# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**WASHINGTON, D.C. 20549**

# FORM 8-K

**CURRENT REPORT**
**Pursuant to Section 13 or 15(d)**
**of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): April 14, 2021**

# Taysha Gene Therapies, Inc.
**(Exact name of registrant as specified in its Charter)**

| **Delaware** | **001-39536** | **84-3199512** |
|---|---|---|
| **(State or Other Jurisdiction of Incorporation)** | **(Commission File Number)** | **(IRS Employer Identification No.)** |

| | |
|---|---|
| **2280 Inwood Road**<br>**Dallas, Texas**<br>**(Address of Principal Executive Offices)** | **75235**<br>**(Zip Code)** |

**(214) 612-0000**
**(Registrant's Telephone Number, Including Area Code)**

**Not Applicable**
**(Former Name or Former Address, if Changed Since Last Report)**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instructions A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

| Title of each class | Trading Symbol(s) | Name of each exchange on which registered |
|---|---|---|
| **Common Stock, $0.00001 par value** | **TSHA** | **The Nasdaq Stock Market LLC** |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

**Item 7.01 Regulation FD Disclosure.**

On April 14, 2021, Taysha Gene Therapies, Inc. (the "Company") updated its corporate presentation for use in meetings with investors, analysts and others. The presentation is available through the Company's website and a copy is attached as Exhibit 99.1 to this Current Report on Form 8-K.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.1, is being furnished pursuant to Item 7.01 and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") or otherwise subject to the liabilities of that section, and it shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or under the Exchange Act, whether made before or after the date hereof, except as expressly set forth by specific reference in such filing to this item of this report.

**Item 8.01 Other Events.**

On April 14, 2021 the Company issued, and posted to its website, a press release entitled "Taysha Gene Therapies Announces New Data on Multiple Preclinical Programs and Upcoming R&D Day." The full text of the press release is attached as Exhibit 99.2 to this Current Report on Form 8-K and incorporated herein by reference.

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibits

| Exhibit No. | Description |
|---|---|
| 99.1 | Corporate presentation, dated April 14, 2021. |
| 99.2 | Press release, dated April 14, 2021. |

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

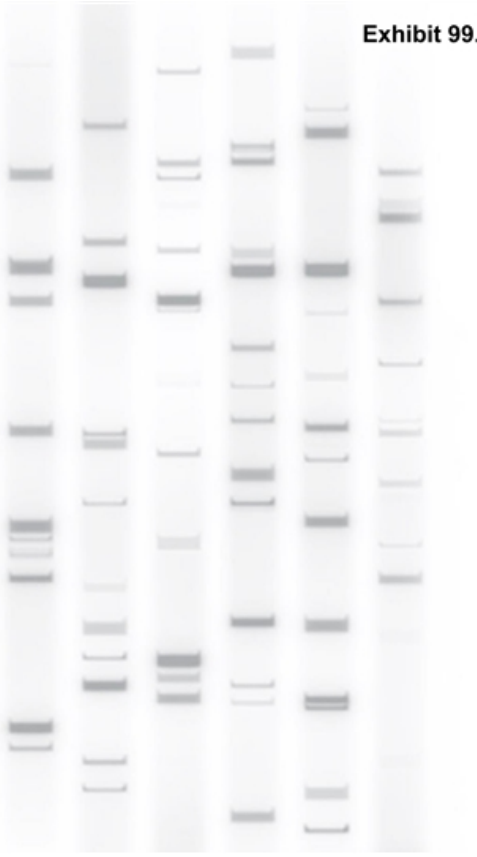
**Taysha Gene Therapies, Inc.**

Dated: April 14, 2021

By: /s/ Kamran Alam
Kamran Alam
Chief Financial Officer

Exhibit 99.1

TAYSHA GENE THERAPIES



# Bringing New Cures to Life

**Corporate Presentation**
**April 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<br>– Additional clinical data for TSHA-120 in GAN in 2H 2021<br>– Open IND for TSHA-118 in CLN1 disease; initiation of Phase 1/2 trial in 2H 2021<br>– Submit four IND/CTA filings, including Rett syndrome, in 2021<br>– 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<br>– 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<br>– 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<br>– Highly scalable suspension HEK293 manufacturing process with excellent yield<br>– 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<br>– 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**<br>*Founder, President & CEO* | |
| **Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM**<br>*Chief Medical Officer and Head of R&D* | |
| **Kamran Alam, CPA, MBA**<br>*Chief Financial Officer* | |
| **Fred Porter, PhD**<br>*Chief Technical Officer* | |
| **Mishima Gerhart**<br>*Chief Regulatory Officer and Head of Quality* | |
| **Sean McAuliffe**<br>*Chief Commercial Officer* | |
| **Jim Rouse**<br>*Chief Information Officer* | |
| **Emily McGinnis**<br>*Chief Patient Officer & Head of Government Affairs* | |
| **Tim Douros, JD**<br>*Chief Legal Officer and Corporate Secretary* | |
| **Tracy Porter, M.Ed., SPHR**<br>*Chief People Officer* | |

## Advisors

| | |
|---|---|
| **Steven Gray, PhD**<br>*Chief Scientific Advisor* | |
| **Berge Minassian, MD**<br>*Chief Medical Advisor* | |

## Board of Directors

| | |
|---|---|
| **Sean Nolan**<br>*Chairman* | |
| **Paul Manning** | |
| **Phillip Donenberg** | |
| **Sukumar Nagendran, MD** | |
| **Laura Sepp-Lorenzino, PhD** | |
| **Kathleen Reape, MD** | |
| **RA Session II** | |

# 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

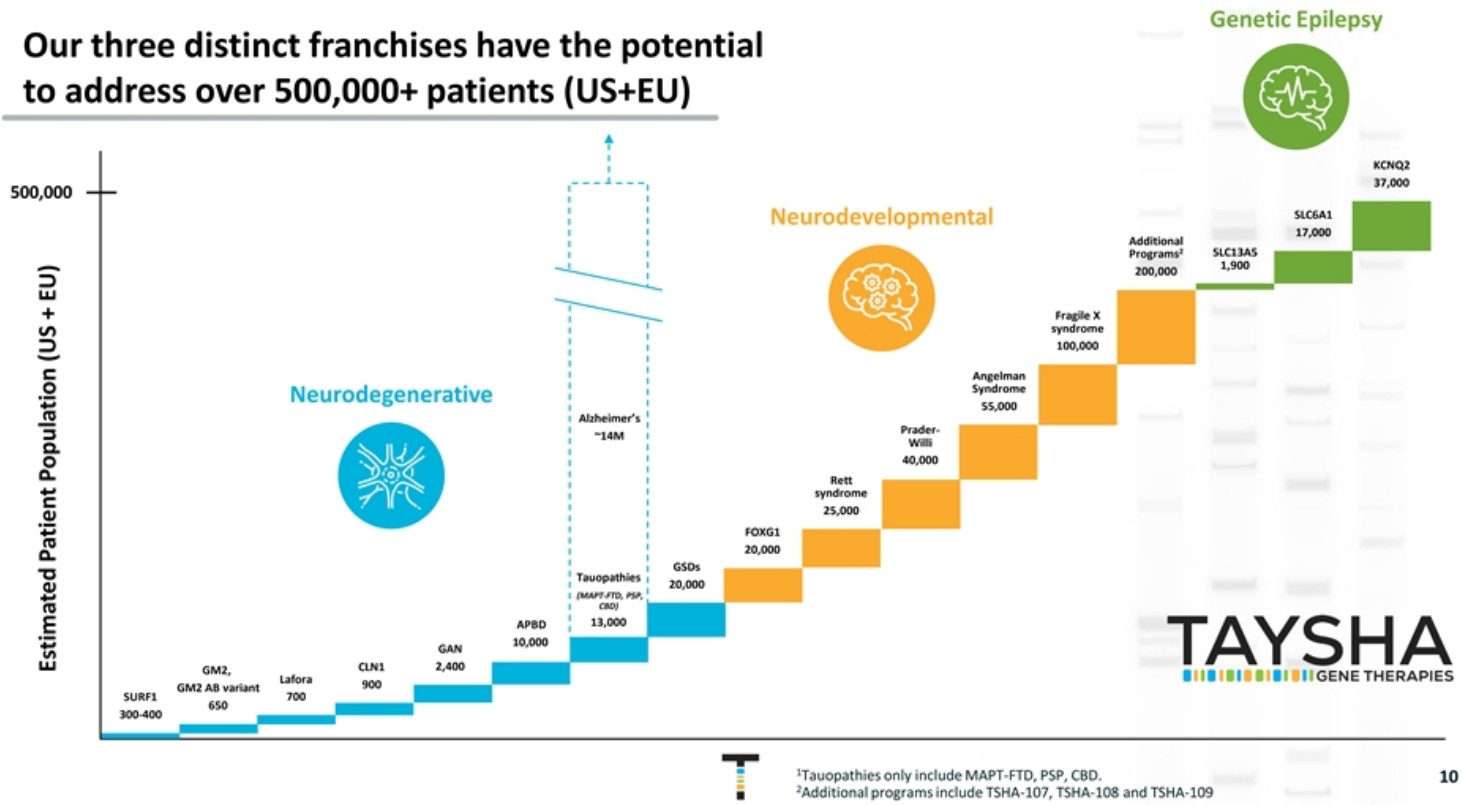
Disorders characterized by recurrent seizures often leading to abnormal development of the brain

# 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 | | | | | 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 2H21 | |
| **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 2H21 | 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

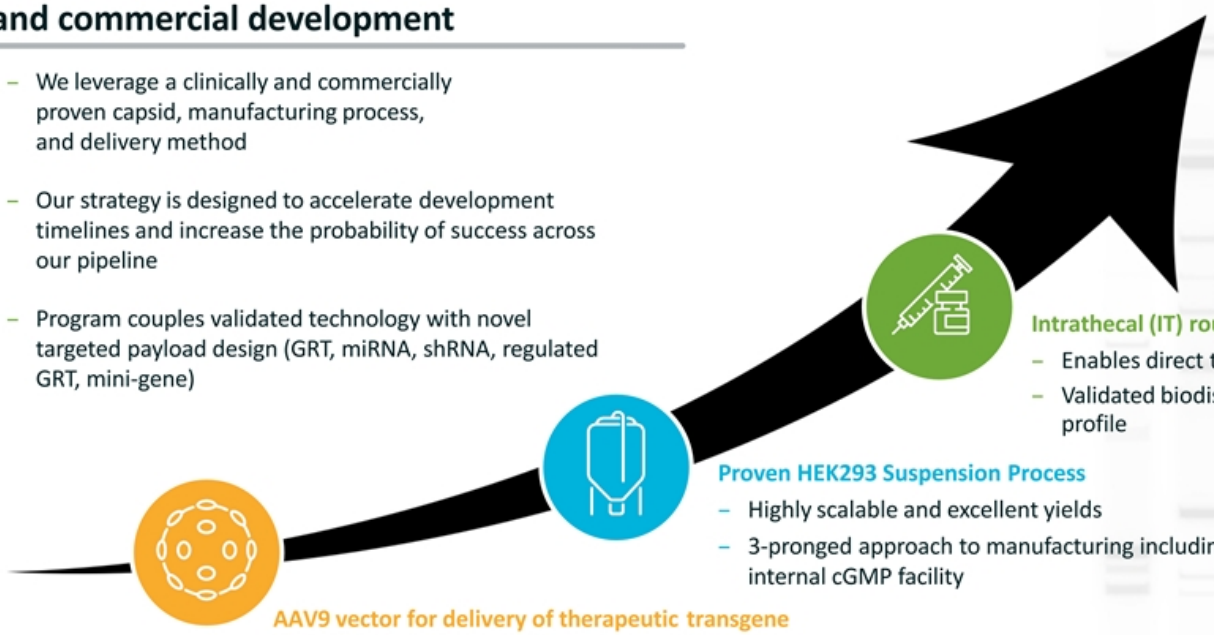
# Our three distinct franchises have the potential to address over 500,000+ patients (US+EU)




[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
- Program couples validated technology with novel targeted payload design (GRT, miRNA, shRNA, regulated GRT, mini-gene)



**Intrathecal (IT) route of administration**

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

**Proven HEK293 Suspension Process**

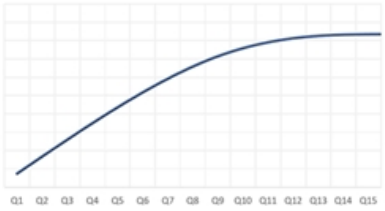
- Highly scalable and excellent yields
- 3-pronged approach to manufacturing including UTSW, Catalent and internal cGMP facility

**AAV9 vector for delivery of therapeutic transgene**

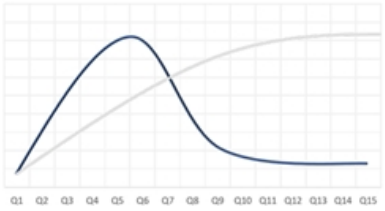
- Demonstrated safety and efficacy across multiple CNS indications

# Creating a sustainable business model for gene therapy

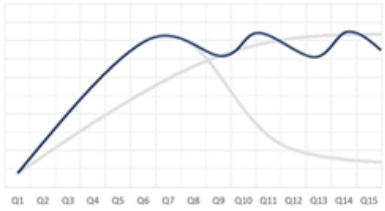
**Traditional chronic dosing business model**




**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 sub-therapeutic
- Built-in regulation system harnesses endogenous systems

## Novel Capsid Identification

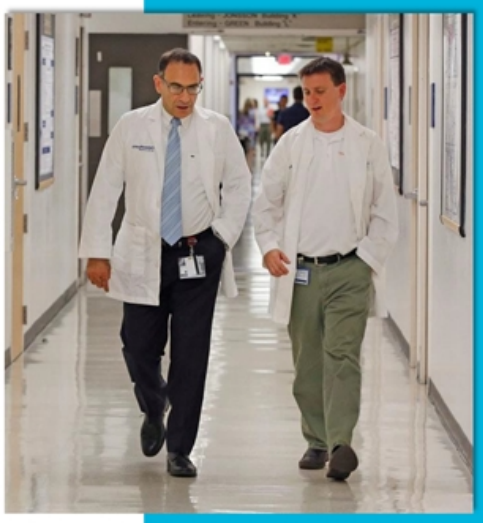
- Improves targeted delivery through use of machine learning, capsid shuffling and directed evolution
- Allows rapid identification of capsids with improved properties in mice and Non- Human Primates (NHPs) to maximize translational relevance
- Potential to drive new product candidates with novel biodistribution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

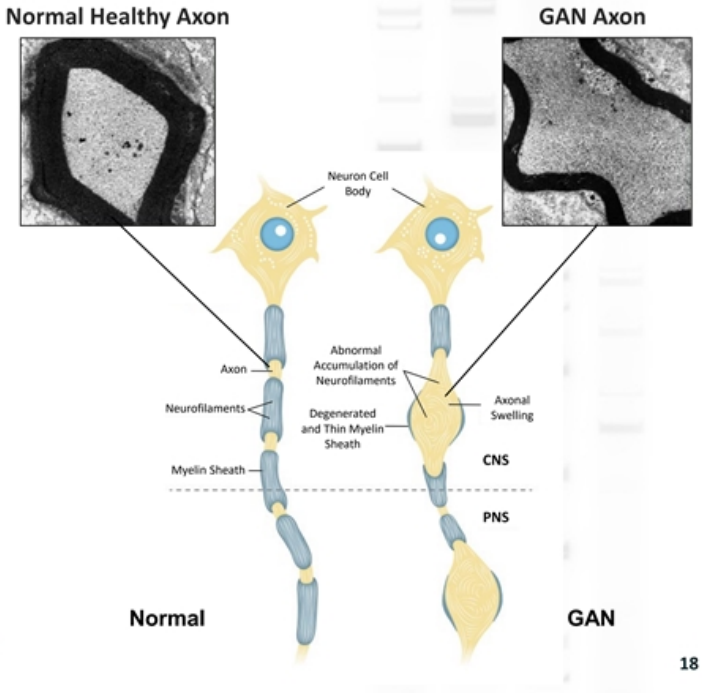
- Build internal manufacturing facility to support clinical and commercial manufacturing
  - Initial build includes two vector manufacturing trains, one fill/finish suite, QC and technical development labs
  - Building secured in Durham, NC
    - Growing hub for gene therapy manufacturing
- Facility 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

TSHA-120
GAN

- 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)

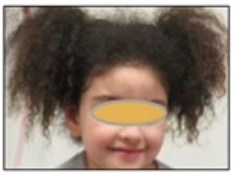


# Giant axonal neuropathy (GAN) is a rare inherited genetic disorder that affects both the central and peripheral nervous systems

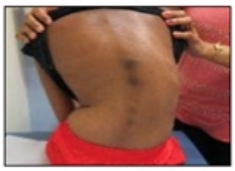
TSHA-120
GAN

- 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)

