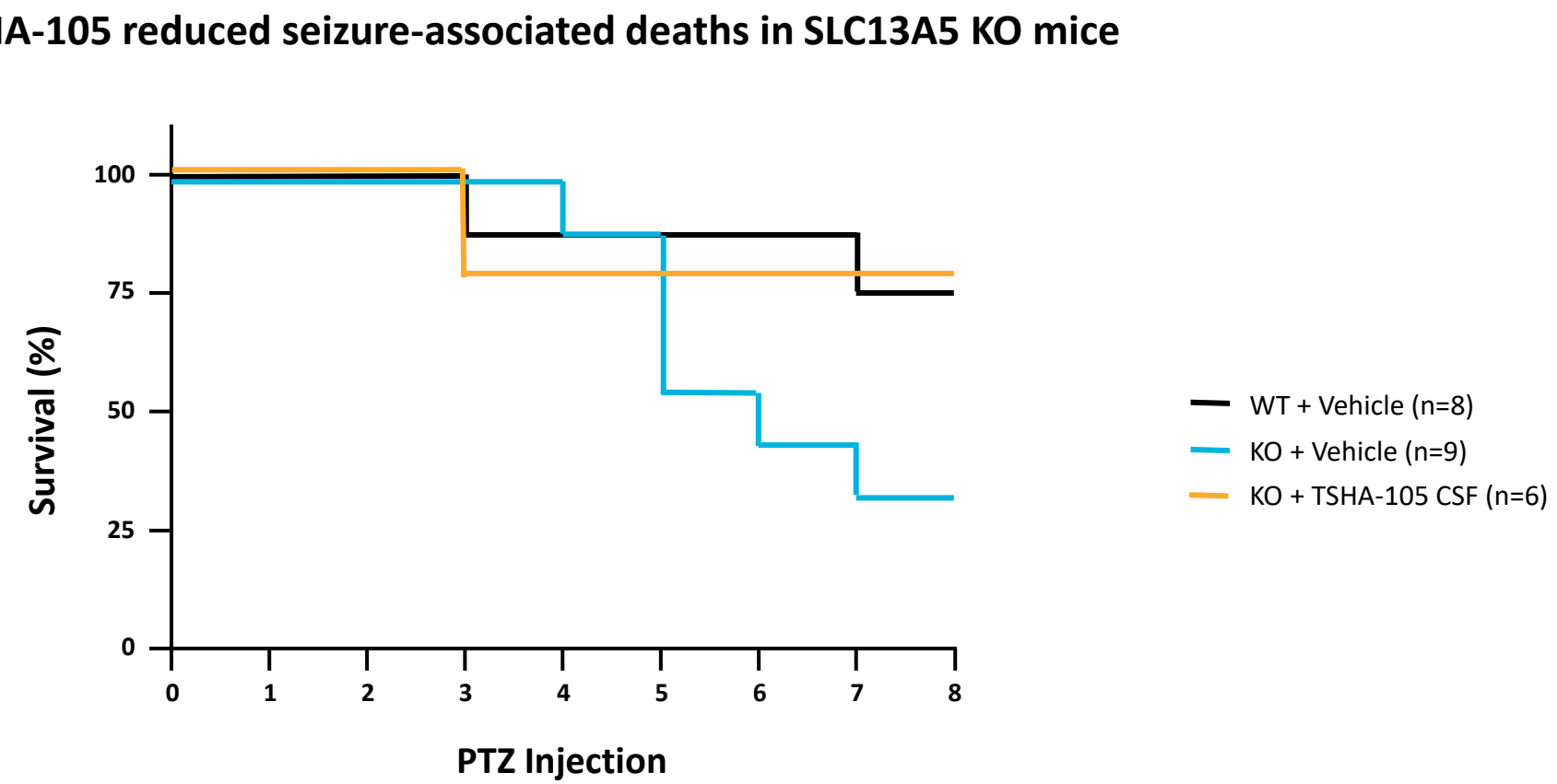
TSHA-105 improved EEG activity in SLC13A5 KO mice





Bailey, R. 2020

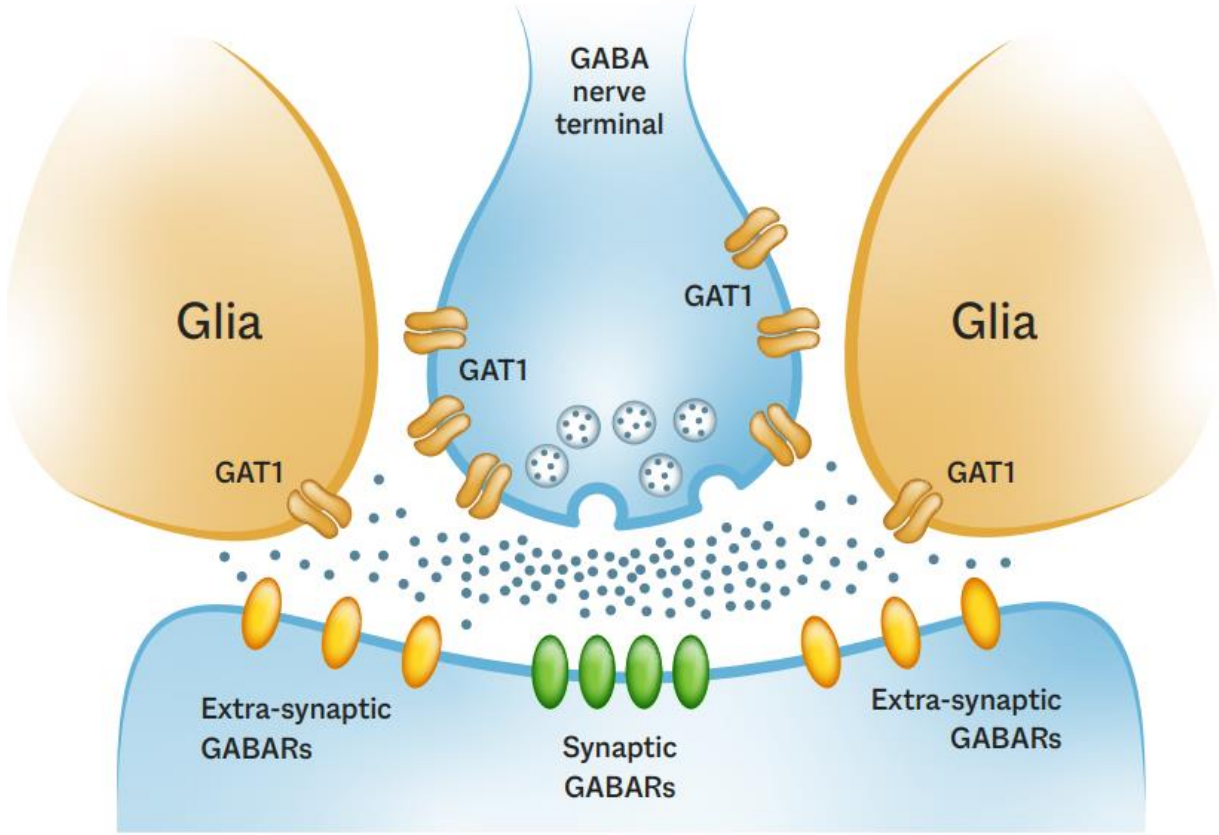
TSHA-105 reduced seizure-associated deaths in SLC13A5 KO mice



Bailey, R. 2020

SLC6A1 haploinsufficiency disorder results in persistent seizures and developmental delays

