TAYSHA GENE THERAPIES

Bringing New Cures to Life

RESEARCH & DEVELOPMENT DAY

DAY 2 – June 29, 2021 | 9:00 AM – 12:00 PM CT

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.

Introductions

RA Session II

President, Founder & CEO

TSHA-104 for SURF1-Associated Leigh Syndrome

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

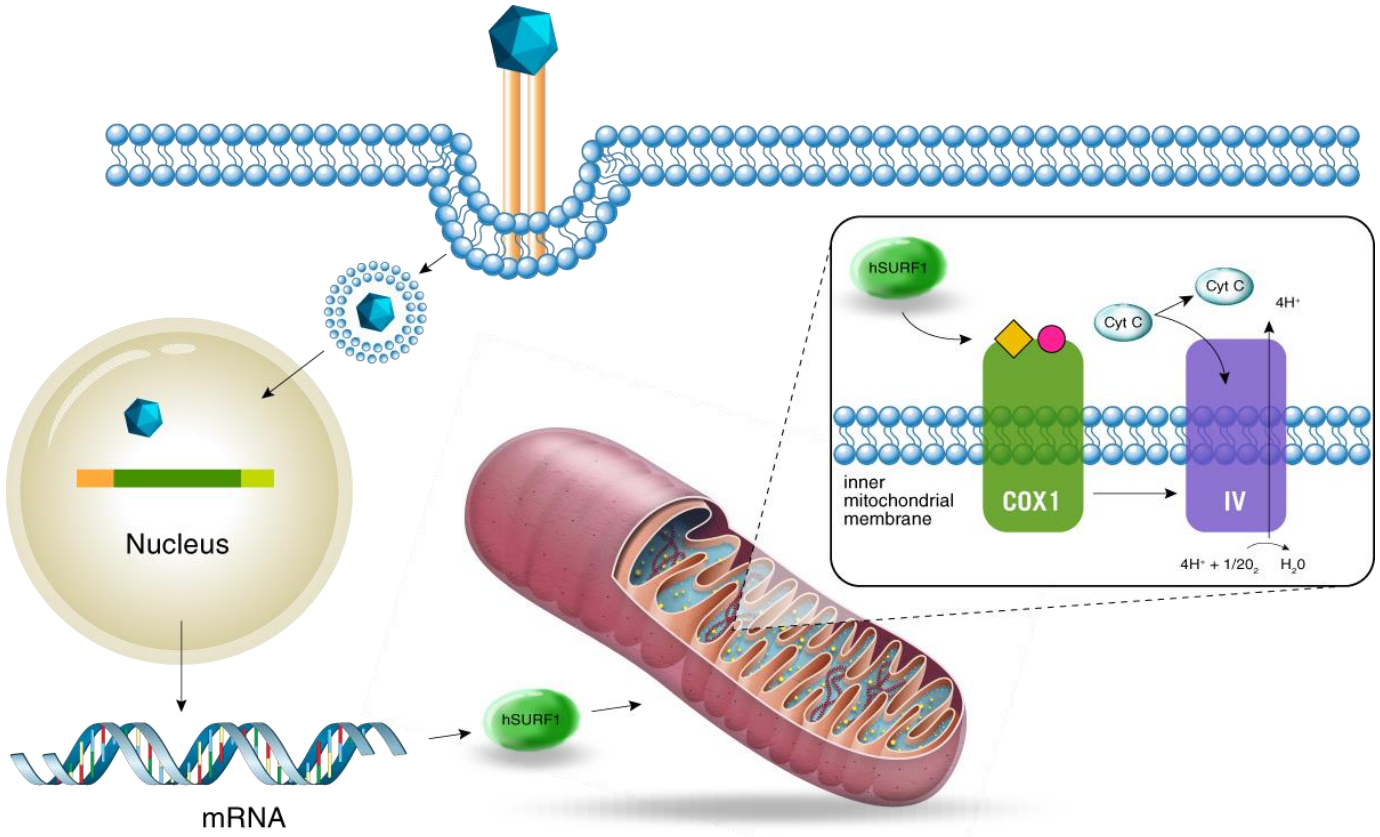
Chief Medical Officer and Head of R&D

Steven Gray, PhD

Chief Scientific Advisor, UTSW Gene Therapy Program

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)



SURF1 deficiency – the most challenging symptoms as reported by families and caregivers

Movement and motor skills
(8 caregivers)

- Loss of balance (x4)
- Tremors (x4)
- Crawling (x2)
- Inability to walk
- Reaching
- Dystonia and chorea

Nearly all caregivers cited a symptom related to movement; however, the specific symptom varied greatly based on the disease progression, the child's interests, and age. For example, interests in drawing, writing, or school caused tremors to top the list.