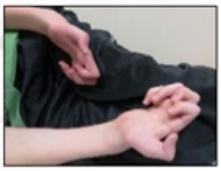
**Tightly Curled Hair**



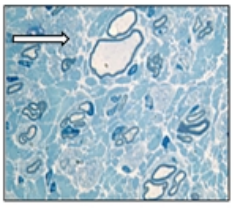
**Progressive Scoliosis**



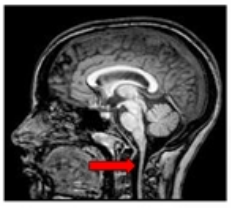
**Contractures**



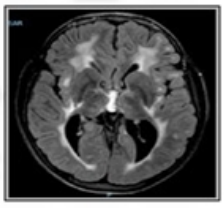
**Giant Axons**



**Spinal Cord Atrophy**



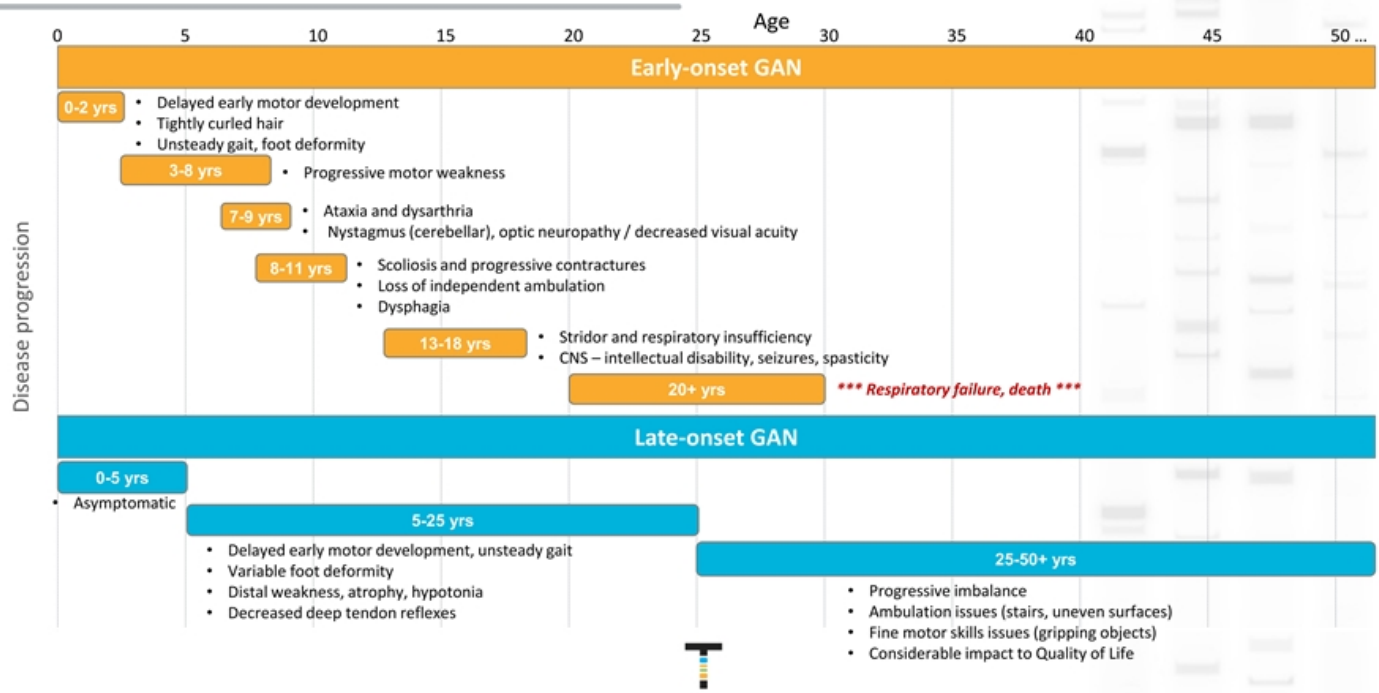
**White Matter Abnormality**



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

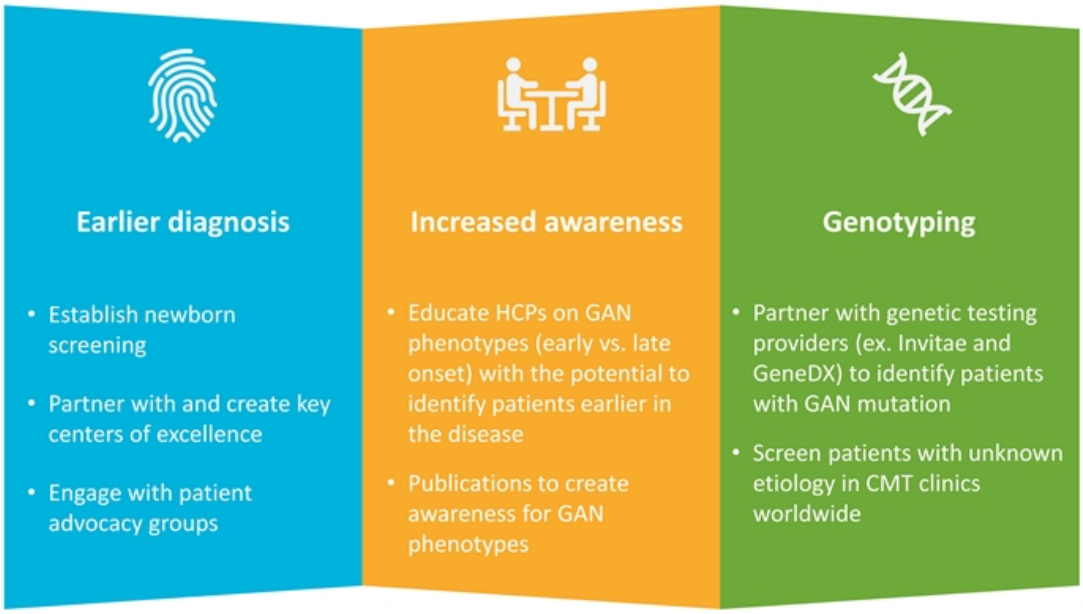
# GAN natural history and disease progression





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

TSHA-120
GAN

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# 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

## Examples of tasks

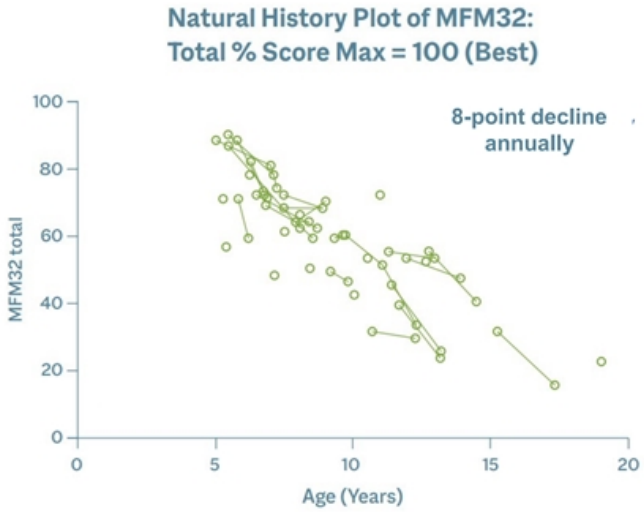
| No. | Domain | Starting Position | Exercise Requested |
|---|---|---|---|
| 1 | D1 | Supine, lower limbs half-flexed, kneecaps at zenith, and feet resting on mat | Raise the pelvis; the lumbar spine, the pelvis and the thighs are aligned and the feet slightly apart |
| 2 | D1 | Supine | Without upper limb support, sits up |
| 3 | D1 | Seated on the mat | Stands up without upper limb support |
| 4 | D1 | Standing | Without upper limb support, sits down on the chair with the feet slightly apart |
| 5 | D1 | Seated on chair | Stands up without upper limb support and with the feet slightly apart |
| 6 | D1 | Standing with upper limb supported | Releases the support and maintains a standing position for 5s with the feet slightly apart, the head, trunk, and limbs in the midline position |
| 7 | D1 | Standing with upper limb supported on equipment | Without upper limb support, raises the foot for 10s |
| 8 | D1 | Standing | Without support, touches the floor with 1 hand and stands up again |
| 9 | D1 | Standing without support | Takes 10 steps forward on both heels |
| 10 | D1 | Standing without support | Takes 10 steps forward on a line |
| 11 | D1 | Standing without support | Runs for 10m |
| 12 | D1 | Standing on 1 foot without support | Hops 10 times in place |

# 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**

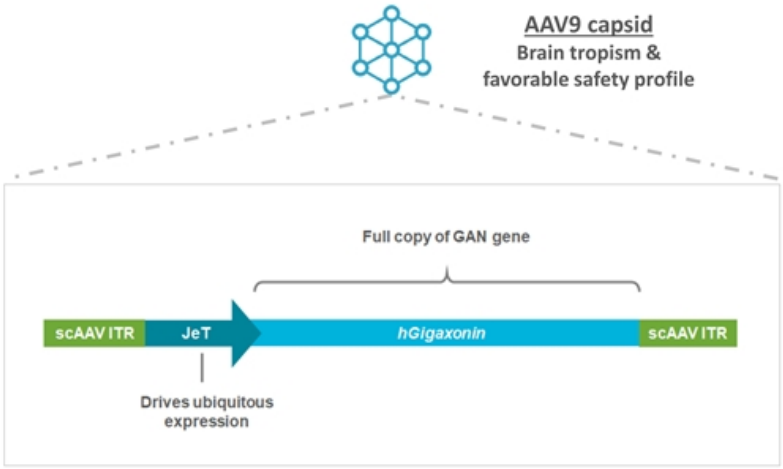



Bönnemann, C. et al; 2020

# TSHA-120 program overview and construct

TSHA-120
GAN

- 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

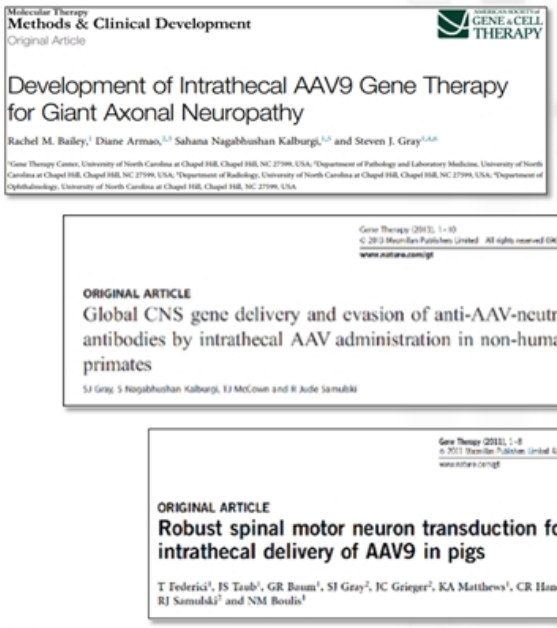


# Preclinical data supported intrathecal dosing of TSHA-120



**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

Development of Intrathecal AAV9 Gene Therapy for Giant Axonal Neuropathy

Rachel M. Bailey,[1] Diane Armao,[2,3] Sahana Nagabhushan Kalburgi,[1,3] and Steven J. Gray[1,3,4]



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, EJ McCown and R Jude Samulski



ORIGINAL ARTICLE

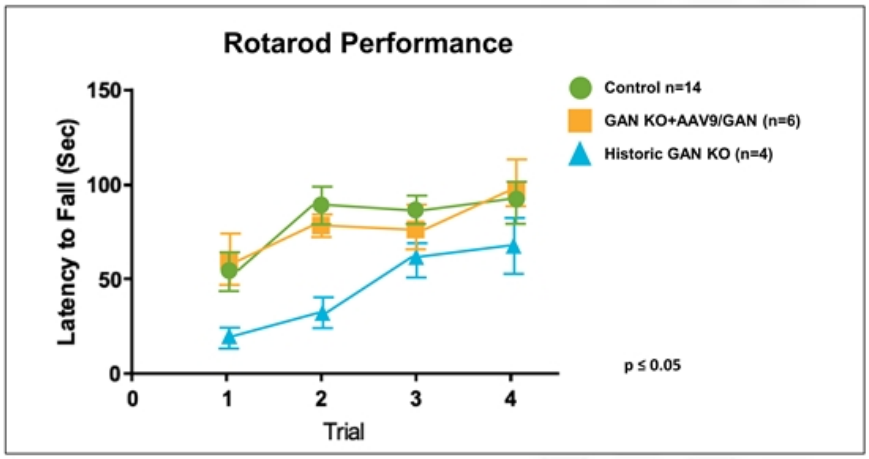
Robust spinal motor neuron transduction following intrathecal delivery of AAV9 in pigs

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

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

TSHA-120
GAN

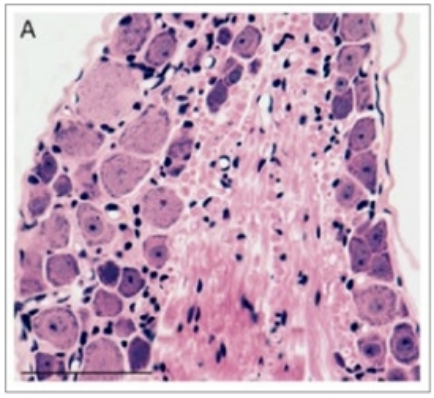
- Untreated GAN rodents performed significantly worse than heterozygous controls
- GAN rodents treated at 16 months old performed significantly better than untreated GAN rodents at 18 months old
- GAN rodents treated at 16 months old performed equivalently to heterozygous controls



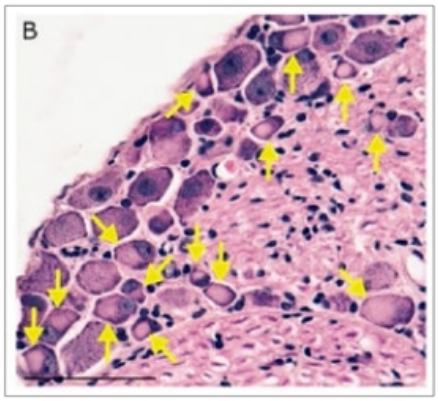

Gray, S.J., unpublished

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

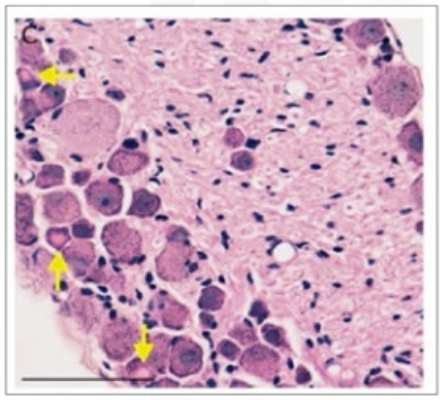
TSHA-120
GAN




Normal control




GAN KO – vehicle injected



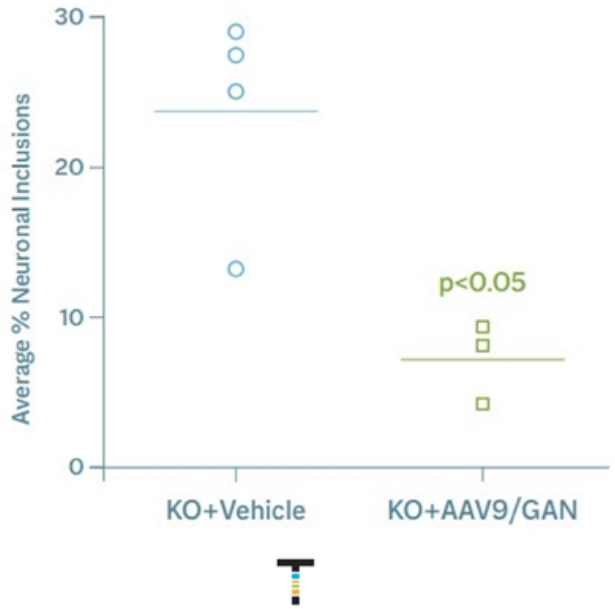

GAN KO – AAV9-GAN

Bailey, R. et al, 2018, MTMCD

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

TSHA-120
GAN

**Significant reduction in % neuronal inclusions**




Bailey, R. et al, 2018, MTMCD

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

**Goals and Targets of Trial**

### Goals

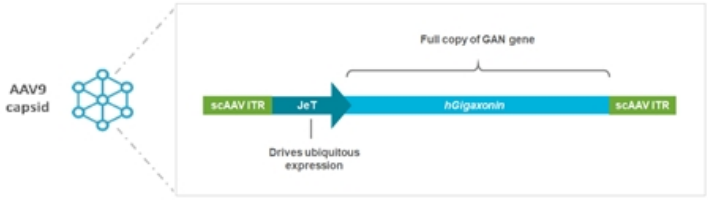
- **Primary** – Safety: clinical and laboratory assessments
- **Secondary** – Efficacy: pathologic, physiologic, functional and clinical markers

### Target Recruitment

- 14 subjects injected
- > 5 years old

### Target Areas to Transduce

**Product Details and Dose Cohorts**



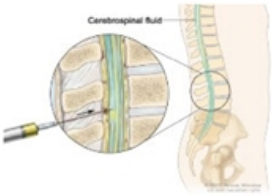

### Dose Cohorts*

| | |
|---|---|
| 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**

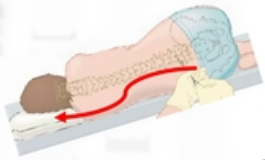
### Administration

- 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

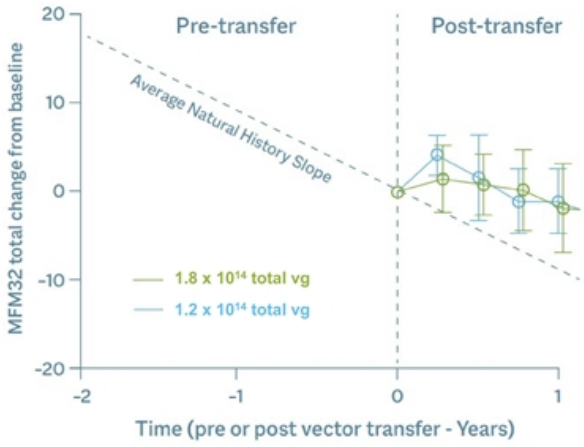
Clinical Trial: NCT02362438

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

TSHA-120
GAN

- 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

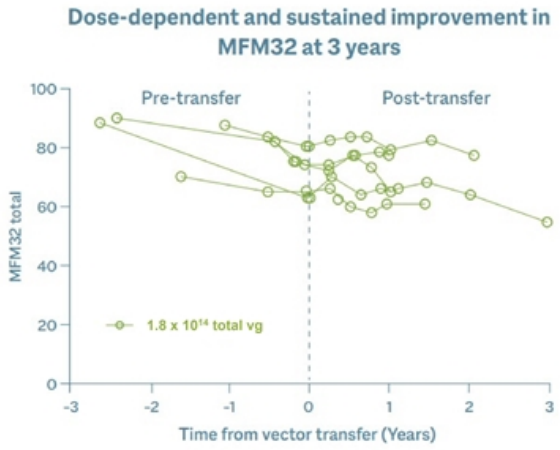
## Dose-dependent and sustained improvement in MFM32 at 1 year