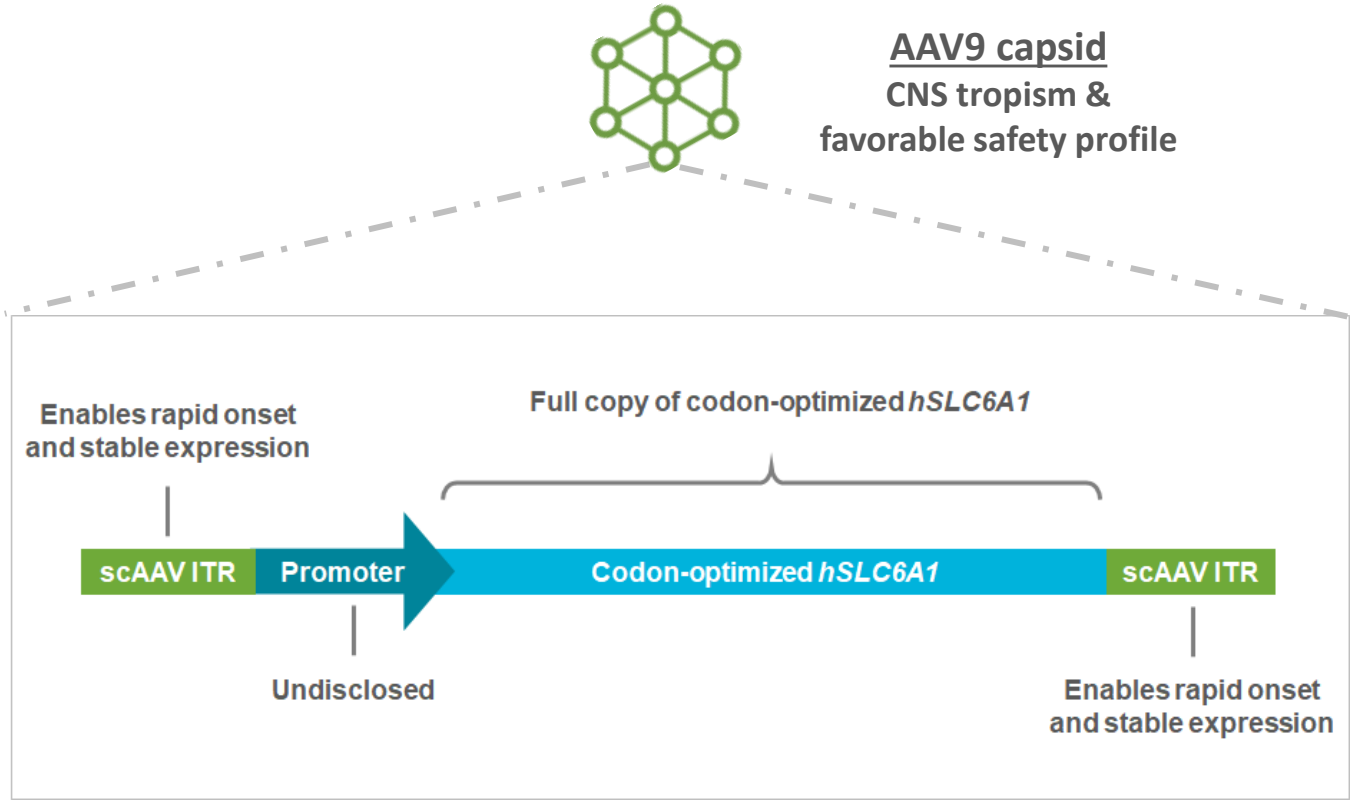
- Autosomal dominant genetic disorder characterized by the loss of function of one copy of the *SLC6A1* gene
- SLC6A1 encodes the GABA transporter protein type 1 (GAT1), which is responsible for the reuptake of GABA into presynaptic neurons and glia
- Clinical manifestations include epilepsy, developmental delays, including mild or moderate intellectual disability, ataxia and autism
- No approved therapies
- Estimated prevalence of SLC6A1 haploinsufficiency disorder is 17,000 patients in the US and EU



TSHA-103 in IND/CTA-enabling studies

TSHA-103
SLC6A1 haploinsufficiency disorder

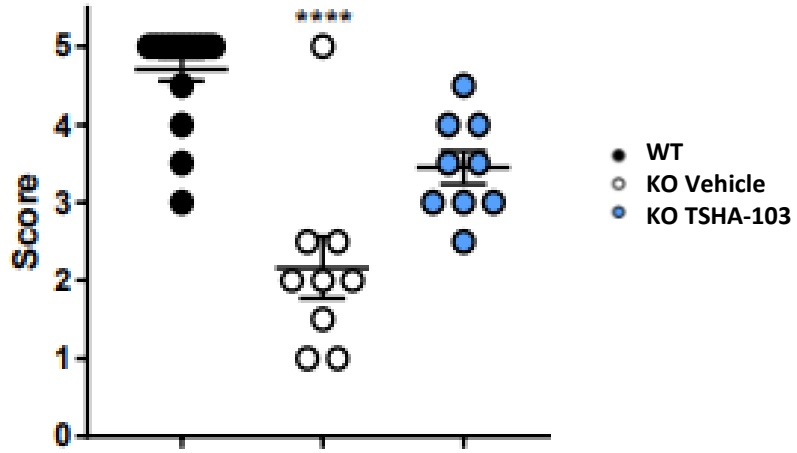
- Self-complementary AAV9 viral vector designed to deliver a functional copy of hSLC6A1
- Proof-of-concept demonstrated in knockout SLC6A1 mouse model
- Delivered intrathecally
- Received orphan drug and rare pediatric disease designations
- Currently in IND/CTA-enabling studies

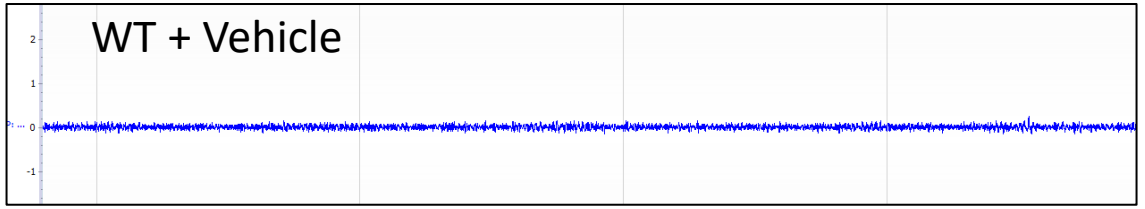


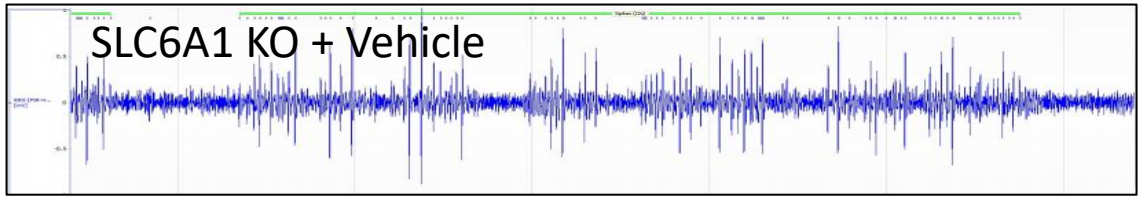
TSHA-103 improved nesting and EEG activity in SLC6A1 KO mouse model