Feeding/nutrition
(6 caregivers)

- Failure to thrive (x3)
- Feeding issues (x2)
- Swallowing issues (x2)
- Constipation (x2)
- Vomiting

Several caregivers mentioned a symptom related to nutrition and / or strength. Nutrition was seen as the root of other issues and caregivers felt improvements there could mean improvements in overall strength and other symptoms.

Strength
(6 caregivers)

- Muscle weakness (x4)
- Inability to sit (x3)
- Head and trunk control (x2)
- Inability to stand

Vision
(4 caregivers)

- Nystagmus (x4)
- Strabismus (x2)

Breathing
(3 caregivers)

- Breathing issues (x3)

While breathing issues were only experienced by a few, if children experienced breathing issues, they most certainly topped the list.

Speech
(3 caregivers)

- Speech (x3)

Other

- Sleep issues (x2)
- Scoliosis

Caregiver insights generated through workgroup

SURF1 deficiency natural history study – Initial symptoms

- Review of 44 cases with SURF1 deficiency
- Median age for first symptom onset was 9.5 months (range 0–60 months); majority presented in the first year (32/44, 73%)
- Most frequently noted initial symptoms included poor feeding/vomiting (frequently attributed to gastroesophageal reflux) and poor weight gain
- Neonatal period uneventful in majority of patients (41/44, 93%)
- Most (26/44, 59%) presented with combination of GI symptoms, poor weight gain and hypotonia
- Developmental regression (loss of cognitive or motor skills) was initial symptom in 3/44 (7%) patients

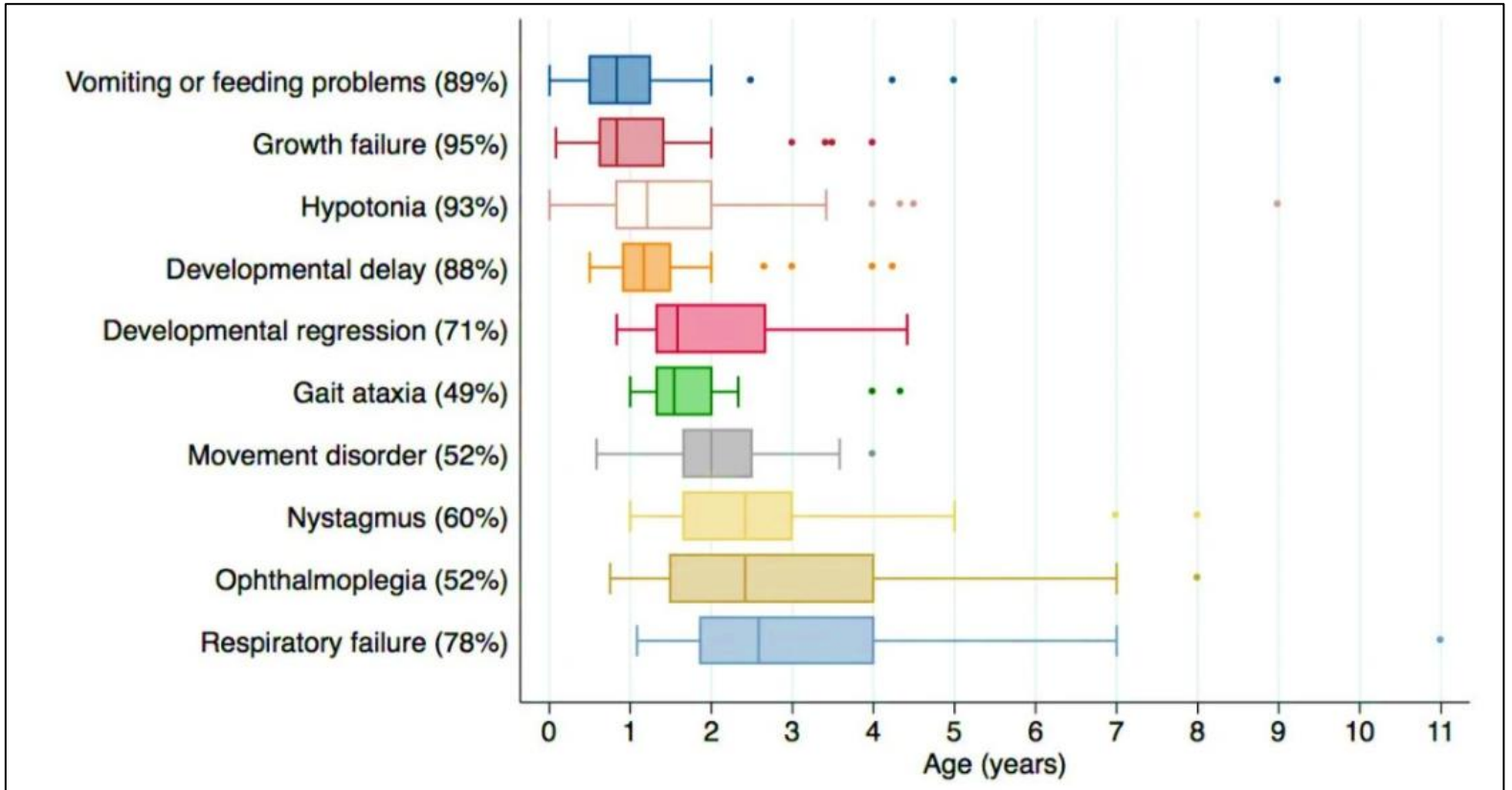
Initial symptoms in 44 patients with SURF1 deficiency