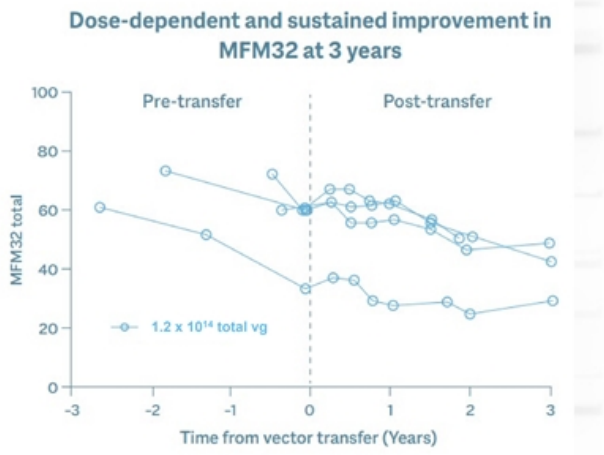



Bönnemann, C. et al; 2020

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

TSHA-120
GAN




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

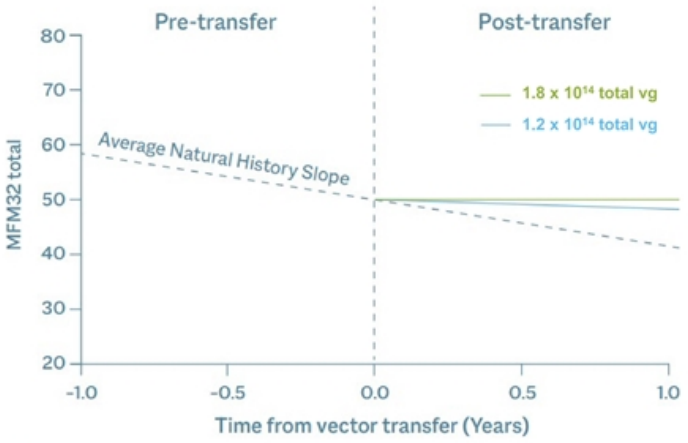
- 6 patients treated for 3+ years supporting long-term durability
- Plan to engage with agencies in US, EU and Japan to discuss regulatory pathway as soon as possible

Bönnemann, C. et al; 2020

# Additional analysis using Bayesian methodology confirmed arrest of disease progression

TSHA-120
GAN

- 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 1.8x$10^{14}$ 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: 1.8x$10^{14}$ total vg | 7.78 | 1.94 | 7.78 | 1.89 | <0.001 |
| Post infusion: 1.2x$10^{14}$ 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 |

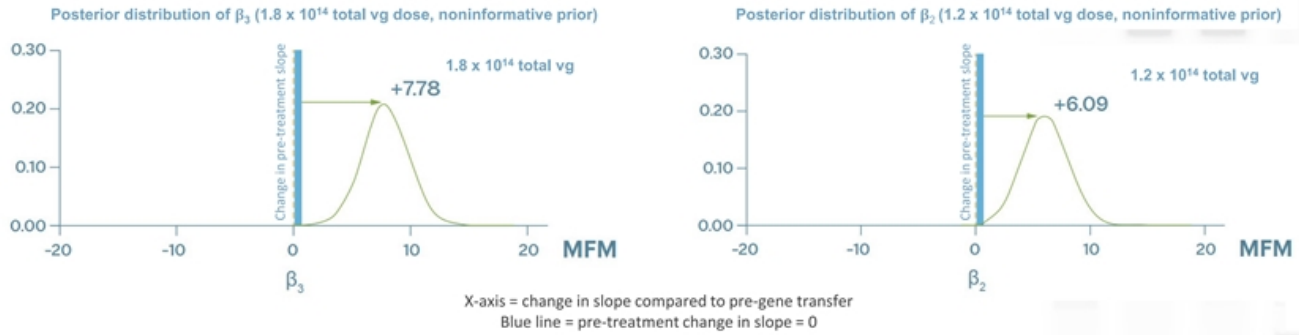
Bönnemann, C. et al; 2020

# 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**




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

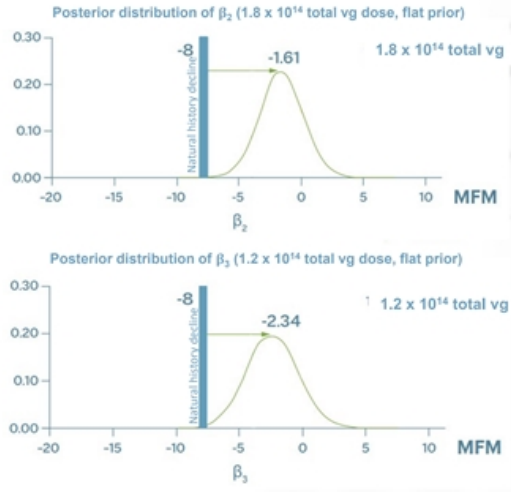
- Graphs depict treated population average annual post-treatment decline for both the $1.8x10^{14}$ total vg cohort and the $1.2x10^{14}$ total vg cohort
- $1.8x10^{14}$ vg halted patient pre-treatment rate of decline, avg annual slope improvement of 7.78 points
- $1.2x10^{14}$ vg resulted in clinically 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



- 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

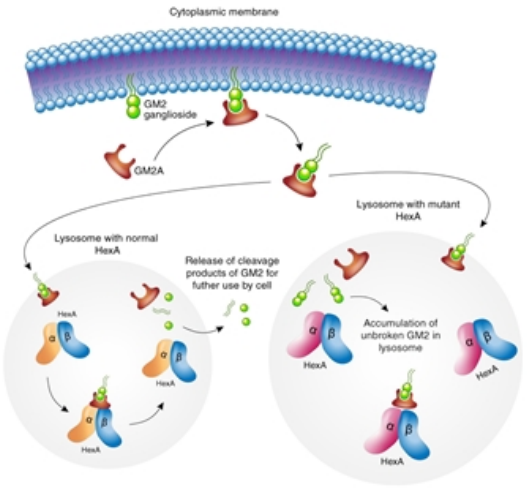
TSHA-120
GAN

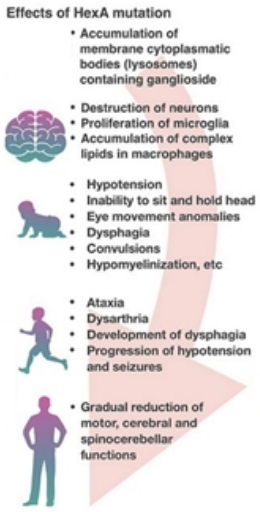
- Complete transfer data from the NIH
- Initiate manufacturing of commercial-grade GMP material
- Request an end-of-Phase meeting; discuss the regulatory pathway for TSHA-120
- Request regulatory guidance from EMA and PMDA
- Initiate new clinical sites in US and EU
- Update on regulatory interactions 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

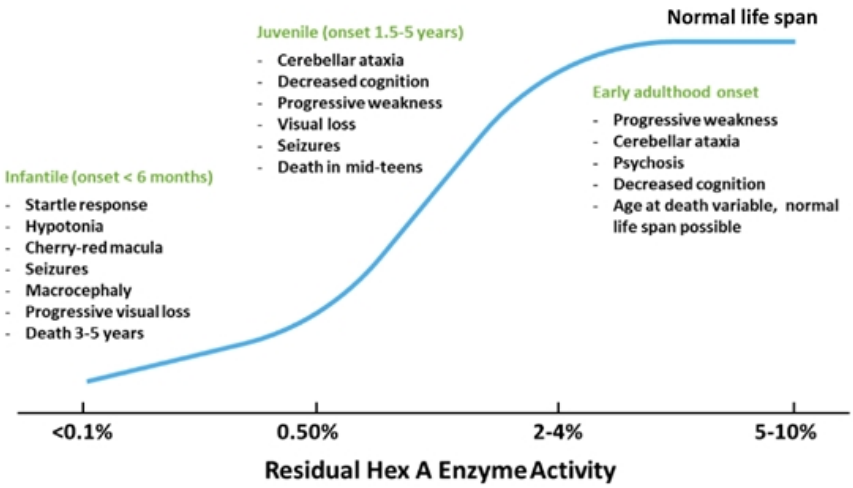


# Residual Hex A activity determines the severity of GM2



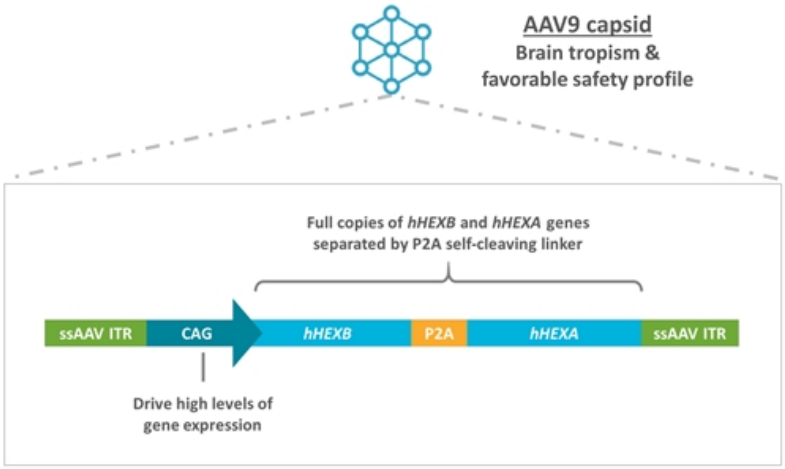
- Small increases in Hex A activity may lead to significant improvements in clinical outcomes and quality of life
- Infantile onset is the most severe form of GM2
- Infantile forms may die within the first 4 years of life, and juvenile onset patients rarely survive beyond mid-teens



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

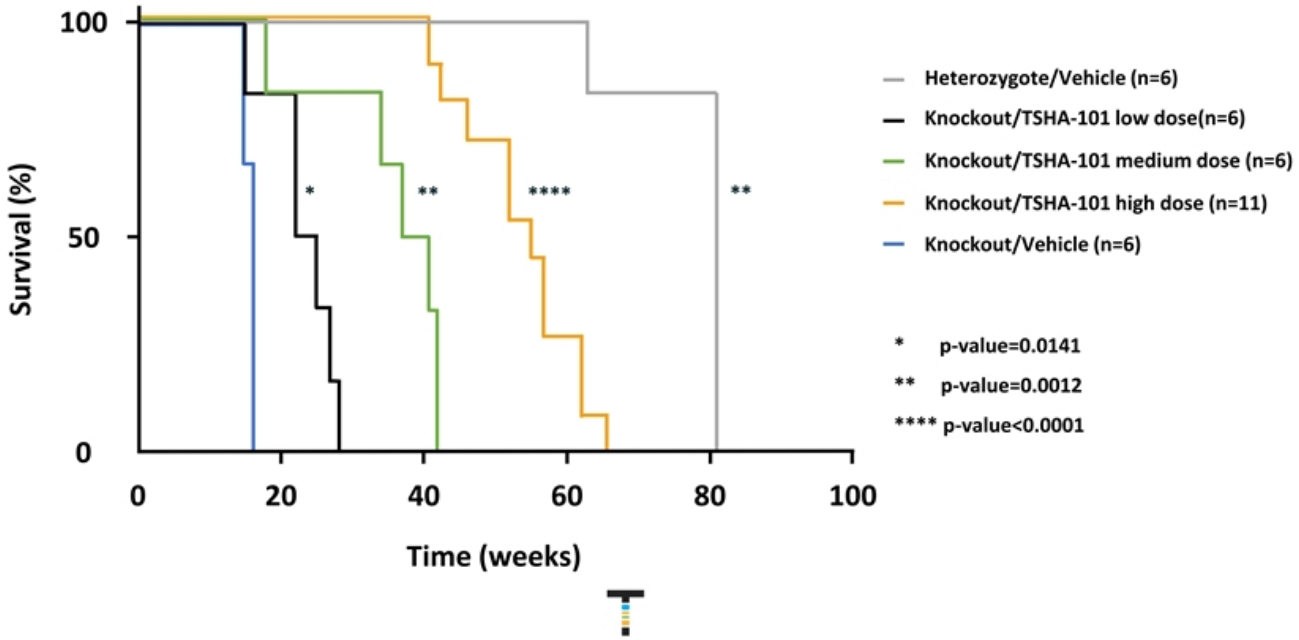
TSHA-101
GM2 gangliosidosis

- *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



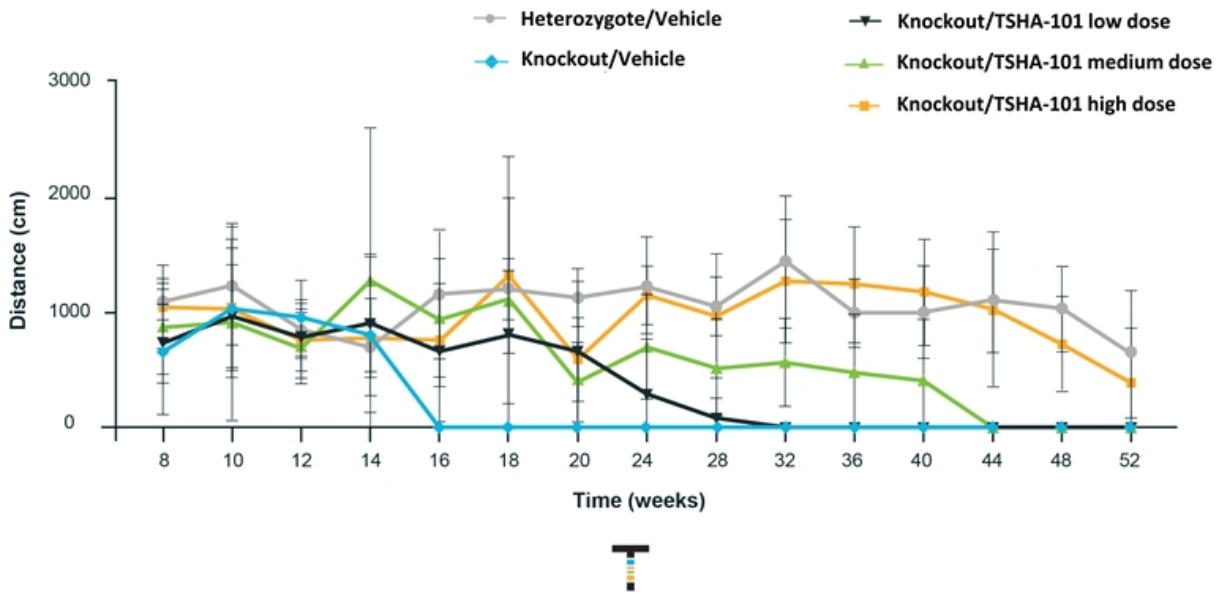
# Significant, dose-dependent improvement in survival observed in mice treated with TSHA-101





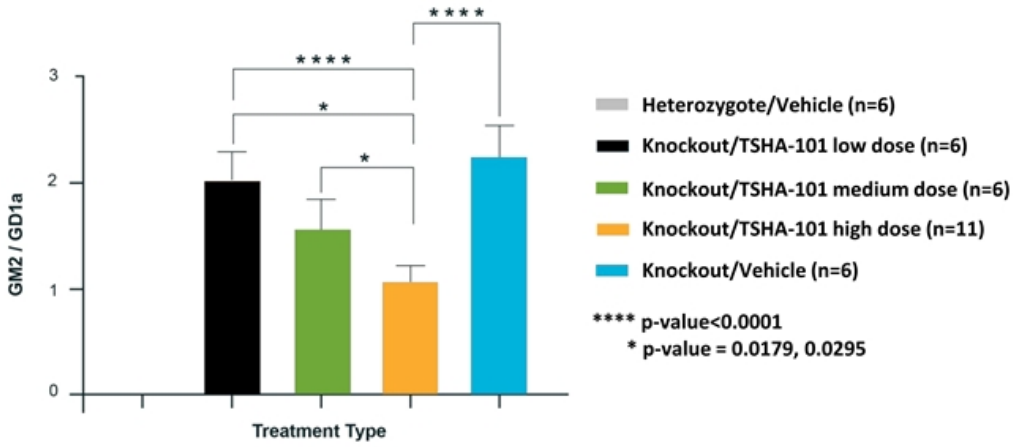
# Dose-dependent improvements observed in rotarod assessments in mice treated with TSHA-101

TSHA-101
GM2 gangliosidosis



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

TSHA-101
GM2 gangliosidosis



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

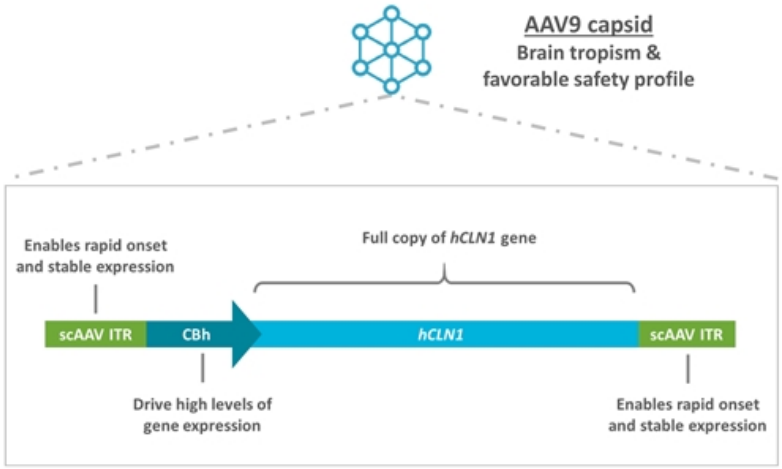
TSHA-101
GM2 gangliosidosis

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

# CLN1 disease is a severe neurodegenerative lysosomal storage disease

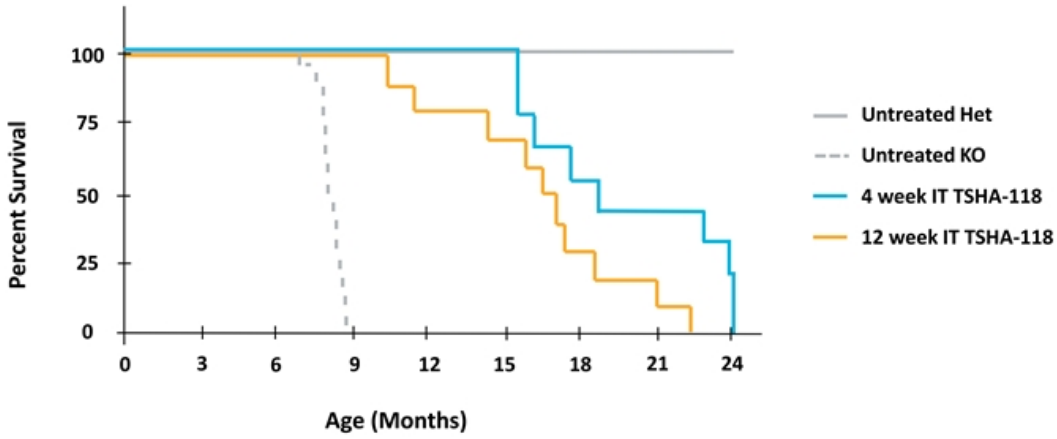


- Severe, progressive, neurodegenerative lysosomal storage disease, with no approved treatment
- Caused by mutations in the *CLN1* gene, encoding the soluble lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1)
- The absence of PPT1 leads to the accumulation of palmitoylated substrate within the 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