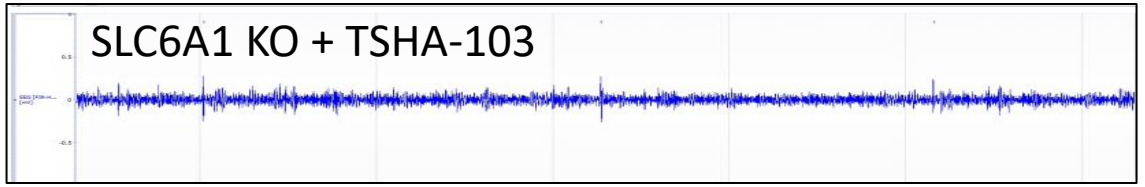
Nesting

2 months post-injection

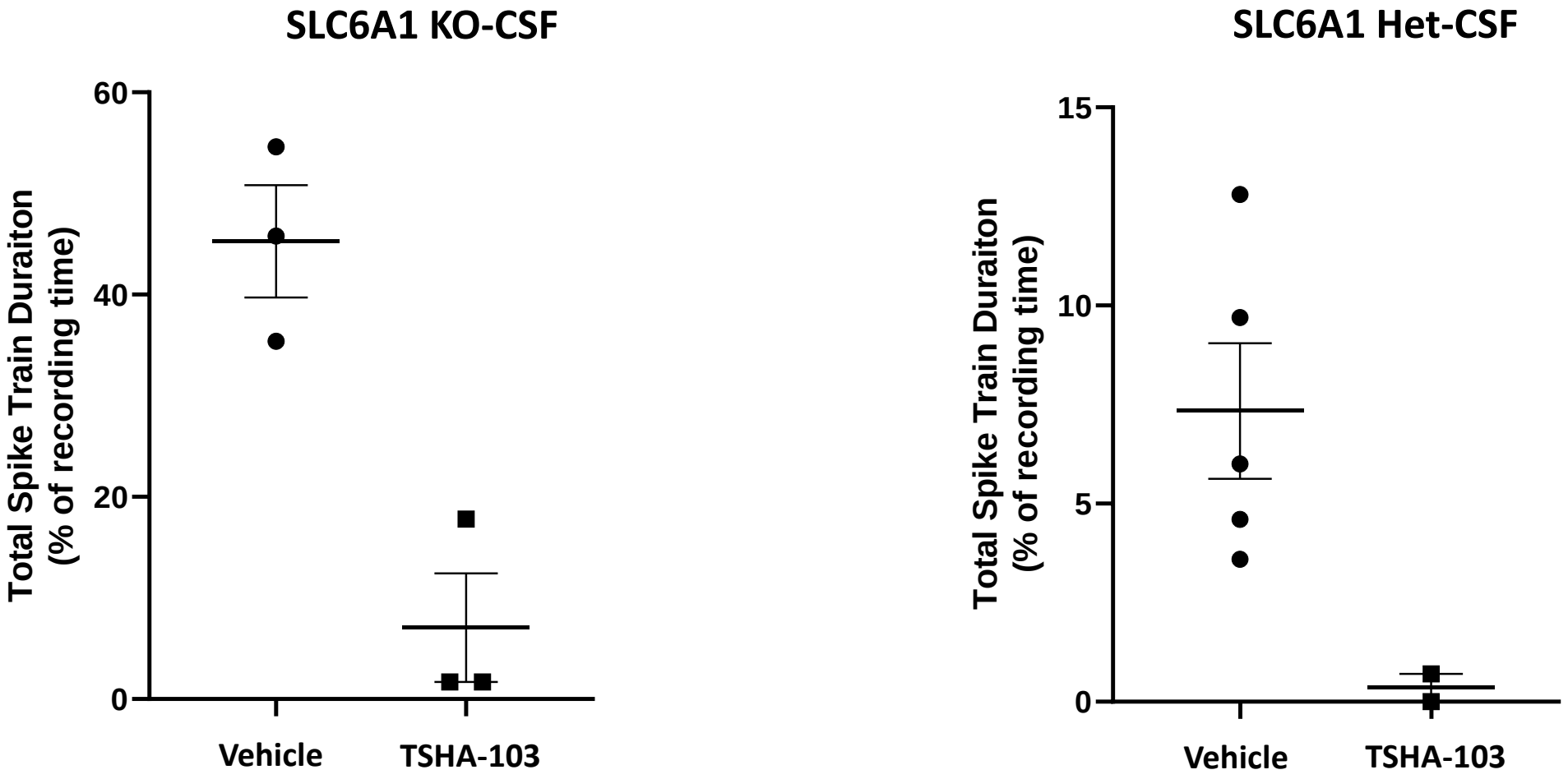








TSHA-103 reduced spike train activity in SLC6A1 KO and heterozygous mouse models

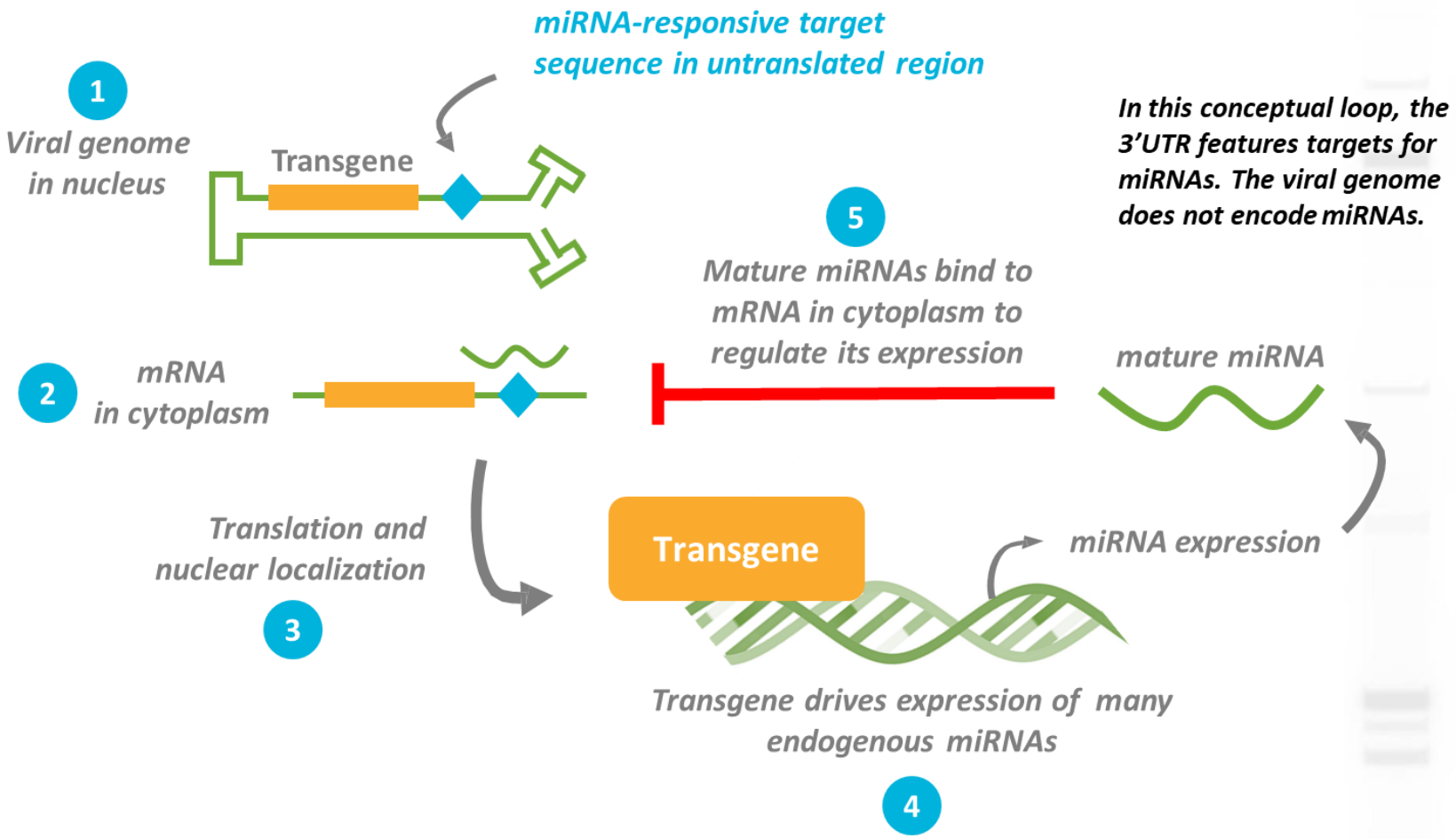


Deep pipeline of gene therapies targeting genetic epilepsies

TSHA-110 GRT **KCNQ2** **Preclinical**	• Diminished KCNQ2 function results in seizures in the first week of life, accompanied by developmental delay involving one or more domains of motor, social, language, or cognition • Some children may have autistic features • Estimated prevalence of 37,000 patients in the US and EU