Initial symptoms	Number of patients (%)	Age range of initial presentation (months)
poor feeding/vomiting	20 (46)	0-24
poor weight gain	19 (43)	1.5-20
developmental delay	10 (23)	9-51
hypotonia	9 (21)	0-10
movement disorder	3 (7)	10-24
developmental regression	3 (7)	10-18
ataxia	2 (5)	14-60

Wedatilake et al. *Orphanet J Rare Dis* 2013

SURF1 deficiency natural history study – Major clinical features

- Symptoms occurring in ~80%+: vomiting / feeding problems, growth failure, hypotonia, developmental delay and respiratory failure.
- Median time to onset of most symptoms was 1-2 years

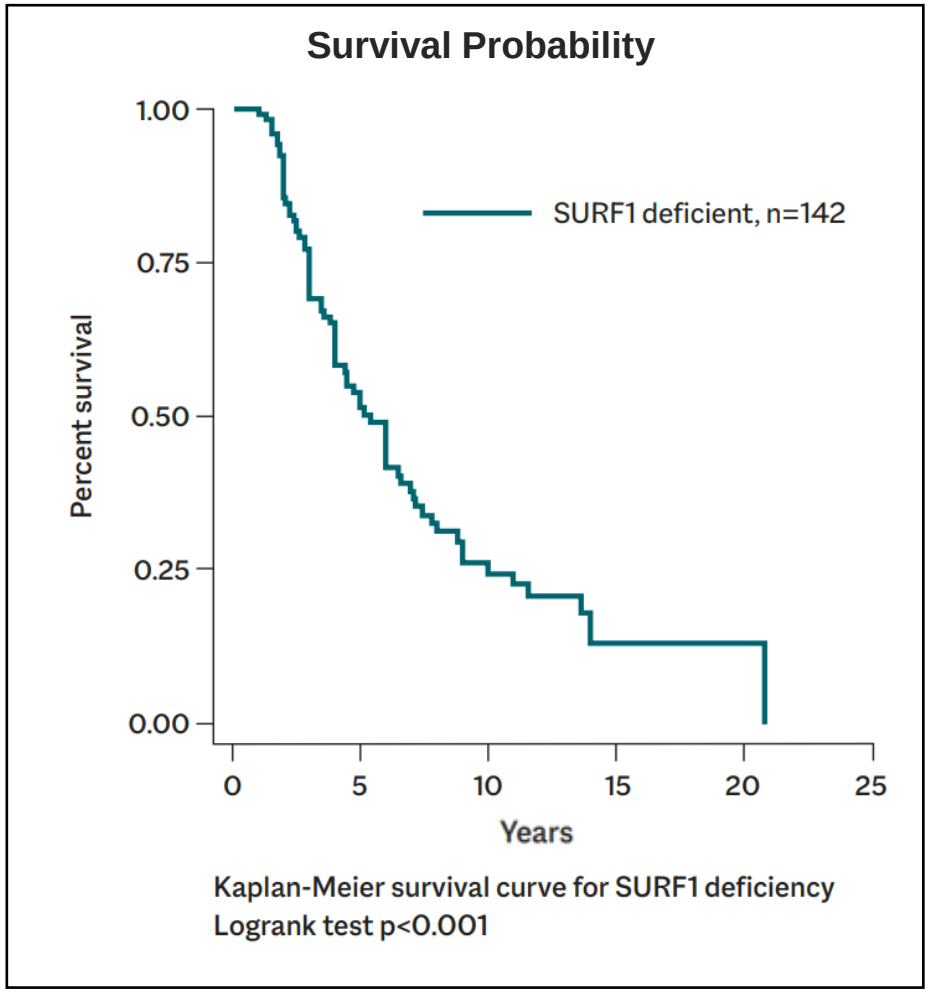


Clinical features in 44 patients with SURF1 deficiency. The x axis indicates the age of onset (years) and the y axis indicates the clinical features. Percentages denote the proportion of patients with a given clinical feature, and box-and-whisker plots show the age of onset. The median age of onset is indicated by the vertical line within the boxes. Boxes represent upper and lower quartiles, whiskers represent extreme values, and dots represent outliers which are ≥1.5 times the interquartile range from the median. Other less commonly observed features included hypertrichosis (41%), optic atrophy (23%), encephalopathy (20%), seizures (14%) and cardiomyopathy (2%).

Wedatilake et al. *Orphanet J Rare Dis* 2013

SURF1 deficiency natural history study – Survival

- Among 44 patients with detailed clinical data, 5 were alive at time of writing (ages 2–19 years); current vital status was unknown for 3
- Of the 36 deceased patients with known cause of death, the **cause was central respiratory failure in 29/36 (80%)**
- Seven patients survived beyond 10 years of age
  - Of these, 6 had neurological symptoms such as ataxia and motor developmental delay; of note, GI symptoms were not the prominent presenting feature in these cases. Furthermore, **these six patients also did not experience developmental regression**
- Literature searches identified 98 SURF1-deficient cases with available survival data, which were pooled together with the data from the 44 cases. The Kaplan-Meier analysis compares the survival experience of 142 SURF1-deficient cases to two other groups with LS due to nuclear gene mutations (56 with LRPPRC deficiency and 63 with nuclear-encoded complex I-deficient LS/“Leigh- like” disease)
- **Median survival length for SURF1 deficiency was 5.4 years (25th centile 3.0, 75th centile 10 years)**