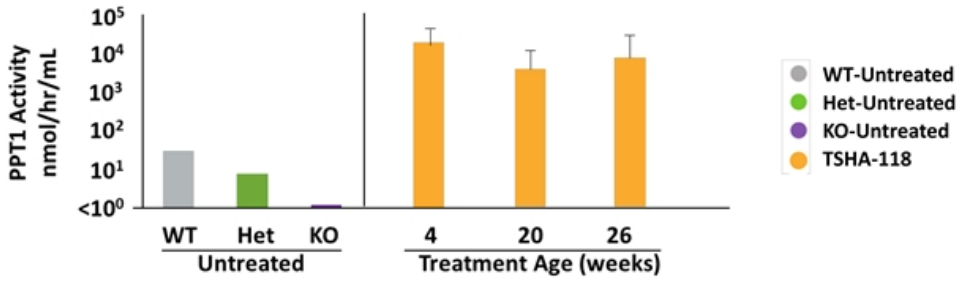





IT administration of TSHA-118 significantly extended survival of *PPT1* KO mice for all ages and at all dose levels

# 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

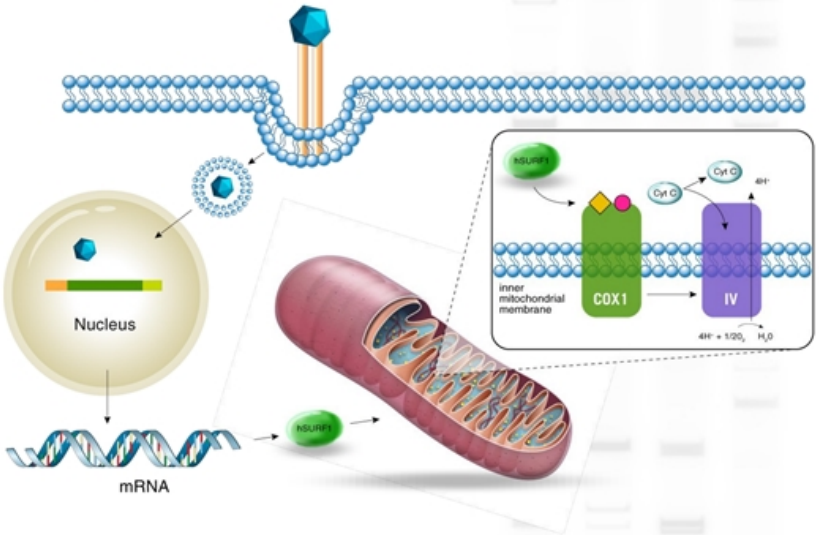
TSHA-118
CLN1 disease

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

# SURF1 deficiency is the most common cause of Leigh syndrome



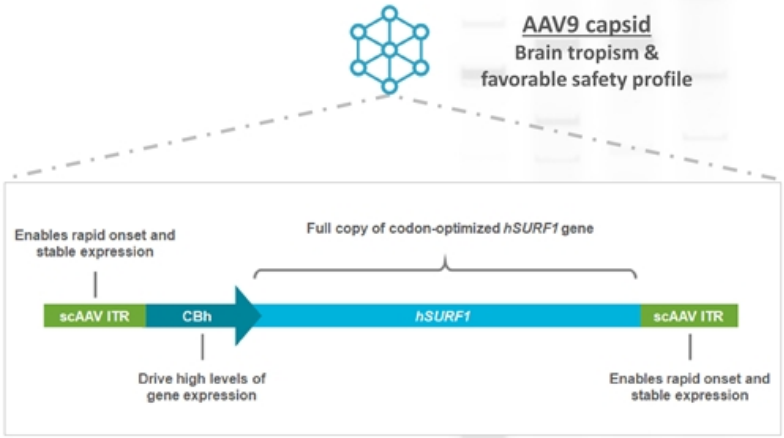
- A monogenic mitochondrial disorder
- Most common cause of cytochrome c oxidase deficient Leigh syndrome
- Leigh syndrome – severe neurological disorder that presents in the first year of life
  - Initially often presents with gastrointestinal symptoms
  - Progressive loss of mental and movement abilities, 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

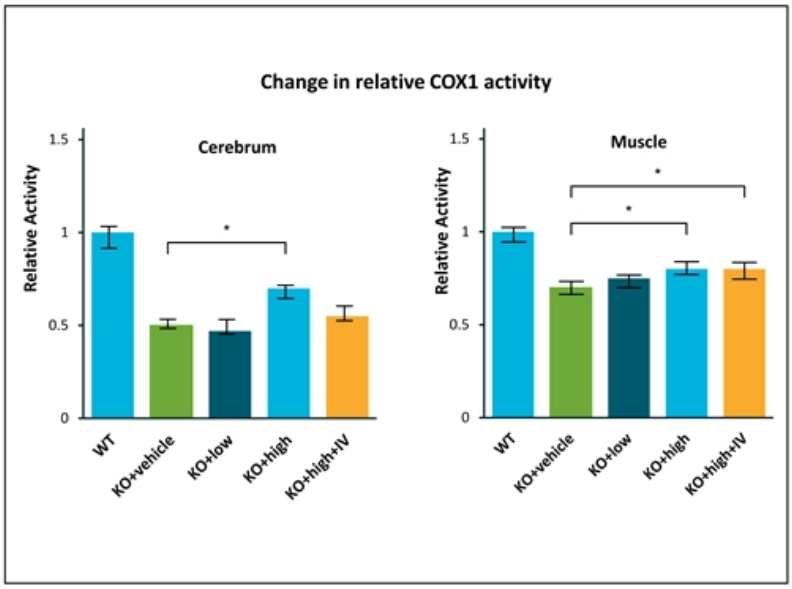
TSHA-104
SURF1 deficiency

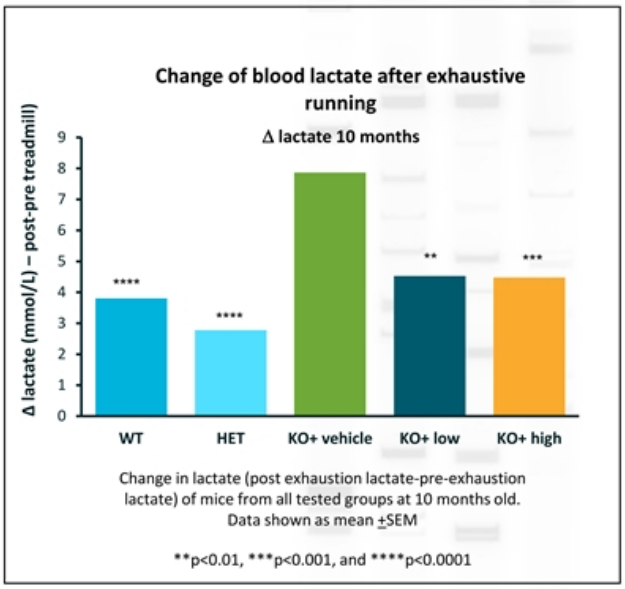
- Recombinant AAV9 viral vector with engineered transgene encoding the human SURF1 protein
- Designed to deliver a functional copy of the SURF1 gene
- Received orphan drug and rare pediatric disease designations
- IND/CTA filing expected in 2H 2021
- Initiation of Phase 1/2 trial expected by the end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



# 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





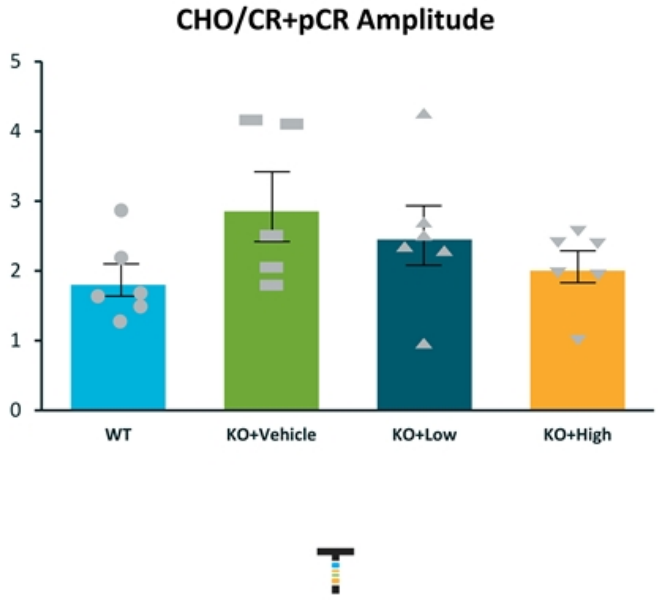

Change in lactate (post exhaustion lactate-pre-exhaustion lactate) of mice from all tested groups at 10 months old. Data shown as mean ±SEM

**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

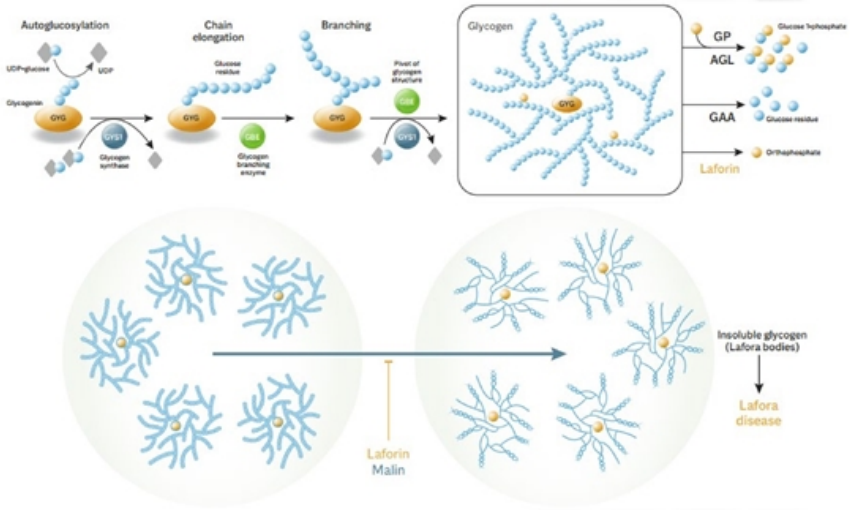
TSHA-104
SURF1 deficiency

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

# Lafora disease is a progressive and fatal neurodegenerative disorder



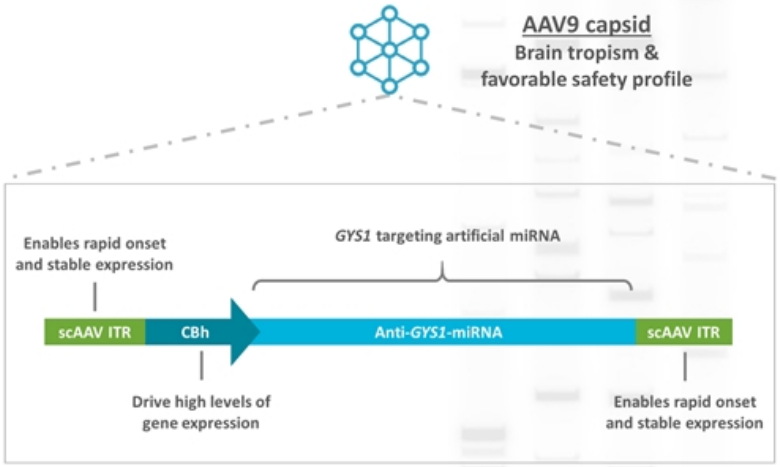
- Inherited, severe form of progressive myoclonus epilepsy
- Caused by loss of function mutations in the *EPM2A* (laforin) or *EPM2B* (malin) genes responsible for glycogen metabolism
- Absence of laforin or malin results in aggregates of polyglucosans or abnormally shaped glycogen molecules known as 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

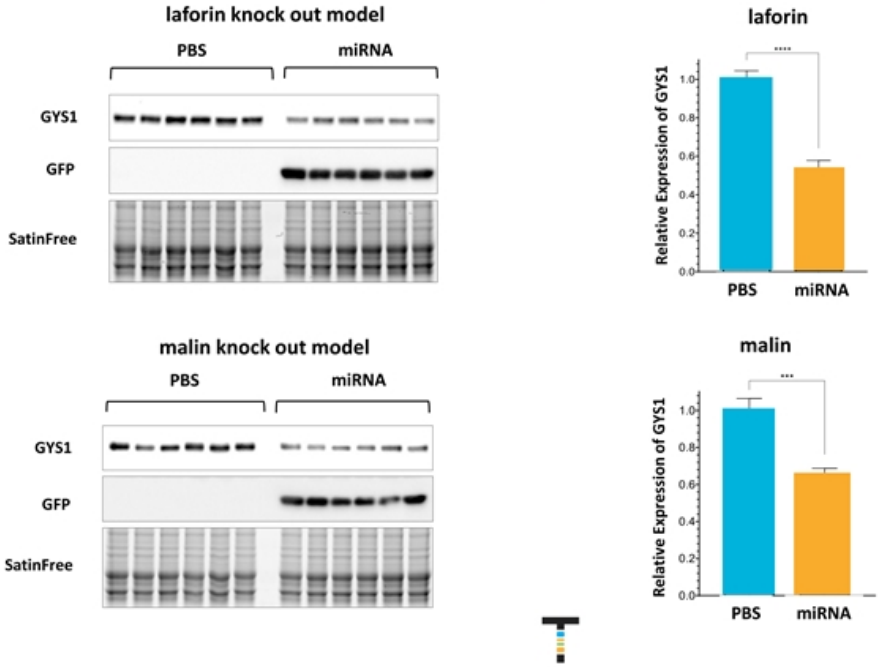
TSHA-111
Lafora disease

- 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



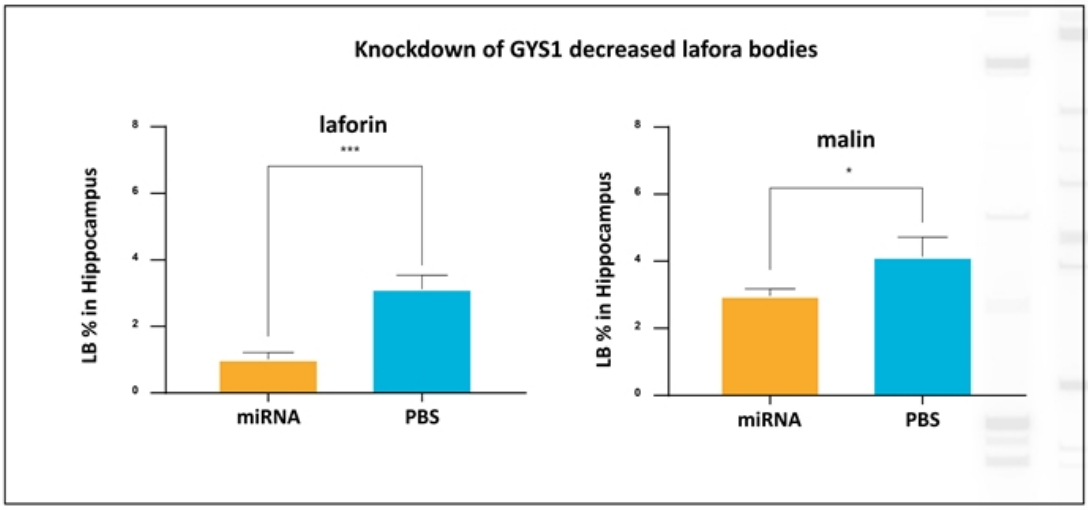
# TSHA-111-LAFORIN and TSHA-111-MALIN reduced GYS1 expression in the laforin and malin KO models





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

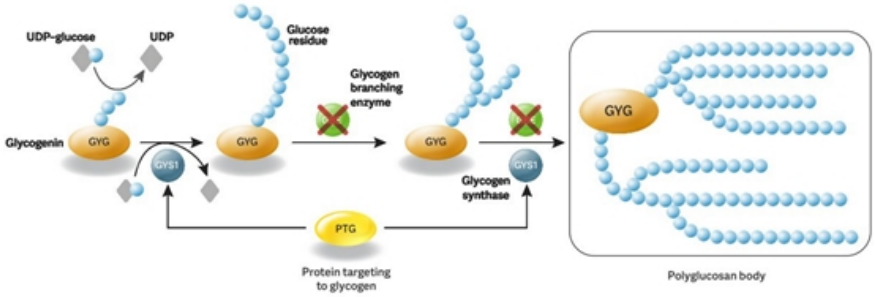




# Adult polyglycosan body disease (APBD)

TSHA-112
APBD

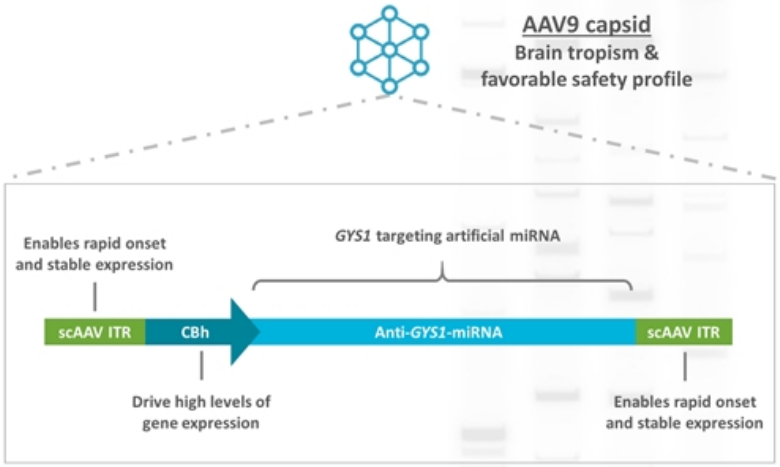
- Caused by a mutation in the *GBE1* gene, responsible for the creation of branches during glycogen synthesis
- Reduction in glycogen synthesis yields elongated glycogen changes that form poorly soluble aggregates in the liver, muscle and CNS
- Prime of life disease, with onset between 40-50 years
- 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

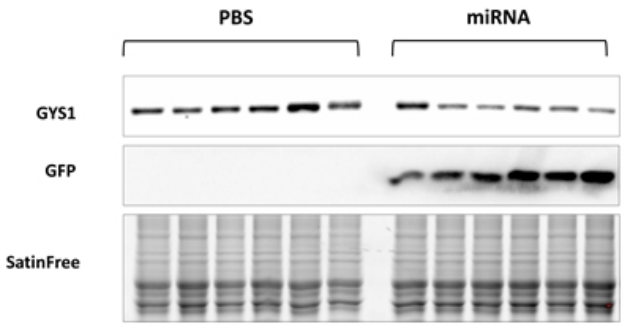
TSHA-112
APBD

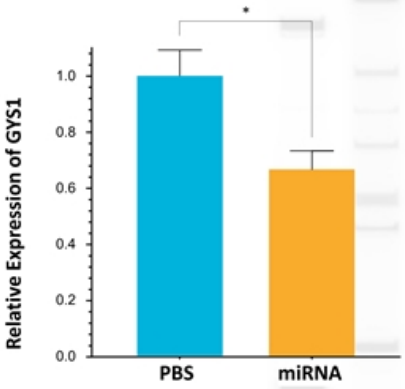
- Recombinant AAV9 viral vector designed for miRNA-mediated knockdown of the *GYS1* gene to treat APBD
- Self-complementary AAV capsid (scAAV) for rapid activation and stable expression
- CBh promoter drives high levels of expression
- Currently in IND/CTA-enabling study