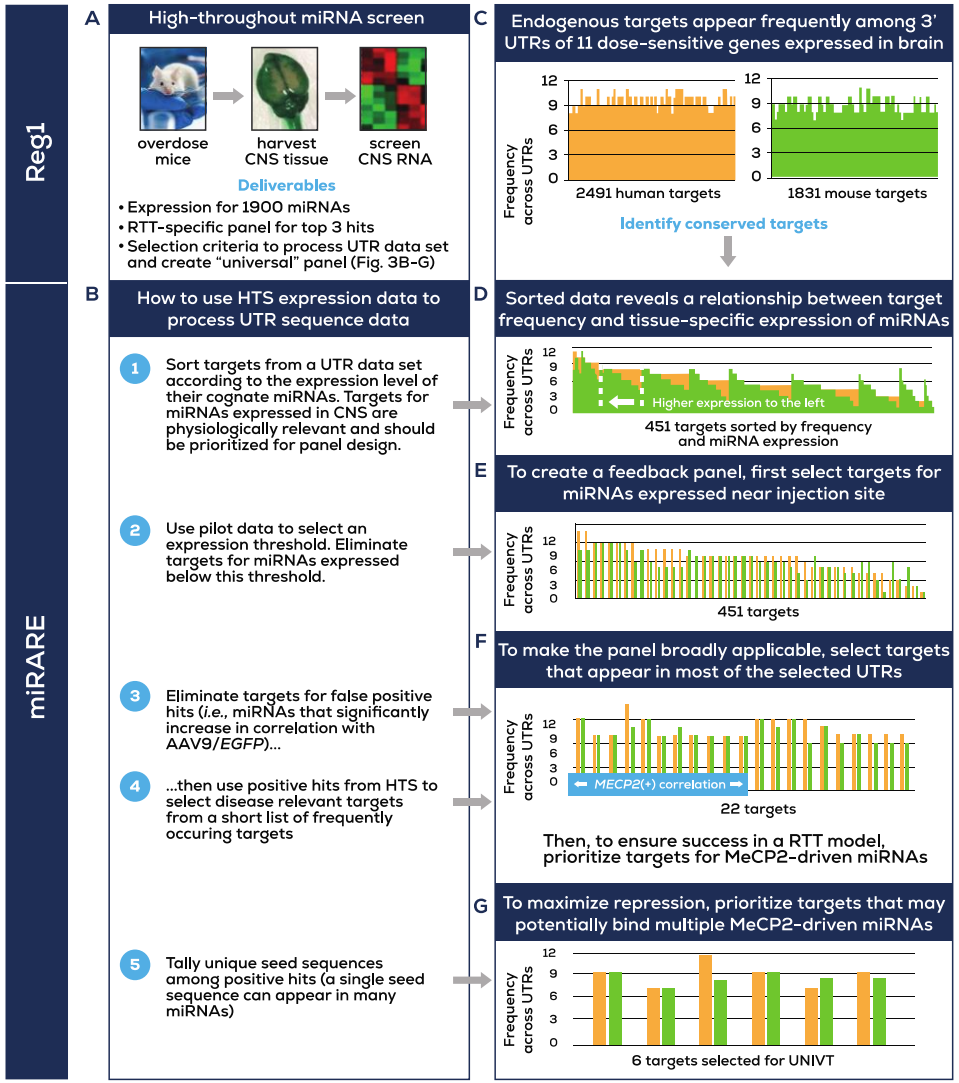
Platform Technologies

miRARE is a targeting panel for endogenous miRNAs which can regulate various transgenes

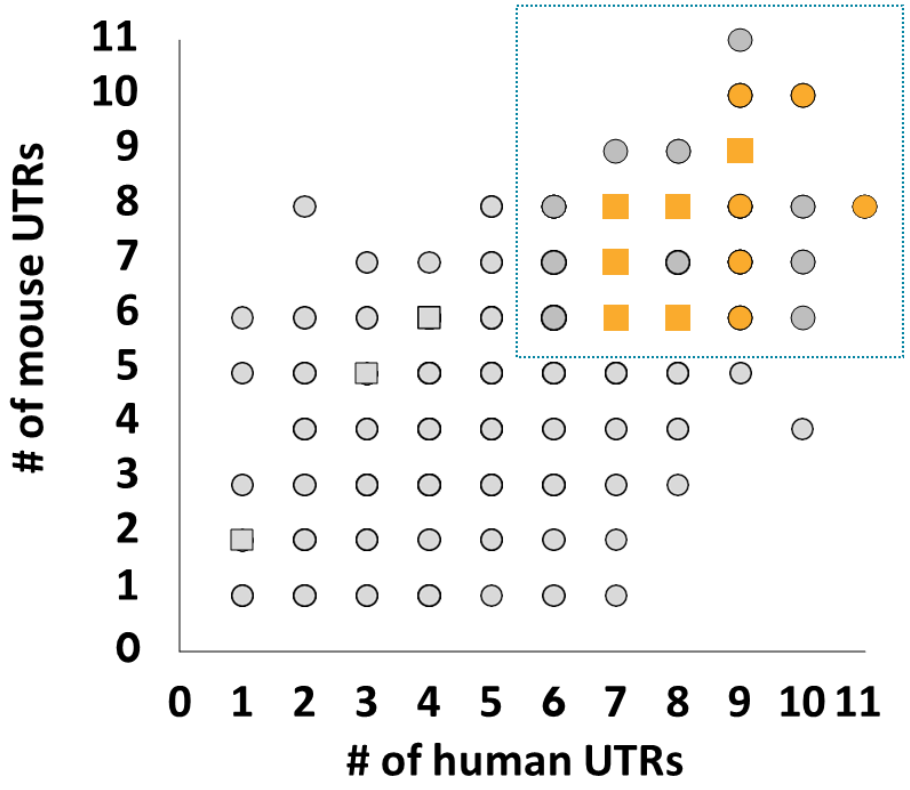


Approaches to create a miRNA target panel for regulating *MECP2* expression

- High-throughput screening of mouse CNS miRNAs upregulated after MECP2 gene therapy overdose
- Identify endogenous miRNA targets that are conserved across species and appear frequently among the UTRs of dose-sensitive genes regulating intellectual ability
- Use positive results from high-throughput screening to filter and rank bioinformatics data
- Merged screening data and genomic sequence information
- Create a small synthetic (and potentially broadly applicable) regulatory panel



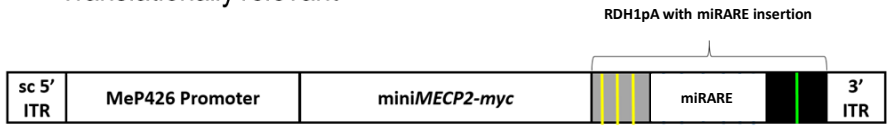
451 targets annotated across both species for selected 3’UTRs



- Many targets appear frequently among the 3’UTRs of dose-sensitive genes mediating disorders characterized by intellectual disability
- Bounded area: targets appear across ≥ 6 selected 3’UTRs
- Orange data points: corresponding miRNAs expressed in CNS tissue
- Squares: corresponding miRNAs are potentially MeCP2-responsive