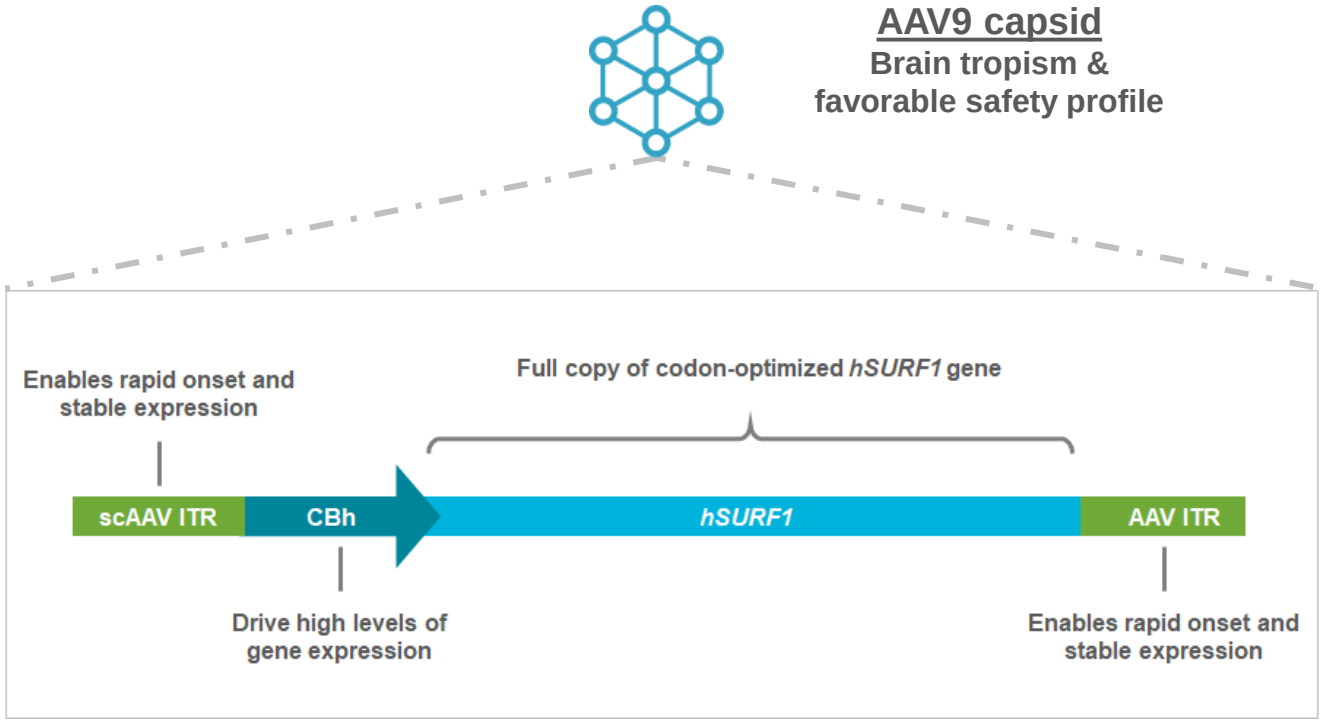


Kaplan-Meier survival curve for SURF1 deficiency
Logrank test p<0.001