# TSHA-112 reduced GYS1 expression in the APBD KO model



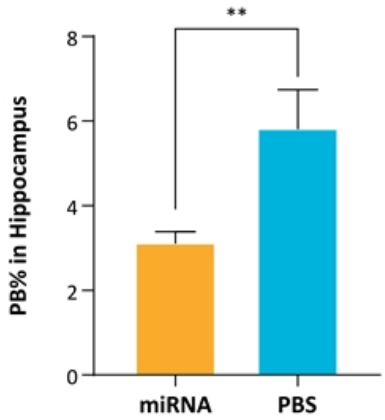



Gumusgoz, E. 2020

# TSHA-112 decreased polyglucosan body formation in mice hippocampus



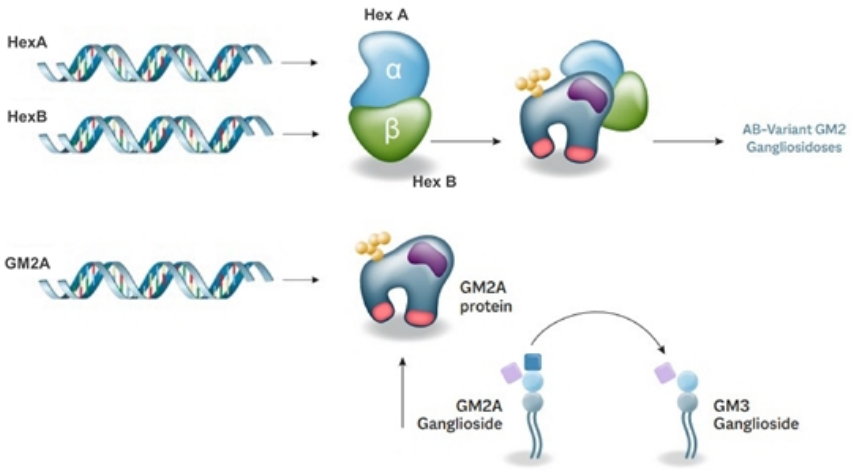



TSHA-112 decreased polyglucosan body formation in the hippocampus

# GM2 gangliosidosis, AB variant



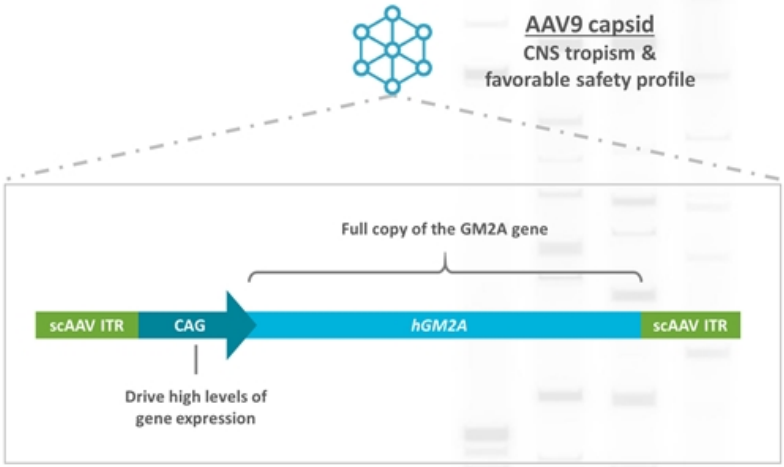
- Characterized by a mutation in the *GM2A* gene, leading to a deficiency of the GM2-activator protein (GM2AP), a required co-factor for the breakdown of GM2-gangliosides by the protein Hex A
- Loss-of-function mutations result in a deficiency of GM2AP causing intra-lysosomal accumulation of GM2 and 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

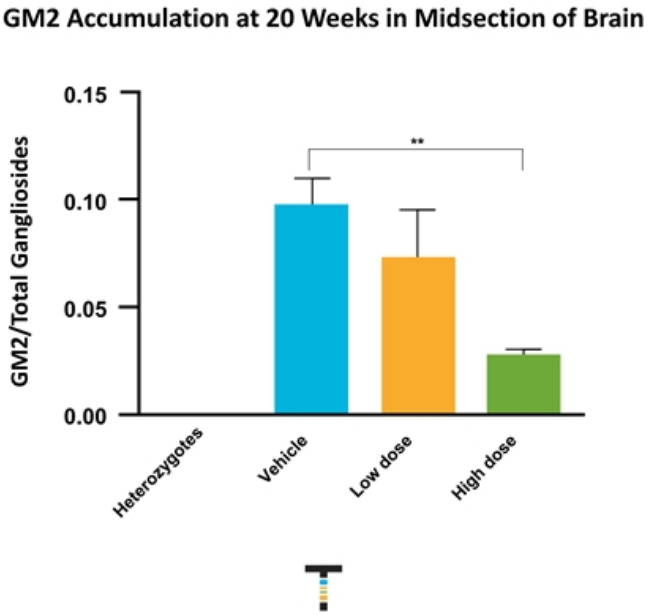
TSHA-119
GM2 AB Variant

- 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

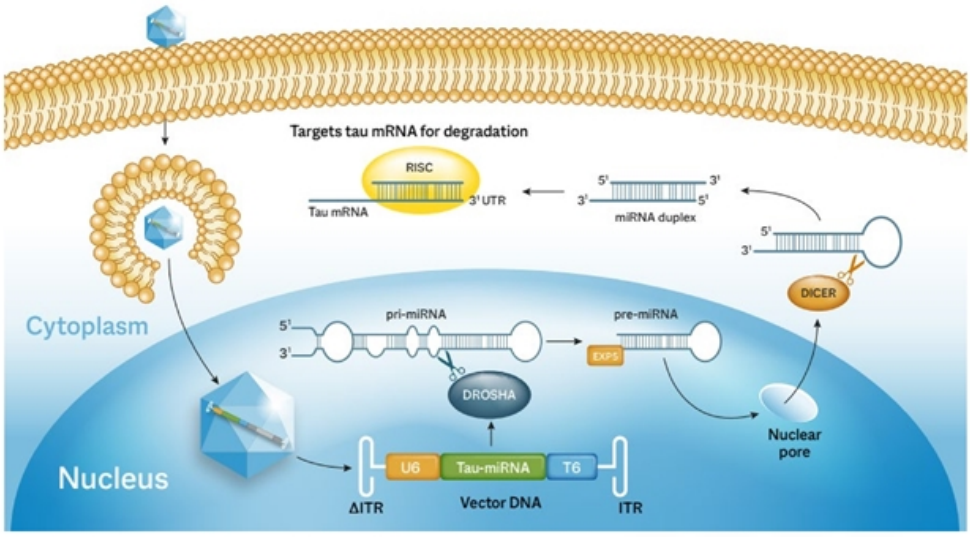




# Tauopathies – Microtubule associated Protein Tau (MAPT)



- 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

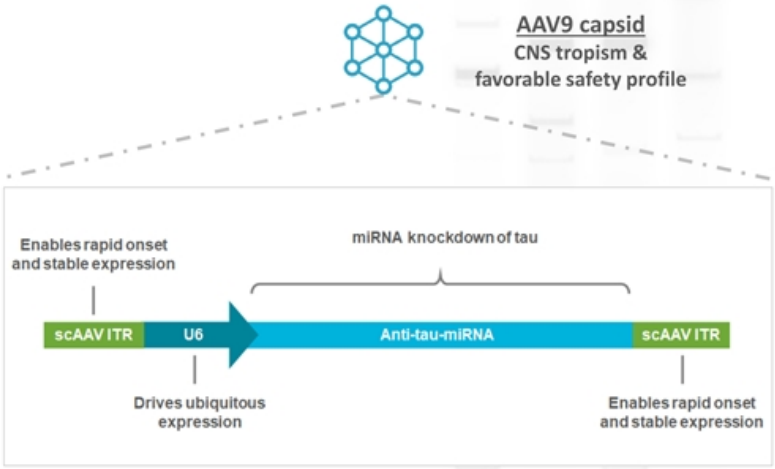



FTD – frontotemporal dementia; PSP – progressive supranuclear palsy; CBD – corticobasal degeneration

# TSHA-113 in preclinical development

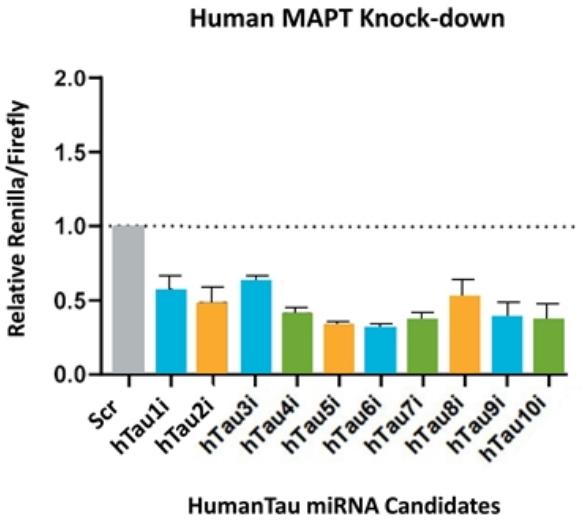
TSHA-113
Tauopathies

- 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



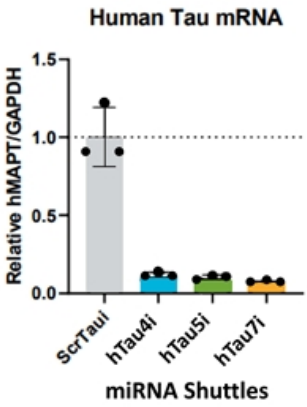


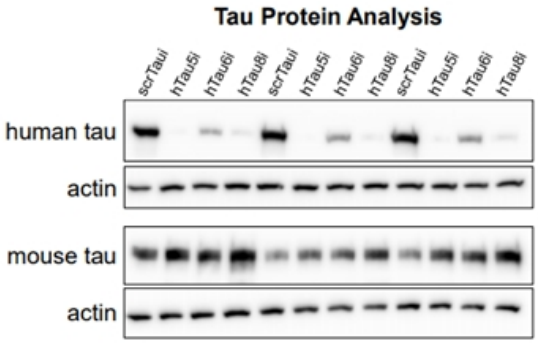

Secondary screening of top candidates: hTau4i, hTau5i, and hTau7i

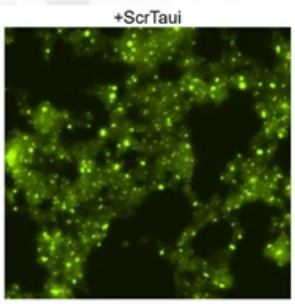
Scr = scrambled tau miRNA
hTau = human-specific tau miRNA

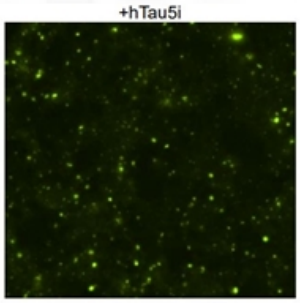
# TSHA-113 reduced K18 tau expression

TSHA-113
Tauopathies

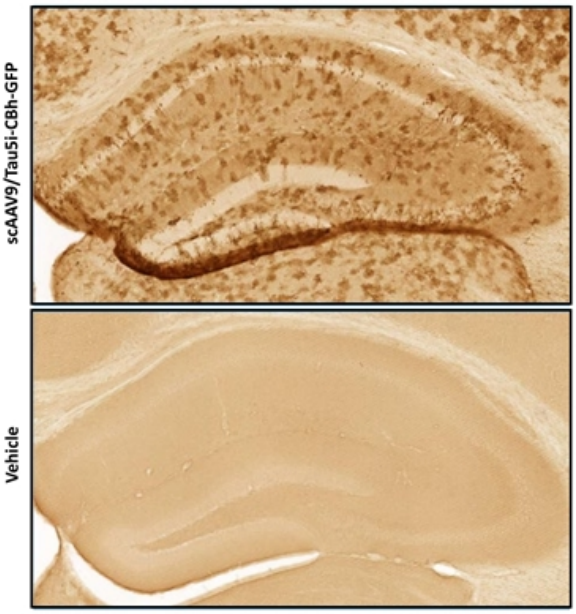


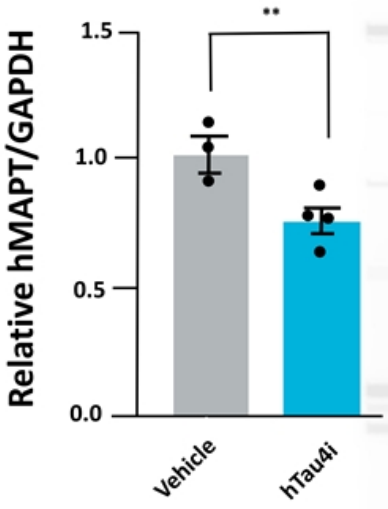



# Mice dosed with TSHA-113 demonstrated widespread function and GFP expression in neurons and glia



# 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 in 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

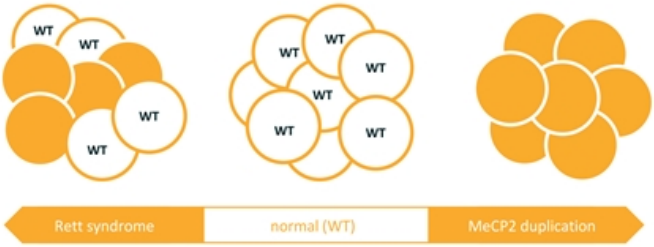
**85-90%** of affected people may **experience growth failure** and **muscle wasting** that worsens with age

1. Guy J et al. Science 2007

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



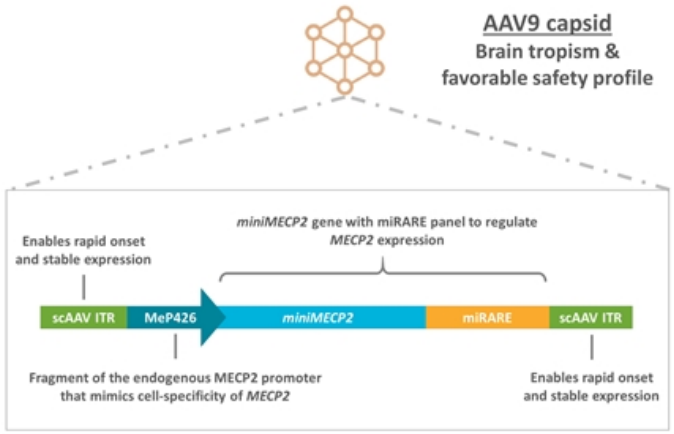
- Characterized by mutations in methyl CpG-binding protein 2 (*MECP2*), a protein that is essential for neuronal and synaptic function in the brain.
- Female heterozygous RTT patients are mosaic carriers of normal and mutated *MECP2*
- RTT falls along a spectrum of *MECP2* activity and toxicity from 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*

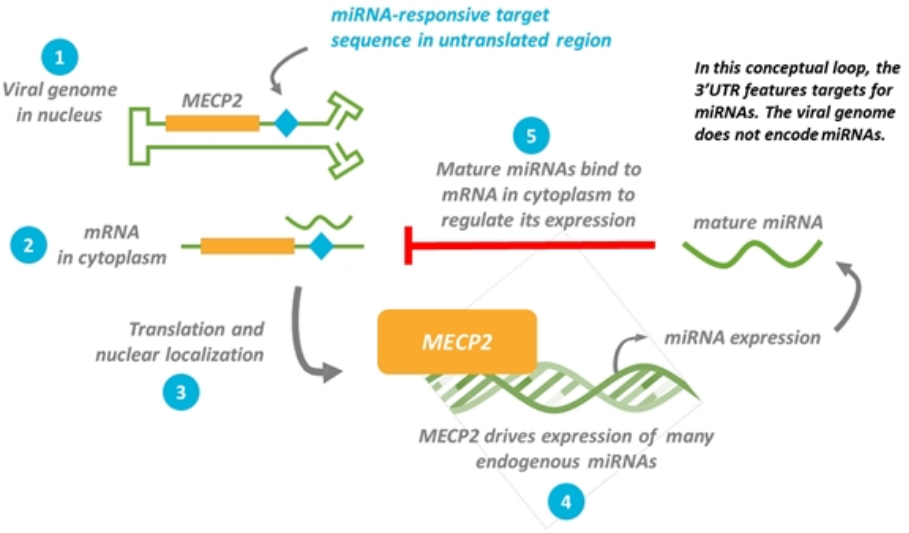
TSHA-102
Rett Syndrome

- 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



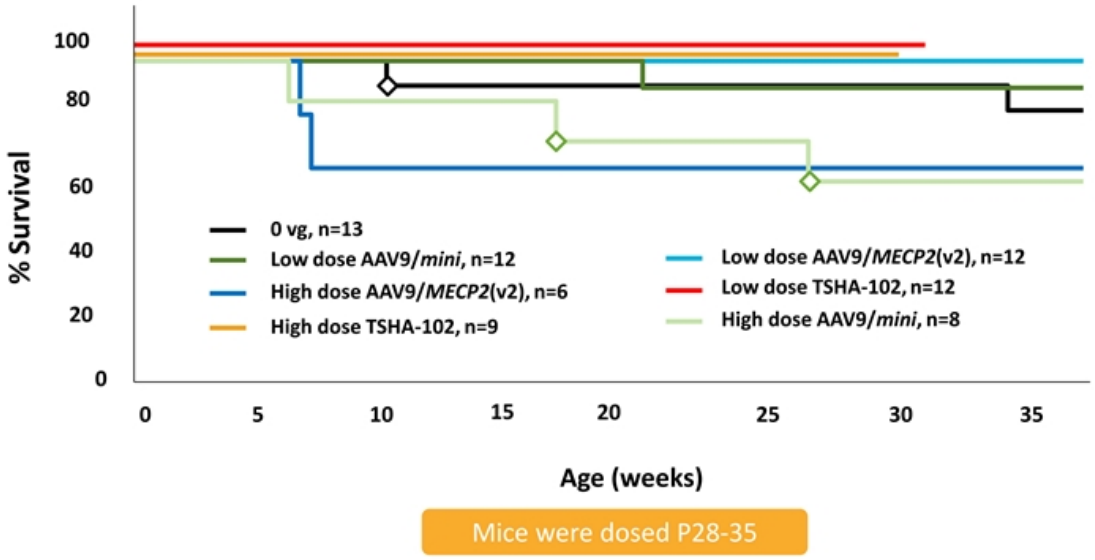
# miRARE is a targeting panel for endogenous miRNAs which regulate MECP2 expression