New target panel miRARE

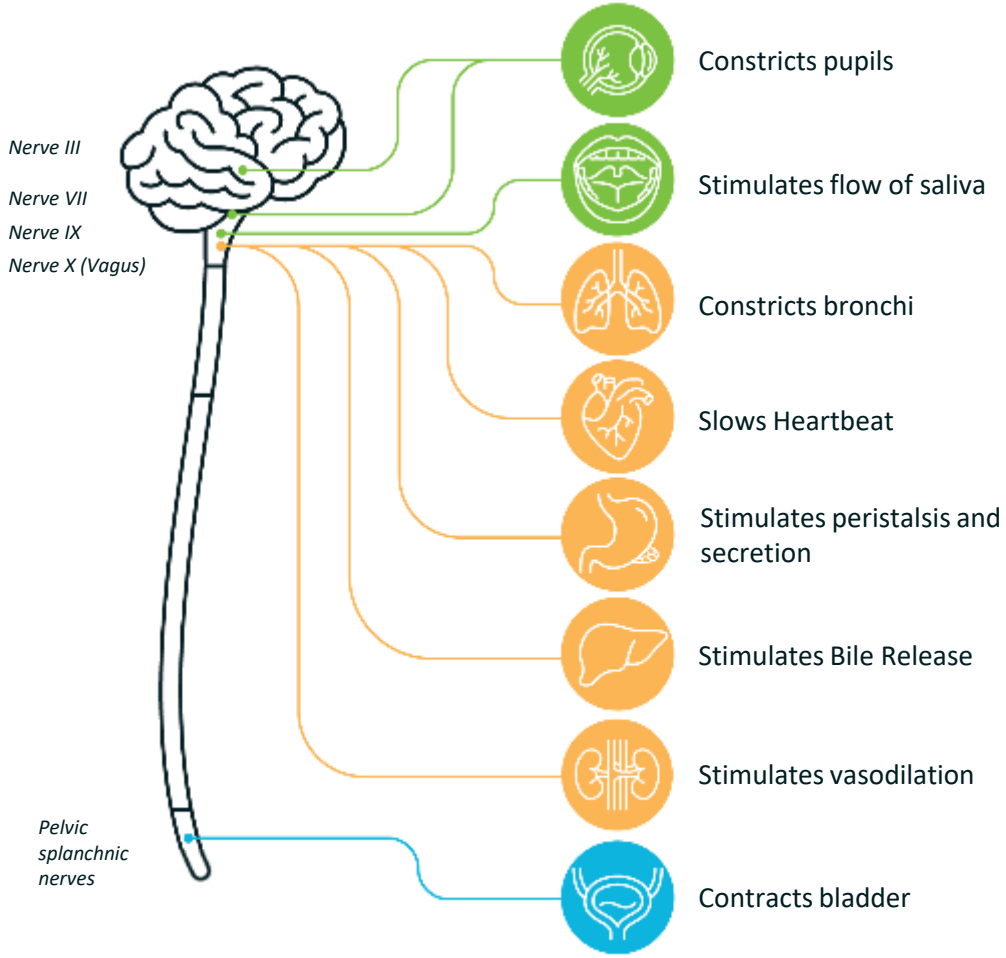
- Compact (6 targets)
- Useful for RTT
- Possibly multipurpose
- Translationally relevant



Opportunity to achieve human POC for vagus nerve redosing

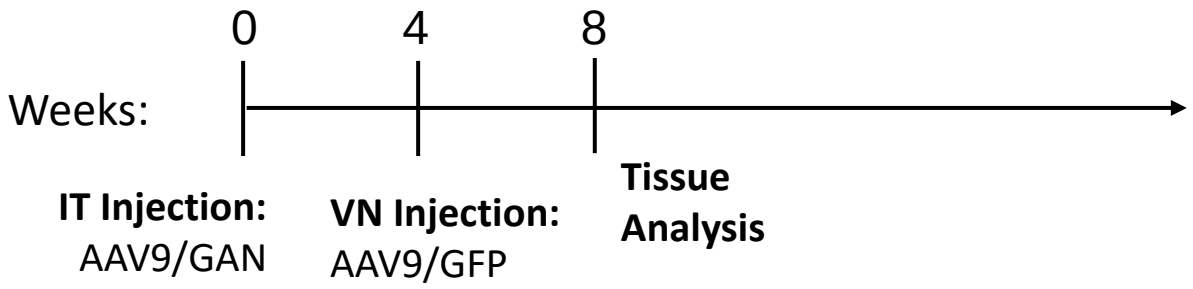
- The vagus nerve represents the main component of the autonomic nervous system
- Direct delivery to the vagus nerve may provide broad coverage of the autonomic nervous system and enable redosing by subverting the humoral immune response
- Proof-of-concept established in rodent and canine models; oral presentation of data at ASGCT 2020
- Plan to execute confirmatory preclinical studies in canines
- Platform may be utilized to facilitate redosing of previously treated patients in the GAN AAV9 clinical trial as well as other indications

Parasympathetic System

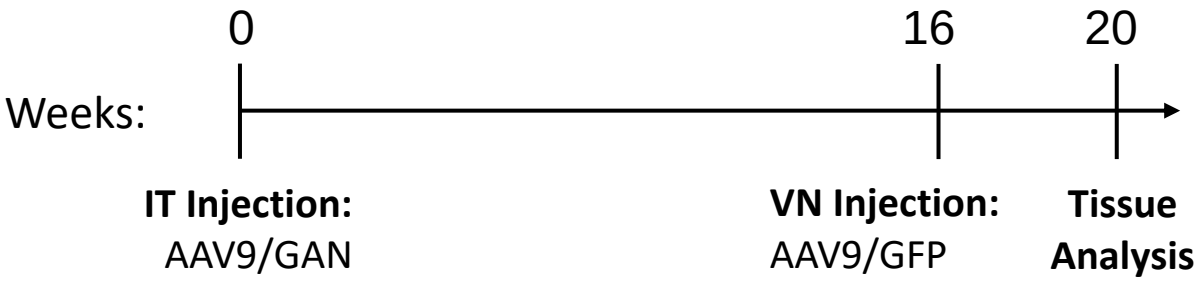


Robust expression of GFP in the vagus nerve and associated nodose ganglia in rats support redosing via vagus nerve injection