Wedatilake et al. *Orphanet J Rare Dis* 2013

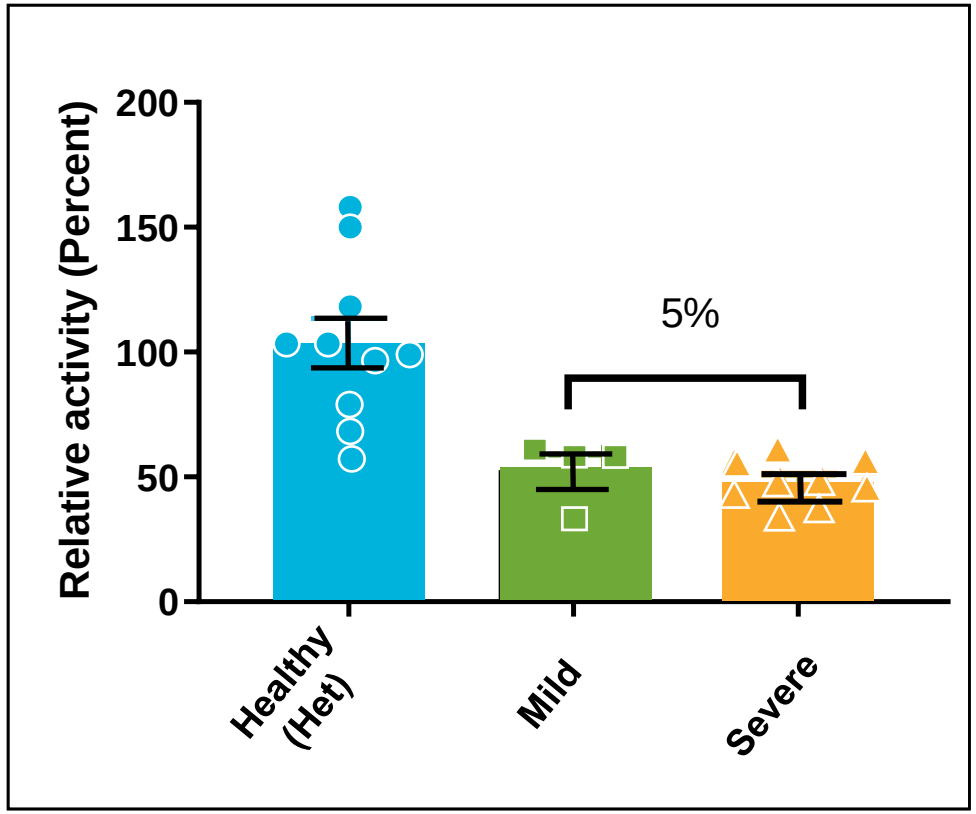
TSHA-104 IND/CTA submission expected by YE 2021