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



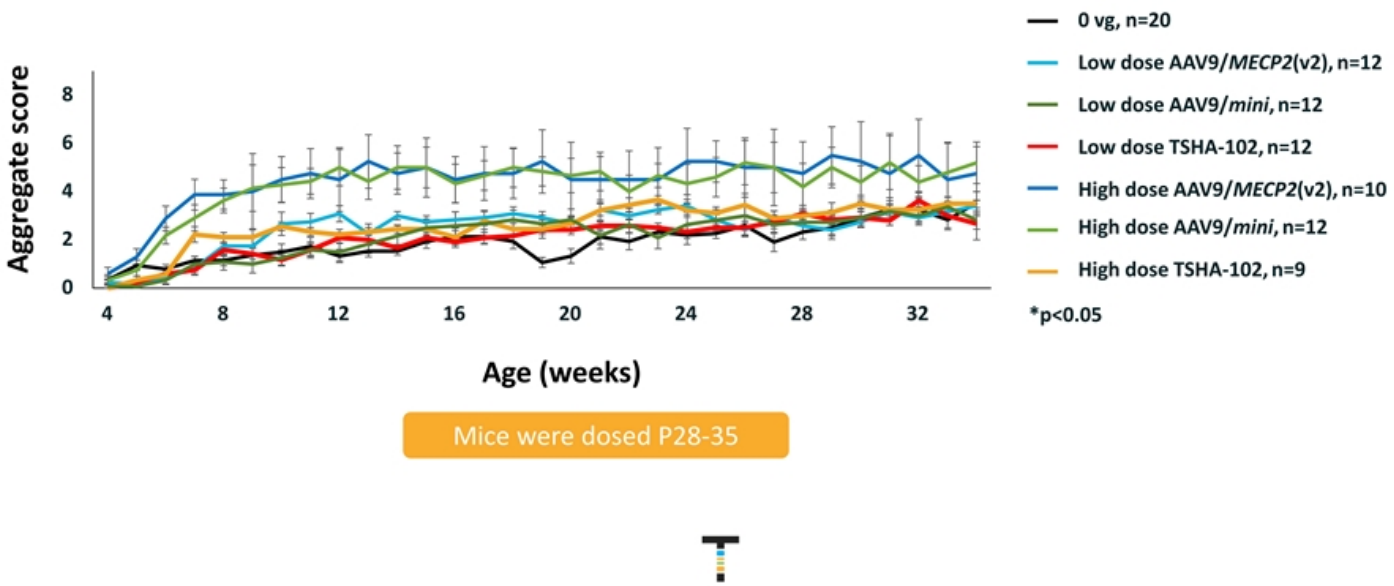



Mice were dosed P28-35

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

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

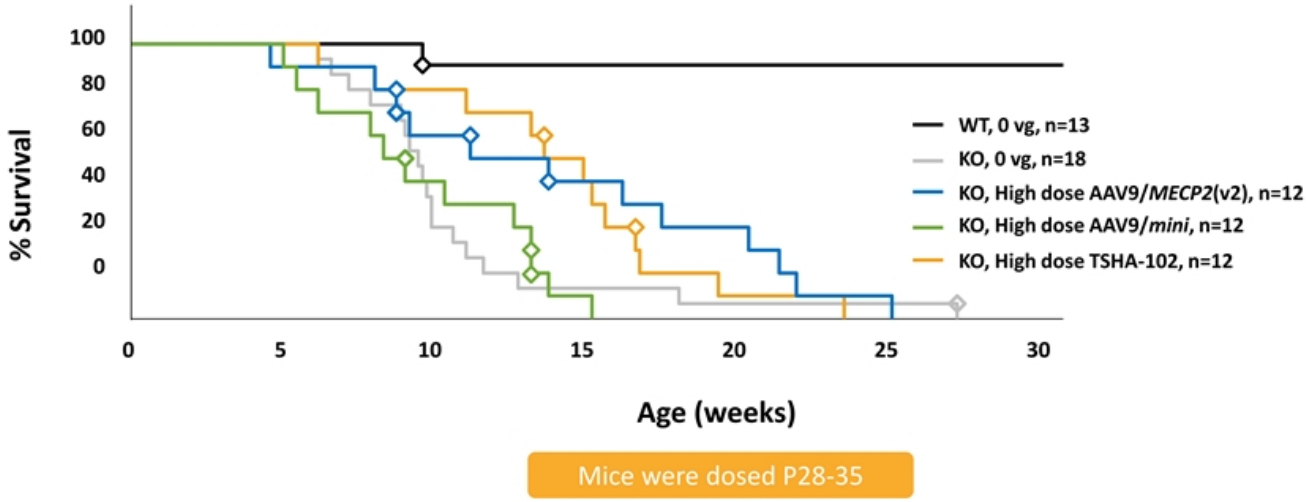





Mice were dosed P28-35

# 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.

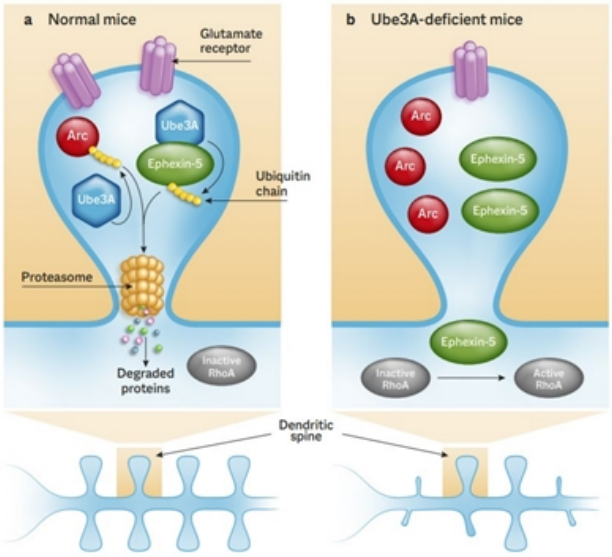
# IND/CTA filing for TSHA-102 in Rett syndrome expected in 2H 2021



| | |
|---|---|
| **Study design and duration** | • Open-label, dose-ranging, randomized, multi-center Phase 1/2 trial<br>• Safety and preliminary efficacy<br>• 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)<br>• Second cohort (n=4): single dose of $1x10^{15}$ total vg of TSHA-102 (AAV9/*MECP2*-miRARE)<br>• Delivered intrathecally |
| **Key clinical assessments** | **Rett-Specific/Global Assessments**<br>• Motor Behavior Assessment Scale (MBA)<br>• Rett Syndrome Hand Apraxia Scale (RHAS)<br>• Rett Syndrome Behavior Questionnaire (RSBQ)<br>• Functional Mobility Scale in Rett Syndrome (FMS)<br>• Clinical Global Impression<br><br>**Behavior/Mood Assessments**<br>• Anxiety, Depression, and Mood Scale (ADAMS)<br>• Aberrant Behavior Checklist (ABC)<br><br>**Seizure Assessments**<br>• EEG and neurophysiology<br>• Seizure diary<br><br>**Respiratory Assessments**<br>• Respiratory Disturbance Index (RDI)<br>• Sleep apnea, sleep study<br><br>**Communication Assessments**<br>• Observer Reported Communication Assessment (ORCA)<br><br>**Quality of Life/Other Assessment**<br>• SF-36 – Quality of life assessment from principal caregiver<br>• RTT-CBI – Caregiver burden inventory<br><br>**Wearables**<br>• 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

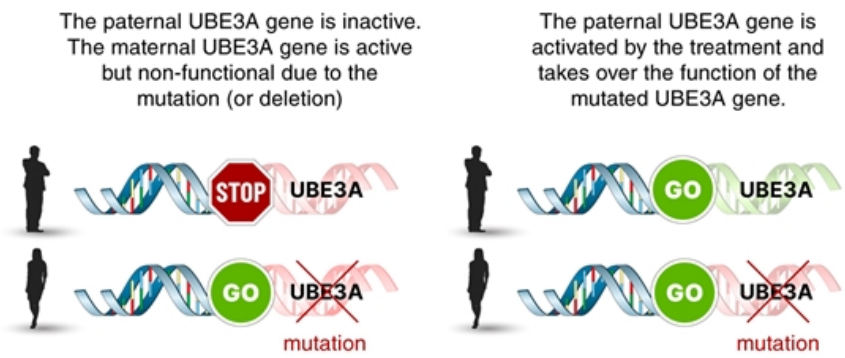



UPD – Uniparental disomy
Scheiffele, P. et al. Nature. 2010

# There are currently no approved treatments for Angelman syndrome



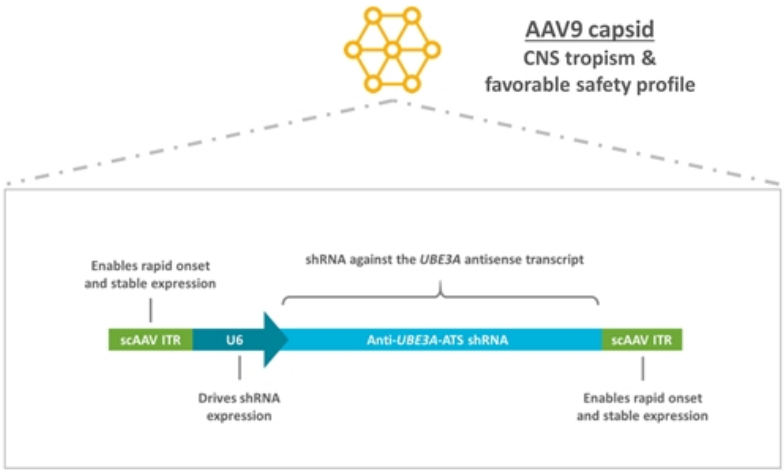
- Signs and symptoms include developmental delay, severe impairments in behavior, motor function, communication and sleep as well as intellectual disability, debilitating seizures and ataxia
- Normal lifespan but unable to live independently
- No currently approved therapies
- The estimated prevalence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



# TSHA-106 for Angelman targets *UBE3A-ATS* transcript through shRNA knock-down

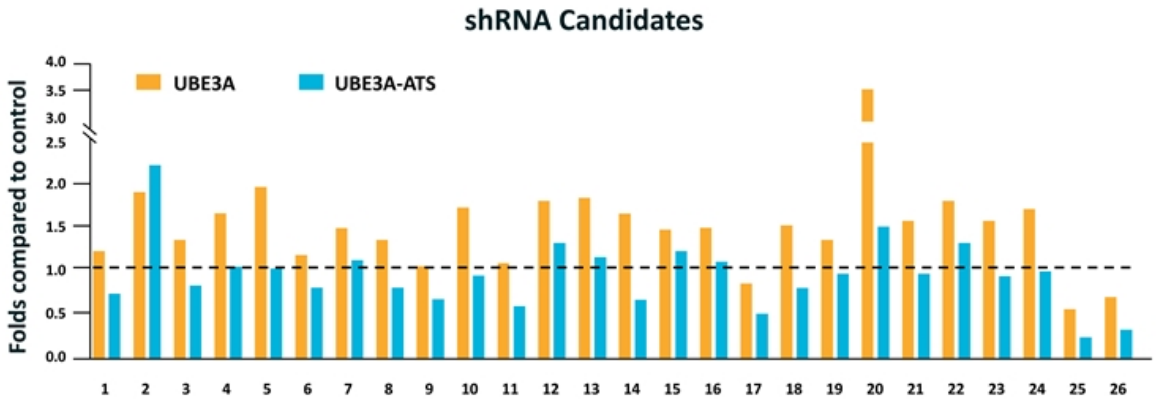


- AAV9 viral vector designed for shRNA-mediated knockdown of *UBE3A-ATS*, the antisense transcript governing the expression of UBE3A through the paternal allele.
- Using AAV-based strategy to achieve broad distribution of the shRNA expression cassette across the entire CNS
- Single intrathecal dose
- 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 knock-down

TSHA-106
Angelman Syndrome




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

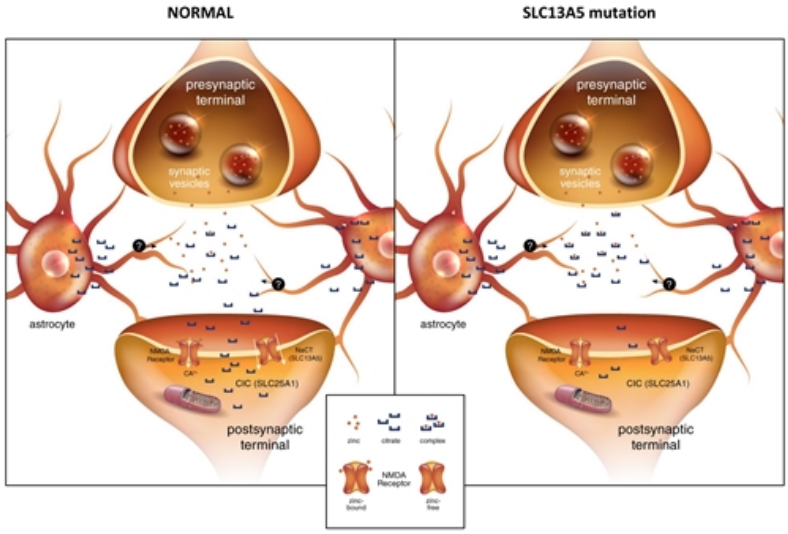
| | |
|---|---|
| **TSHA-114** GRT<br>**Fragile X syndrome**<br>**Preclinical** | • FMR1 is the most common single gene cause of autism and cognitive impairment<br>• Fragile X Syndrome is characterized by anxiety, aggression, hyperactivity, attention deficits, and sleep/communication disruption<br>• Estimated prevalence of 100,000 patients in the US and EU |
| **TSHA-116** shRNA<br>**Prader-Willi syndrome**<br>**Preclinical** | • Loss of function of genes along 15q11-q13 chromosome region due to an imprinting defect<br>• Patients have developmental delay, insatiable eating habits accompanied by obesity and overt diabetes<br>• Estimated prevalence of 40,000 patients in the US and EU |
| **TSHA-117** regulated GRT<br>**FOXG1 syndrome**<br>**Preclinical** | • Newly discovered gene with prevalence expected to steadily rise as more children as tested with autism spectrum disorder<br>• Development and intellectual disabilities, growth restriction with microcephaly, epilepsy, and hyperkinetic-dyskinetic movement disorder<br>• 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

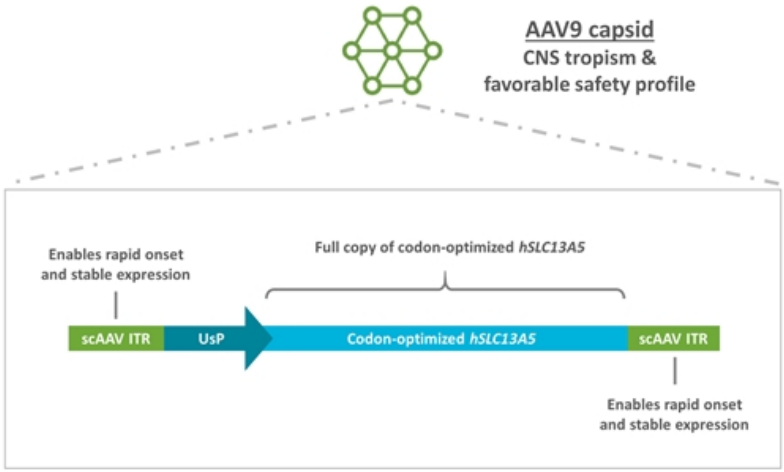



Bhutia, Molecules 2017

# TSHA-105 currently in IND/CTA-enabling studies

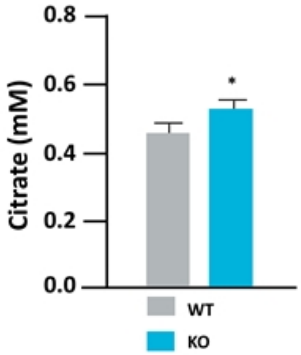


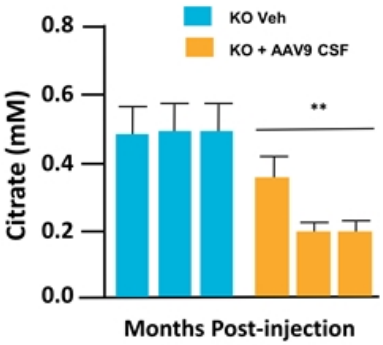
- Recombinant single-stranded AAV9 expressing human SLC13A5 protein under the control of a single promoter vector design
- Delivered intrathecally
- Received orphan drug and rare pediatric disease designations
- Currently in IND/CTA-enabling studies