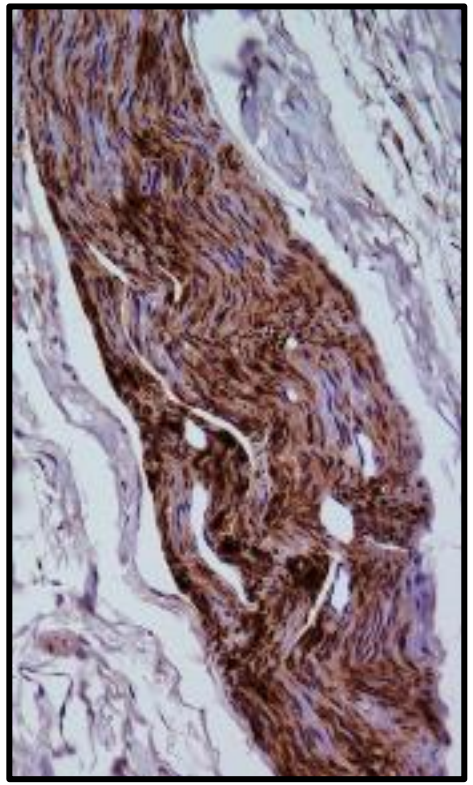
Study 1



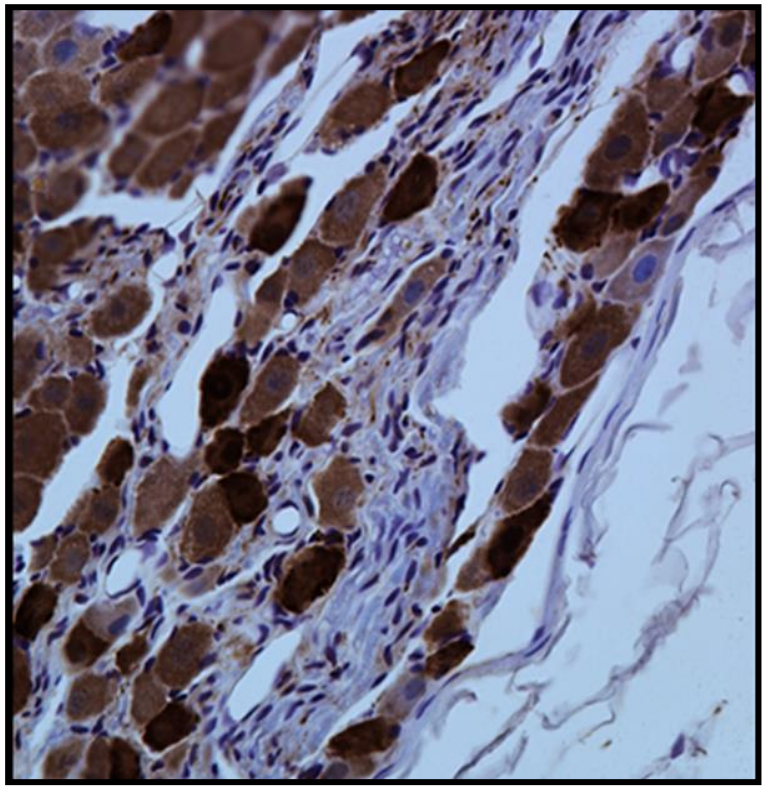
Study 2



Vagus Nerve

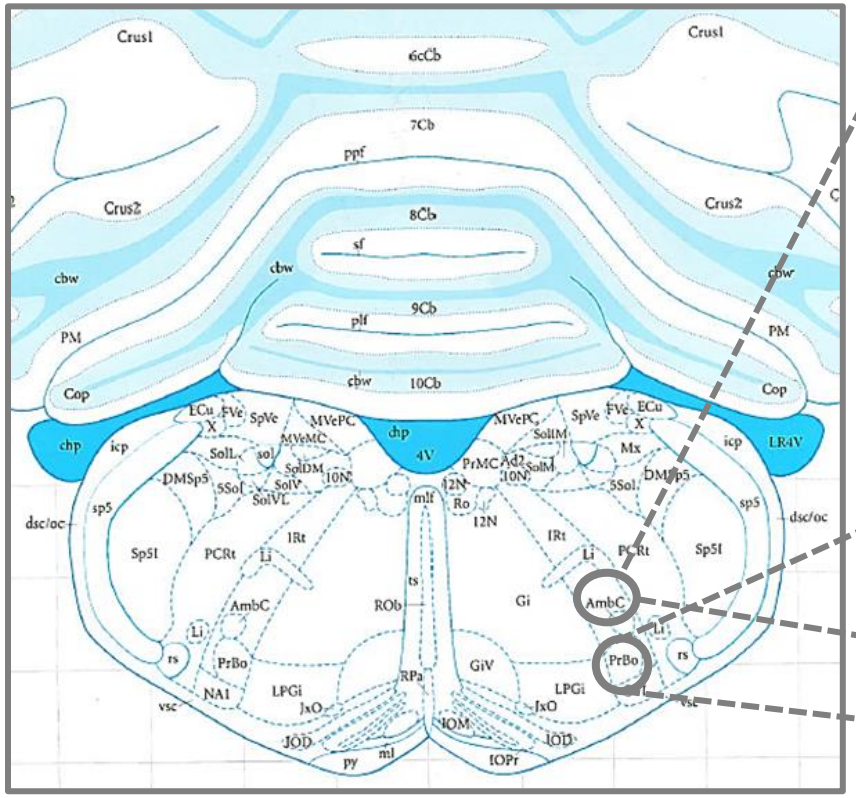


Nodose Ganglia

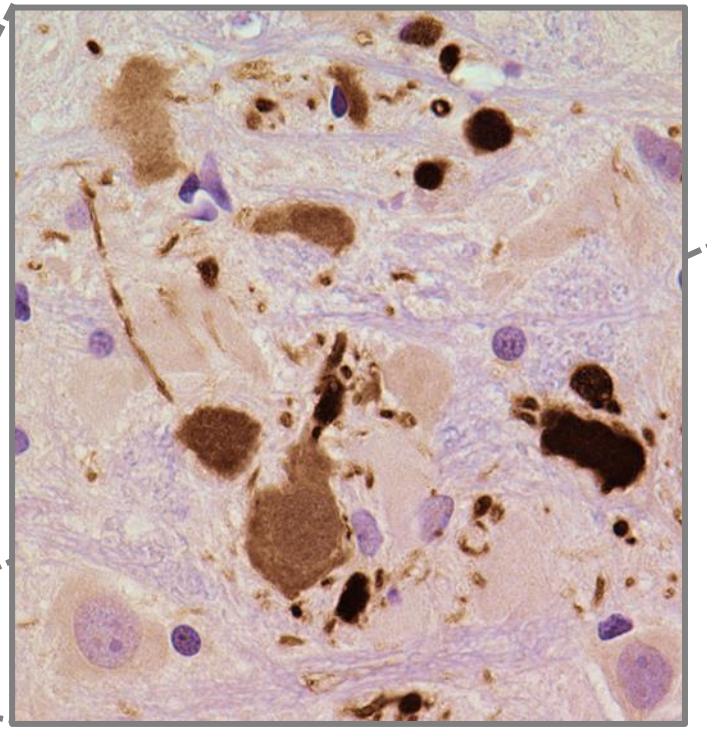


GFP – green fluorescent protein
Courtesy of Dr. Diane Armao

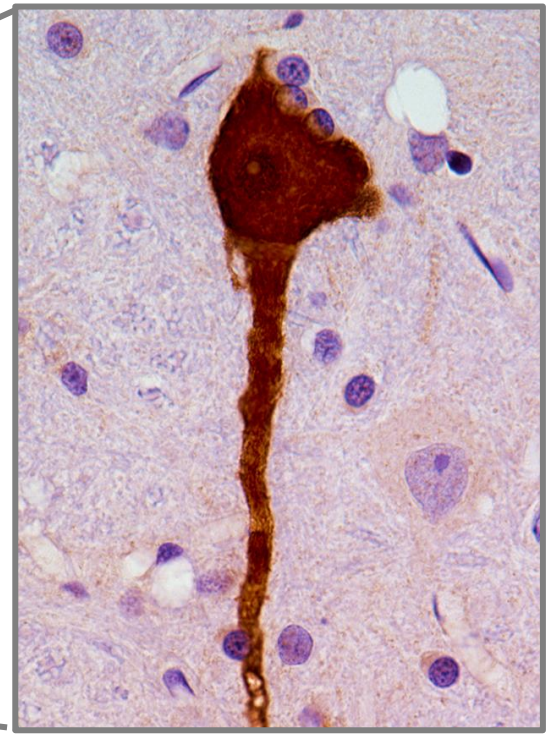
Successful transduction of relevant brain neurons following redosing via vagus nerve injection



Medulla



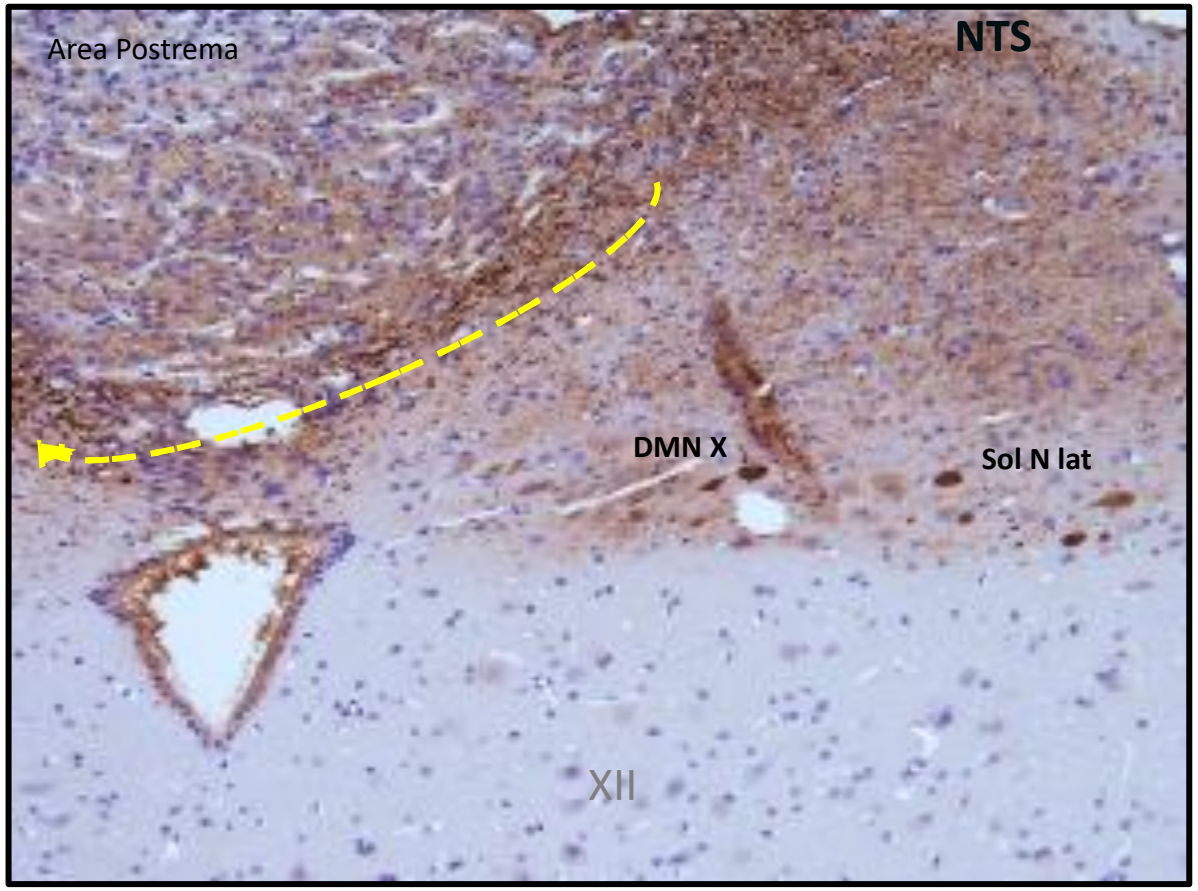
Nucleus Ambiguous



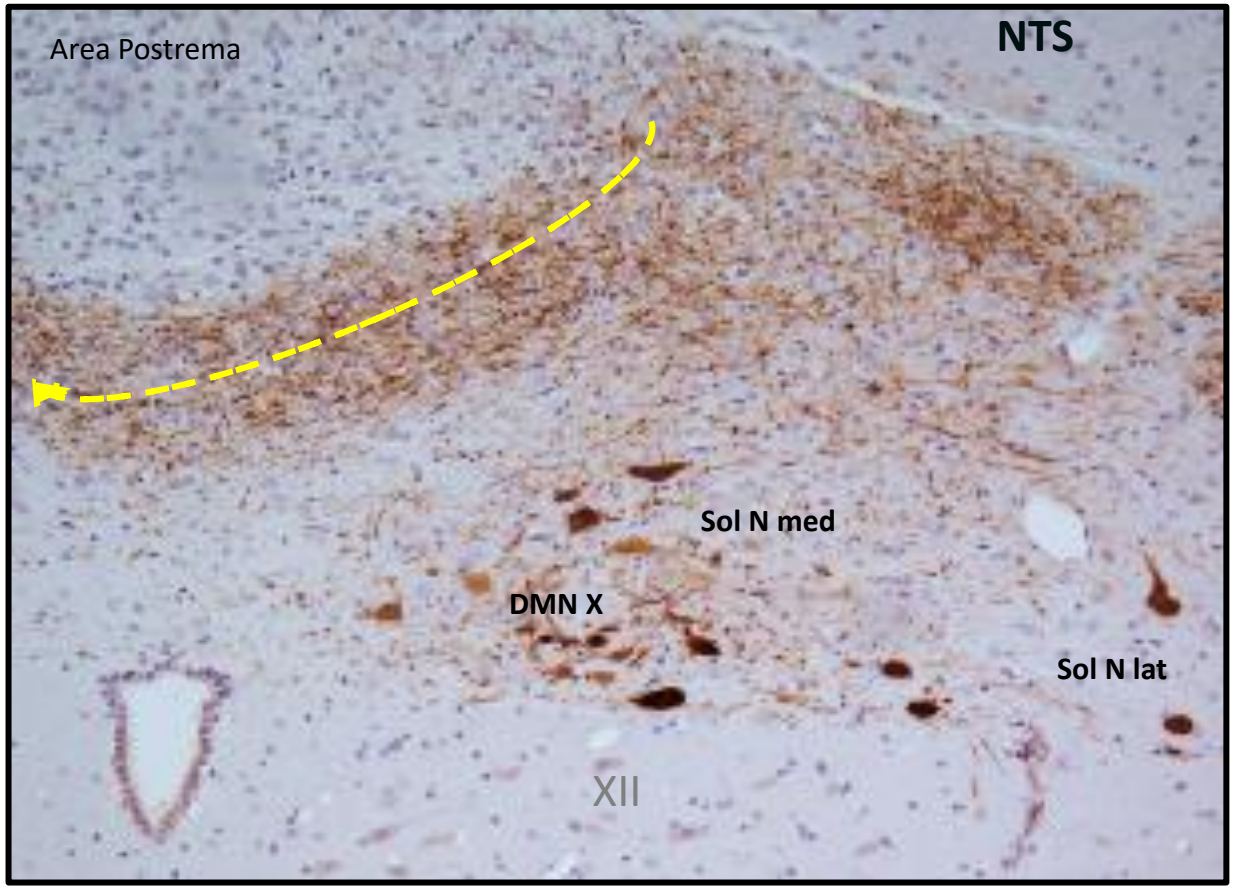
Pre-Botzinger Complex

Courtesy of Dr. Diane Armao

Vagus nerve injection permits AAV9 redosing confirmed in brain slices of AAV9-immunized rats