# TSHA-105 decreased plasma citrate levels in SLC13A5 KO mice



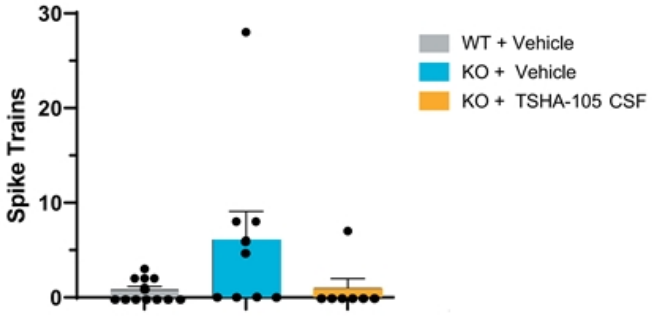


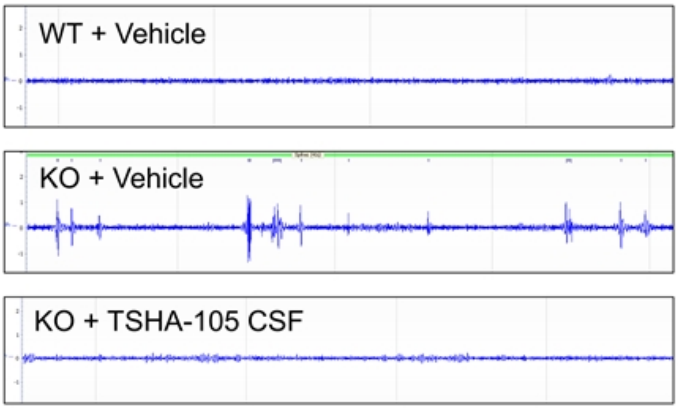




Bailey, R. 2020

# TSHA-105 improved EEG activity in SLC13A5 KO mice



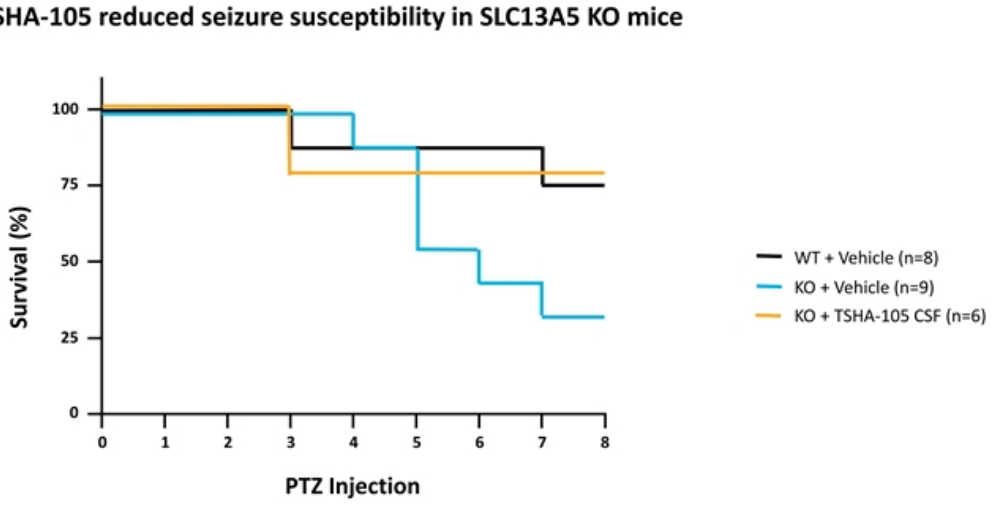



Bailey, R. 2020

# TSHA-105 reduced seizure susceptibility in SLC13A5 KO mice



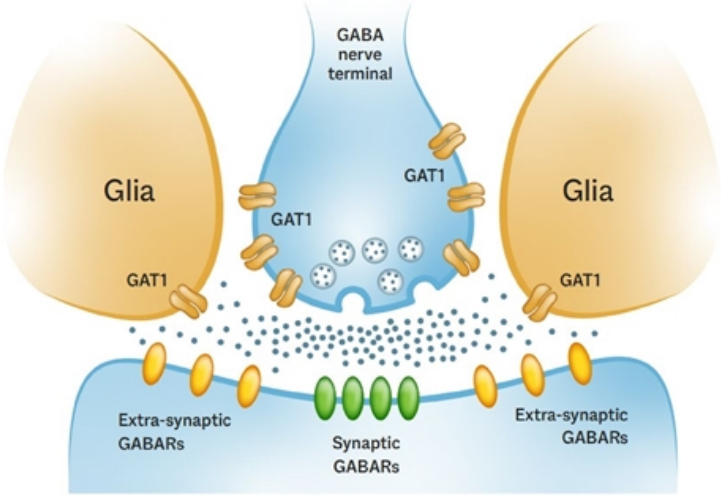



Bailey, R. 2020

# SLC6A1 haploinsufficiency disorder results in persistent seizures and developmental delays

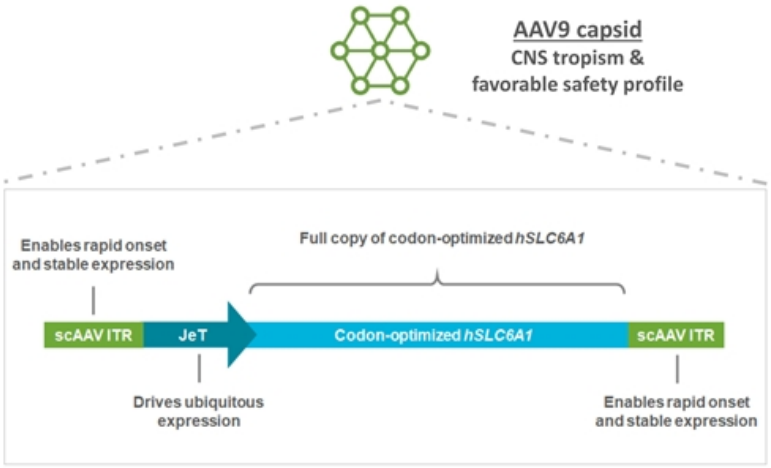


- Autosomal dominant genetic disorder characterized by the loss of function of one copy of the *SLC6A1* gene
- SLC6A1 encodes the GABA transporter protein type 1 (GAT1), which is responsible for the reuptake of GABA into presynaptic neurons and glia
- Clinical manifestations include epilepsy, developmental delays, including mild or moderate intellectual disability, ataxia and autism
- No approved therapies
- Estimated prevalence of SLC6A1 haploinsufficiency disorder is 1,900 patients in the US and EU



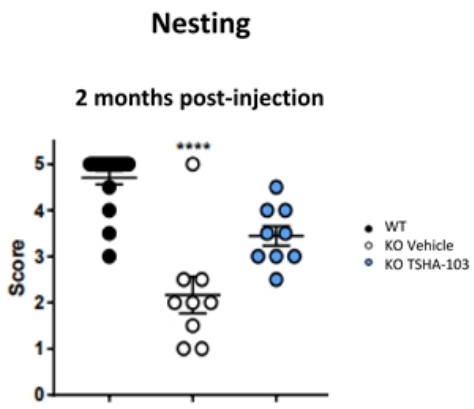
# TSHA-103 in IND/CTA-enabling studies

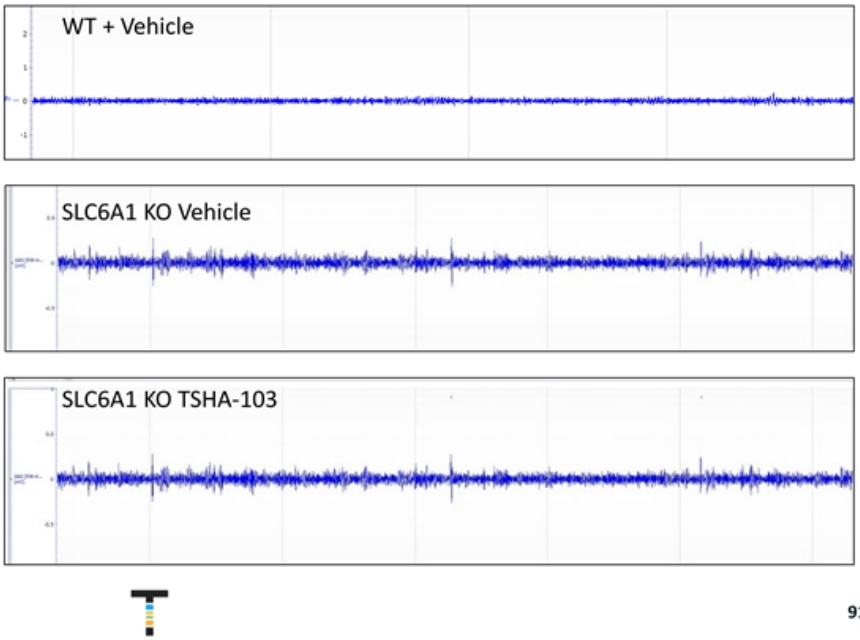
- Self-complementary AAV9 viral vector designed to deliver a functional copy of hSLC6A1
- JeT promoter drives ubiquitous expression, clinically validated in GAN
- Proof-of-concept demonstrated in knockout SLC6A1 mouse model
- Delivered intrathecally
- Received orphan drug and rare pediatric disease designations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



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





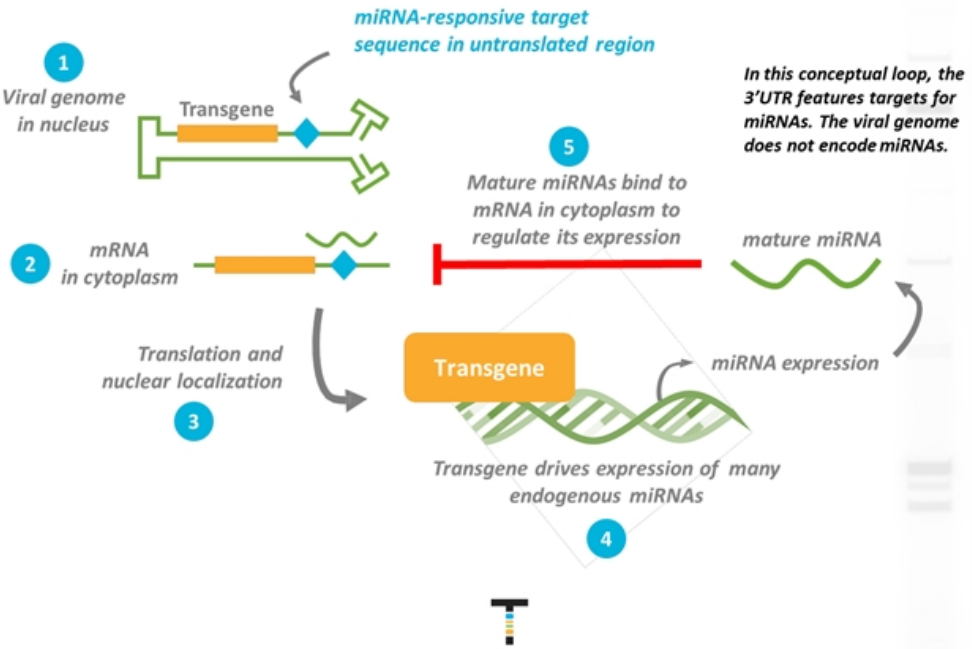
# Deep pipeline of gene therapies targeting genetic epilepsies

**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

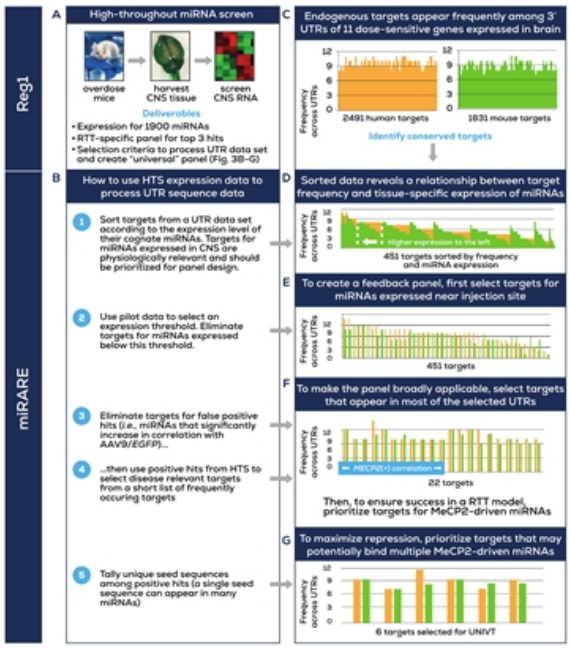
# Platform Technologies

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

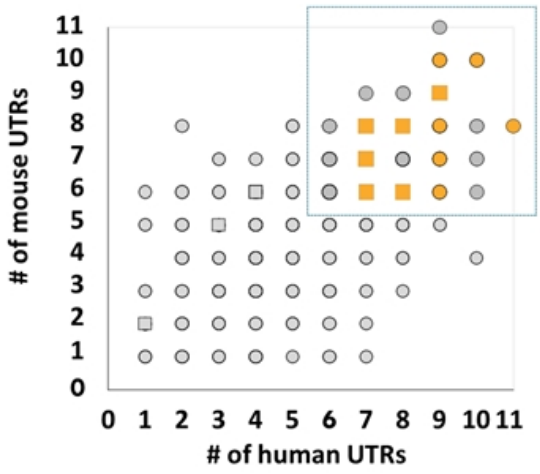


# Approaches to create a miRNA target panel for regulating *MECP2* expression

- 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



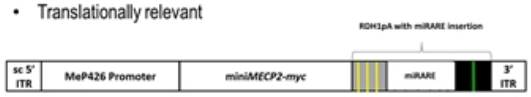
# 451 targets annotated across both species for selected 3’UTRs




- 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

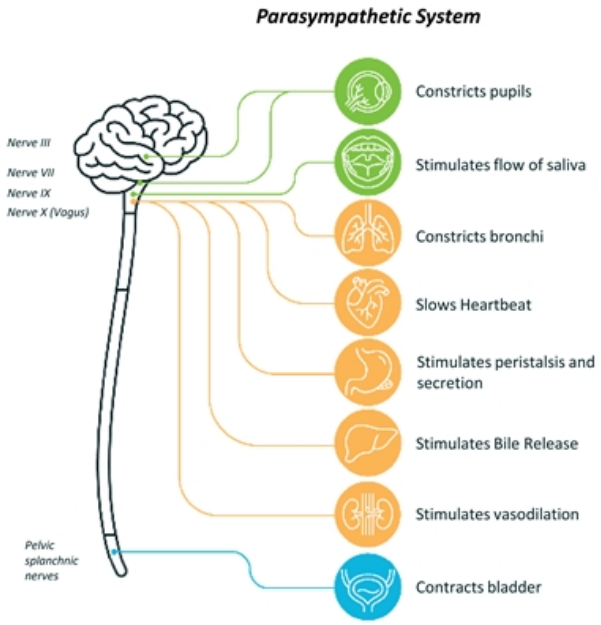
## New target panel miRARE

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



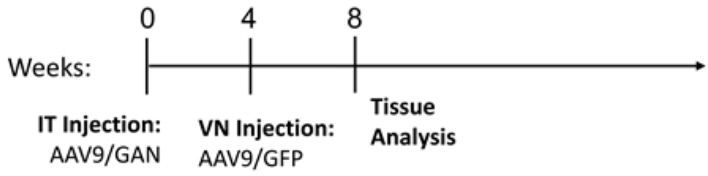
# Opportunity to achieve human POC for vagus nerve redosing

- 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



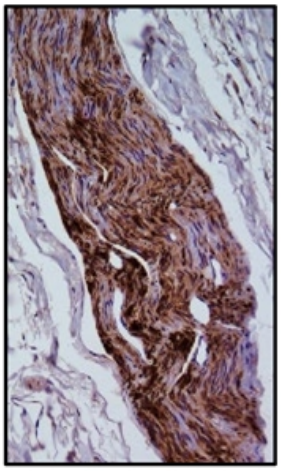
# Robust expression of GFP in the vagus nerve and associated nodose ganglia in rats support redosing via vagus nerve injection

## Study 1

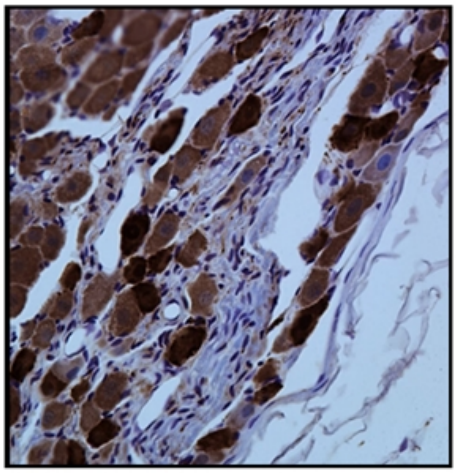



## Study 2


Vagus Nerve

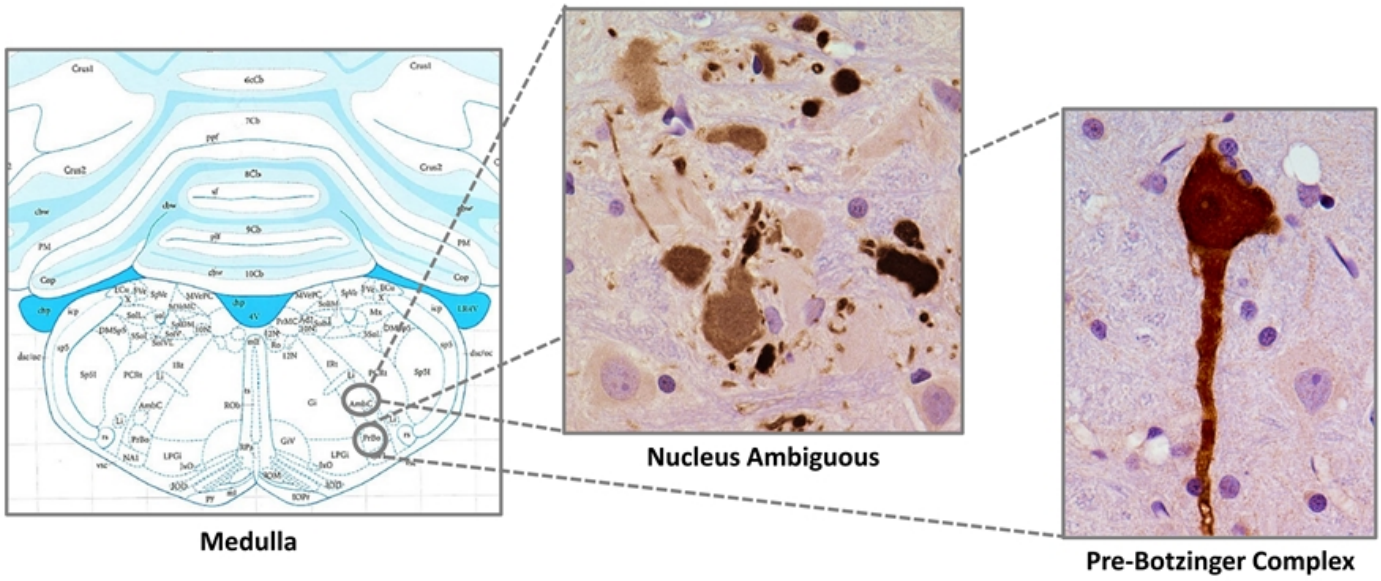


Nodose Ganglia



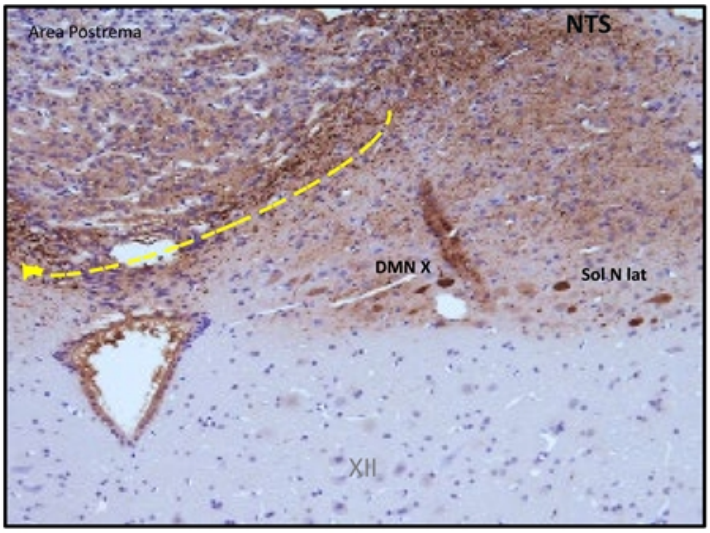
GFP – green fluorescent protein
Courtesy of Dr. Diane Armao