Naive

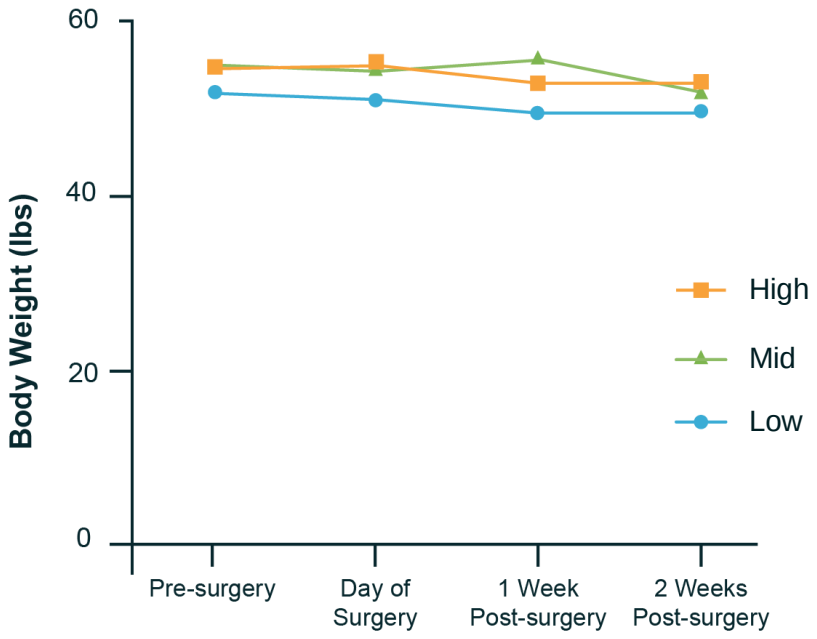


AAV9 Pre-immunized

Courtesy of Dr. Diane Armao

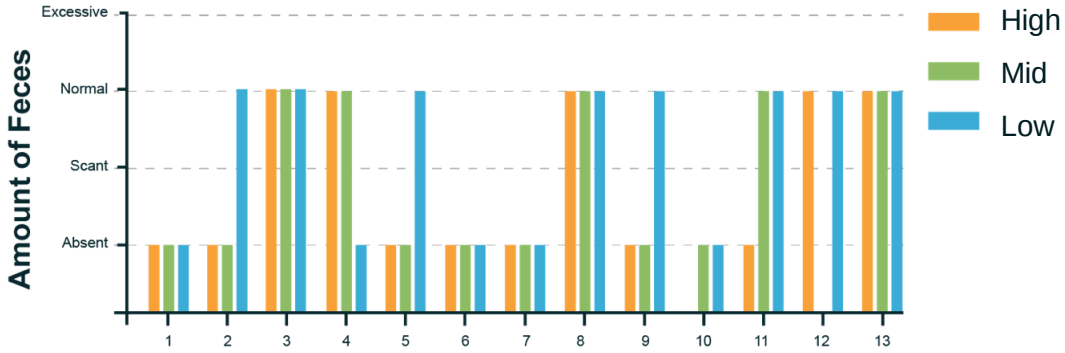
Vagus nerve injection of increasing doses of AAV delivery were well-tolerated in hounds observed over 13 days

Testing VN Delivery Rates

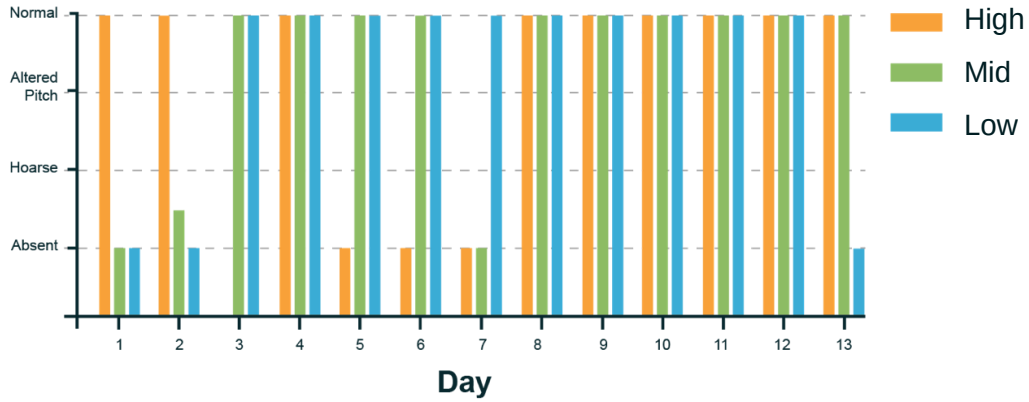


Post-mortem vagal nerves and brain were microscopically normal

Post-surgery Afternoon Fecal Output



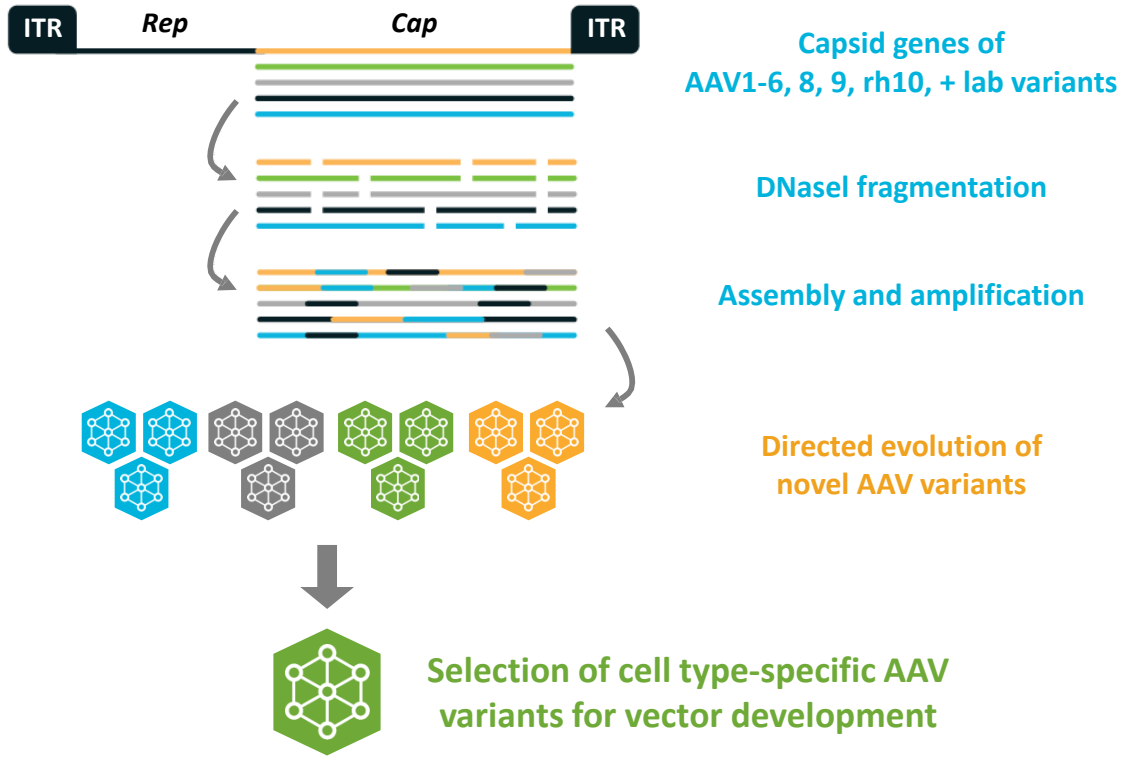
Post-surgery Vocalization



[1]Taysha has exclusive rights to the vagus nerve redosing platform in select indications.

Utilizing machine learning, DNA shuffling, and directed evolution for capsid discovery

- High-content sequencing of recovered capsid pools
- Using sequencing data from *in vivo* selection to feed machine learning algorithms, for *in silico* design of novel capsids
- Development of new libraries, based on capsid-spanning modifications rather than just peptide insertions
- Directed evolution to generate CNS-directed capsids, cross-compatible between mice and NHPs



Focused on achieving anticipated near-term milestones in 2021 and building long-term value

- GAN clinical program update, including 3.5 x 10^{14} total vg cohort
- GM2 gangliosidosis preliminary biomarker data in 2H 2021
- CLN1 program to dose first patient in 2021 under open IND

- 4 open IND/CTAs expected by the end of 2021, including Rett syndrome

- Initiated construction of internal cGMP facility in 1H 2021

- 5 additional programs currently in IND-enabling studies
- R&D Day in June 2021
- Numerous value generating catalysts over the next 18 months