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

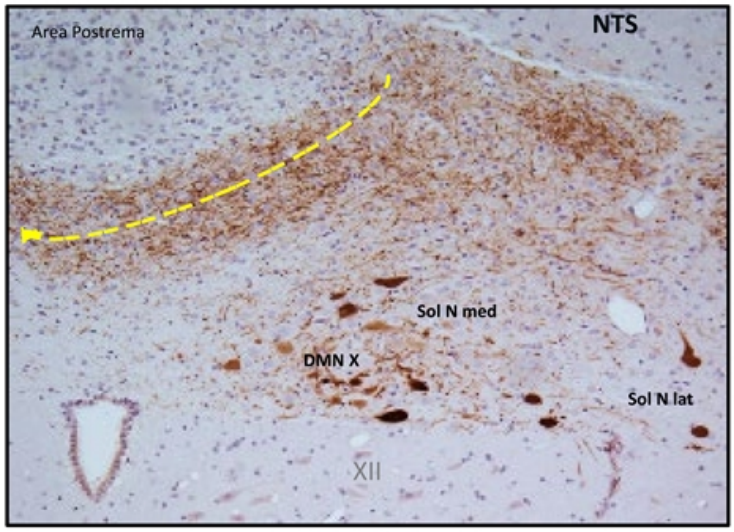



Courtesy of Dr. Diane Armao

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



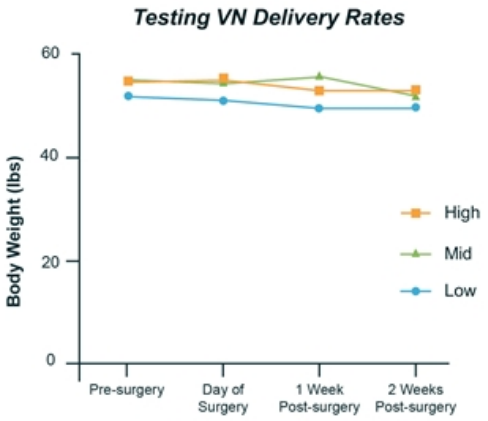

Naive



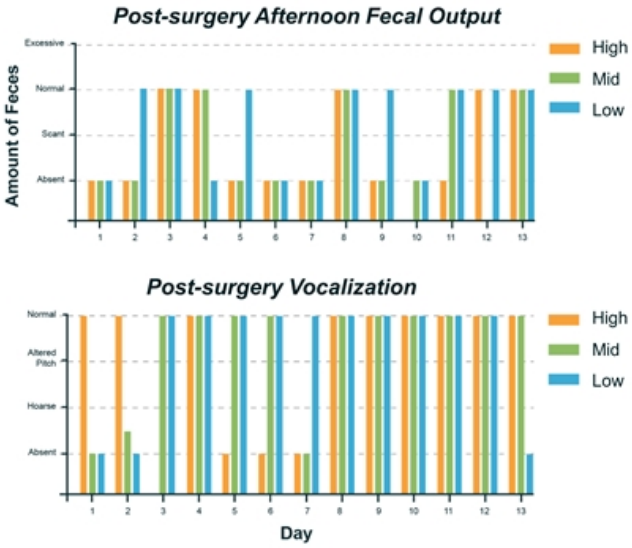

AAV9 Pre-immunized

Courtesy of Dr. Diane Armao

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



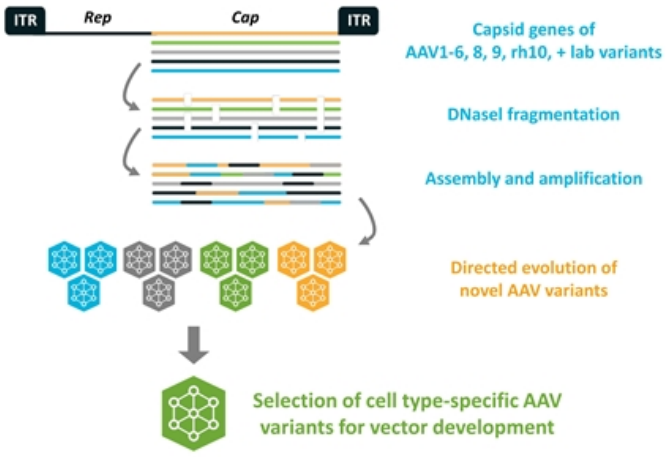

***Post-mortem vagal nerves and brain were microscopically normal***



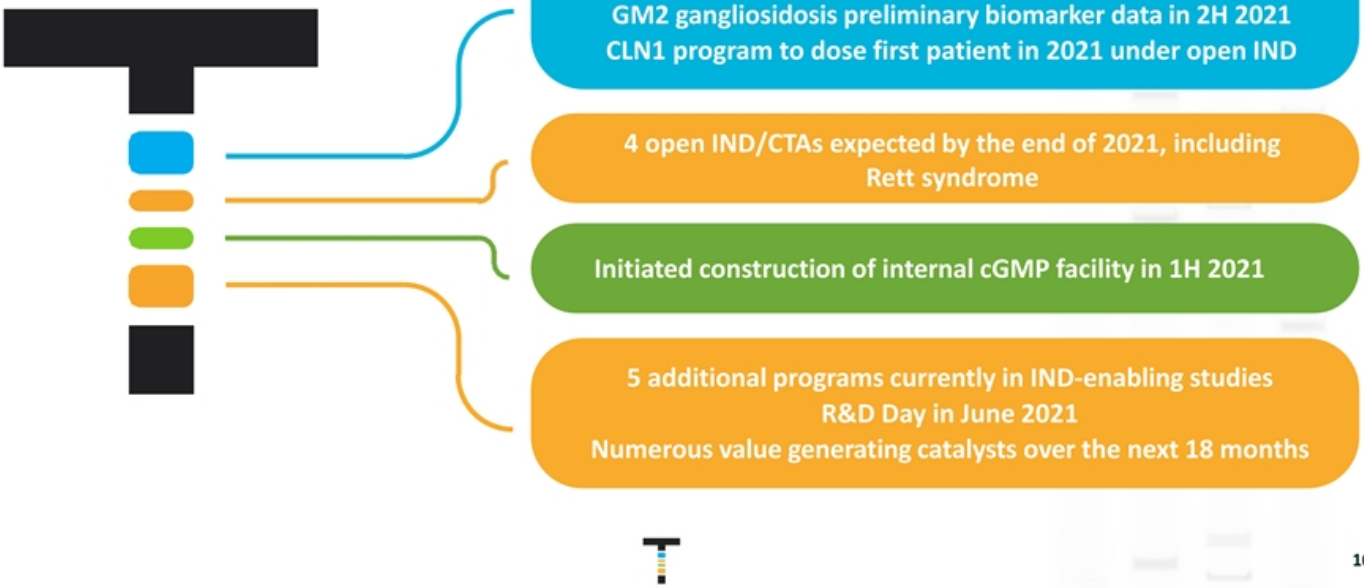

[1]Taysha has exclusive rights to the vagus nerve redosing platform in select indications.

# 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



**Taysha Gene Therapies Announces New Data on Multiple Preclinical Programs and Upcoming R&D Day**

*TSHA-113 significantly reduced tau mRNA and protein levels in mouse models of human tauopathies via cerebral spinal fluid (CSF) delivery supporting further preclinical development*

*TSHA-105 significantly reduced plasma citrate levels, normalized EEG brain activity, and reduced the number of seizures and seizure susceptibility in SLC13A5 knockout mice*

*TSHA-106 increased UBE3A expression through shRNA-mediated knockdown of UBE3A-ATS in in vitro cell lines across 26 distinct shRNA candidates for the treatment of Angelman disease*

*TSHA-112 generated significant reductions in GYS1 protein, abnormal glycogen accumulation and polyglucosan bodies in the APBD knockout mouse model*

*TSHA-111-LAFORIN and TSHA-111-MALIN achieved effective knockdown of GYS1 expression and insoluble glycogen and decreased Lafora body formation in laforin and malin mouse models*

*TSHA-119 caused a dose-dependent reduction of GM2 accumulation at 20 weeks in GM2A knockout mice*

*Positive proof-of-concept data for gene therapy candidates in SCL13A5 deficiency, APBD, Lafora disease and GM2 AB variant support advancement into clinical testing*

*Expect to submit IND/CTA for one of the following programs by the end of 2021: SLC13A5 deficiency, APBD, Lafora disease or GM2 AB variant*

*Taysha's virtual Research and Development Day in June 2021 will highlight progress across R&D pipeline*

**Dallas – April 14, 2021** - Taysha Gene Therapies, Inc. (Nasdaq: TSHA), a patient-centric, pivotal-stage gene therapy company focused on developing and commercializing AAV-based gene therapies for the treatment of monogenic diseases of the central nervous system (CNS) in both rare and large patient populations, today announced new data for multiple preclinical programs and a planned R&D Day, which will be held in June 2021.

"Collectively, these new preclinical data highlight Taysha's next wave of novel gene therapies that have the potential to impact meaningful patient populations. The promising data underscore our ability to rapidly and reproducibly investigate disease biology, design innovative gene therapies and efficiently advance the development of these drug candidates," said RA Session II, President, Founder and Chief Executive Officer of Taysha. "Among the compelling new data, for the first time, we have shown that TSHA-113, an AAV9 gene therapy that utilizes AAV-mediated gene silencing, reduced tau expression in mouse models of human tauopathies. The potential implications of these data are far reaching, and we intend to further evaluate TSHA-113 in additional preclinical studies. The totality of the preclinical data

presented today support the fundamental elements of our scientific approach of coupling validated technology with novel targeted payload design while utilizing a proven HEK293 suspension manufacturing process. We believe our deep pipeline and innovative scientific engine hold tremendous potential, and we are poised to continue delivering meaningful value to patients with monogenic CNS diseases."

"Today's data demonstrate the breadth, depth and velocity of our development engine as a sustainable pivotal-stage gene therapy company. There are no approved disease modifying therapies for any of the programs in our portfolio and we are encouraged by the results of our gene therapy approach of vectorized RNA and gene replacement therapies across our portfolio," said Suyash Prasad, MBBS, M.SC., MRCP, MRCPCH, FFPM, Chief Medical Officer and Head of Research and Development of Taysha. "We are very excited to further develop TSHA-113 in tauopathies, including Alzheimer's disease, MAPT-associated frontotemporal dementia and progressive supranuclear palsy, based on the significant reduction in tau expression demonstrated in transgenic mouse models of human tauopathies. In addition, to date, we have advanced five programs into IND/CTA-enabling studies, including TSHA-105 in SLC13A5 deficiency, TSHA-111-LAFORIN in Lafora disease, TSHA-111-MALIN in Lafora disease, TSHA-112 in APBD and TSHA-119 in GM2 AB variant. We intend to file an IND/CTA for one of these five named programs by the end of 2021. By mid-year, we intend to select a development candidate for Angelman syndrome and obtain interim expression and safety data from confirmatory non-human primate studies by year-end. We remain on track to report Phase 1/2 biomarker data for TSHA-101 in GM2 gangliosidosis in the second half of this year and to provide a clinical and regulatory update for TSHA-120 in giant axonal neuropathy by year-end. Finally, in the second half of the year, we continue to expect dosing of the first patient with CLN1 disease in a Phase 1/2 trial for TSHA-118 under an already open IND, filing an IND/CTA for TSHA-102 in Rett syndrome and TSHA-104 in SURF1-associated Leigh syndrome, and filing an IND for TSHA-101 in GM2 gangliosidosis in the U.S. These anticipated clinical and regulatory milestones are expected to be followed by the initiation of Phase 1/2 clinical trials for each of these indications. We look forward to providing additional updates at our R&D Day in June."

TSHA-113 for Tauopathies

Taysha is developing tau-specific microRNA (miRNA) shuttles designed to target tau mRNA for all six isoforms found in the human brain and/or mouse brain. TSHA-113 is an AAV9 capsid that packages these miRNA shuttles and is delivered in the CSF for the treatment of tauopathies.

- In transgenic mouse models carrying human tau, TSHA-113 significantly reduced tau mRNA and protein levels, while demonstrating widespread expression in neurons and glia
- Together with previous *in vitro* findings, these data further validate selective reduction of tau mRNA and protein levels and warrant further preclinical development
- An estimated 6.2 million Americans and 7.8 million Europeans are living with Alzheimer's disease
- There are an estimated 13,000 patients in U.S. and Europe affected by MAPT-associated frontotemporal dementia, progressive supranuclear palsy and corticobasal degeneration, which represent a significant commercial opportunity

TSHA-105 for SLC13A5 deficiency

TSHA-105 is a recombinant self-complementary AAV9 vector that expresses the human SLC13A5 protein under the control of a ubiquitous promoter. The drug candidate is being developed for the treatment of SLC13A5 deficiency.

- In SLC13A5 knockout mice, treatment with TSHA-105 resulted in a significant, sustainable decrease of plasma citrate levels up to three months post-injection compared to age-matched, wildtype controls
- TSHA-105 normalized electroencephalogram (EEG) brain activity, reduced the number of seizures, and reduced seizure susceptibility compared to vehicle-treated controls
- The company has advanced TSHA-105 into IND/CTA-enabling studies
- There are an estimated 1,900 patients with SLC13A5 deficiency in the United States and in Europe

TSHA-106 for Angelman syndrome

TSHA-106 is an intrathecally delivered AAV9 viral vector designed for shRNA-mediated knockdown of UBE3A-ATS, the antisense transcript governing the expression of UBE3A through the paternal allele.

- *In vitro* testing in a neuroblast cell line demonstrated consistent knockdown of UBE3A-ATS and a subsequent increase in UBE3A expression across 26 distinct shRNA candidates
- Selection of development candidate expected by mid-year
- Interim expression and safety data from confirmatory non-human primate (NHP) studies expected by the end of 2021
- There are an estimated 55,000 patients with Angelman syndrome in the United States and Europe

TSHA-112 for Adult Polyglucosan Body Disease (APBD)

TSHA-112 is an intrathecally delivered AAV9 viral vector designed for miRNA-mediated knockdown of the *GYS1* gene to treat APBD.

- In preclinical studies, miRNA knockdown of GYS1 induced significant reductions in *GYS1* mRNA, GYS1 protein, abnormal glycogen accumulation, and polyglucosan bodies throughout the brain in an APBD knockout mouse model
- TSHA-112 decreased neuroinflammatory markers across three distinct mouse models
- The company has advanced TSHA-112 into IND/CTA-enabling studies
- There are an estimated 10,000 patients with APBD in the United States and in Europe

TSHA-111-LAFORIN for EPM2A and TSHA-111-MALIN for EPM2B for Lafora disease

TSHA-111-LAFORIN and TSA-111-MALIN are intrathecally delivered AAV9 viral vectors designed for miRNA-mediated knockdown of the *GYS1* gene to treat Lafora disease.

- In preclinical studies, TSHA-111-LAFORIN and TSHA-111-MALIN achieved effective knockdown of *GYS1* expression and insoluble glycogen in the Lafora disease laforin and malin mouse models, respectively
- Both product candidates decreased Lafora body formation within the brain in their respective mouse models
- The company has advanced TSHA-111-LAFORIN and TSHA-111-MALIN into IND/CTA-enabling studies
- There are an estimated 700 patients with Lafora disease in the United States and in Europe

TSHA-119 for GM2 AB variant

TSHA-119 is a self-complementary AAV9 vector designed to deliver a functional copy of the *GM2A* gene to treat GM2 AB variant.

- In preclinical studies, TSHA-119 caused a significant, dose-dependent reduction of GM2 accumulation at 20 weeks in mice that were dosed intrathecally at postnatal day 1 or at 6 weeks of age
- Long-term follow up studies, which include bi-monthly behavioral, as well as biochemical and histological analyses, are currently ongoing
- The company has advanced TSHA-119 into IND/CTA-enabling studies
- There are approximately 200 patients with GM2 AB variant in the United States and in Europe

**About Taysha Gene Therapies**

Taysha Gene Therapies (Nasdaq: TSHA) is on a mission to eradicate monogenic CNS disease. With a singular focus on developing curative medicines, we aim to rapidly translate our treatments from bench to bedside. We have combined our team's proven experience in gene therapy drug development and commercialization with the world-class UT Southwestern Gene Therapy Program to build an extensive, AAV gene therapy pipeline focused on both rare and large-market indications. Together, we leverage our fully integrated platform—an engine for potential new cures—with a goal of dramatically improving patients' lives. More information is available at www.tayshagtx.com.

**Forward-Looking Statements**

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "anticipates," "believes," "expects," "intends," "projects," and "future" or similar expressions are intended to identify forward-looking statements. Forward-looking statements include statements concerning the potential of our product candidates, including our preclinical product candidates, to positively impact quality of life and alter the course of disease in the patients we seek to treat, our research, development and regulatory plans for our product candidates, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and whether, if approved, these product candidates will be successfully distributed and marketed, and the potential market opportunity for these product candidates. Forward-

looking statements are based on management's current expectations and are subject to various risks and uncertainties that could cause actual results to differ materially and adversely from those expressed or implied by such forward-looking statements. Accordingly, these forward-looking statements do not constitute guarantees of future performance, and you are cautioned not to place undue reliance on these forward-looking statements. Risks regarding our business are described in detail in our Securities and Exchange Commission ("SEC") filings, including in our Annual Report on Form 10-K for the full-year ended December 31, 2020, which is available on the SEC's website at www.sec.gov. Additional information will be made available in other filings that we make from time to time with the SEC. Such risks may be amplified by the impacts of the COVID-19 pandemic. These forward-looking statements speak only as of the date hereof, and we disclaim any obligation to update these statements except as may be required by law.

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