- Recombinant AAV9 viral vector with engineered transgene encoding the human SURF1 protein
- Designed to deliver a functional copy of the SURF1 gene
- Received orphan drug and rare pediatric disease designations



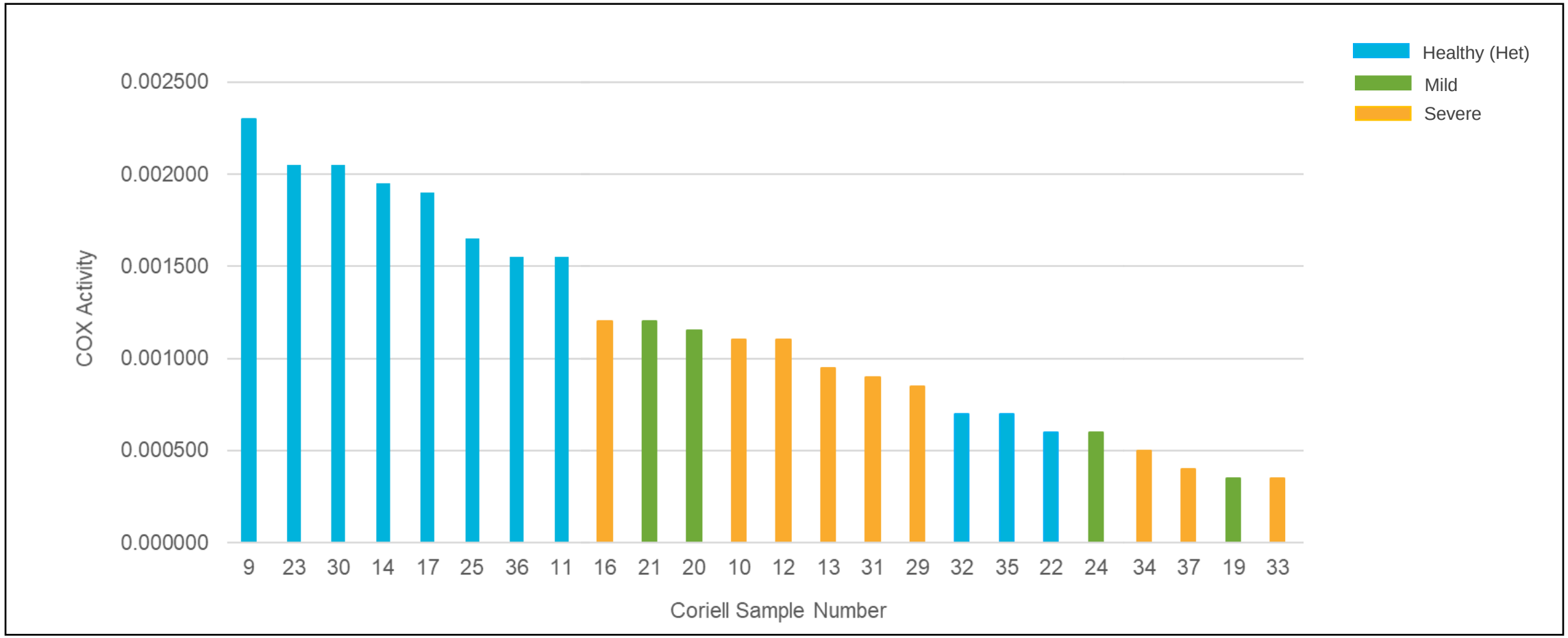
Slight increase in COX1 activity significantly improved clinical phenotype

- Of 17 samples, 14 were assayed
  - 8 Leigh syndrome & 6 healthy donors (hets)
  - Severely affected individuals had roughly 50% of normal activity
  - Mildly affected individuals had roughly 55% of normal activity
- A relatively small difference in activity could have significant clinical consequences
- Other studies measuring COX activity have shown roughly 20% of normal activity for affected individuals
- Potential reason – “healthy” donors are heterozygote parents of affected children; this and their age may affect their COX activity. In other studies, healthy children were used for reference

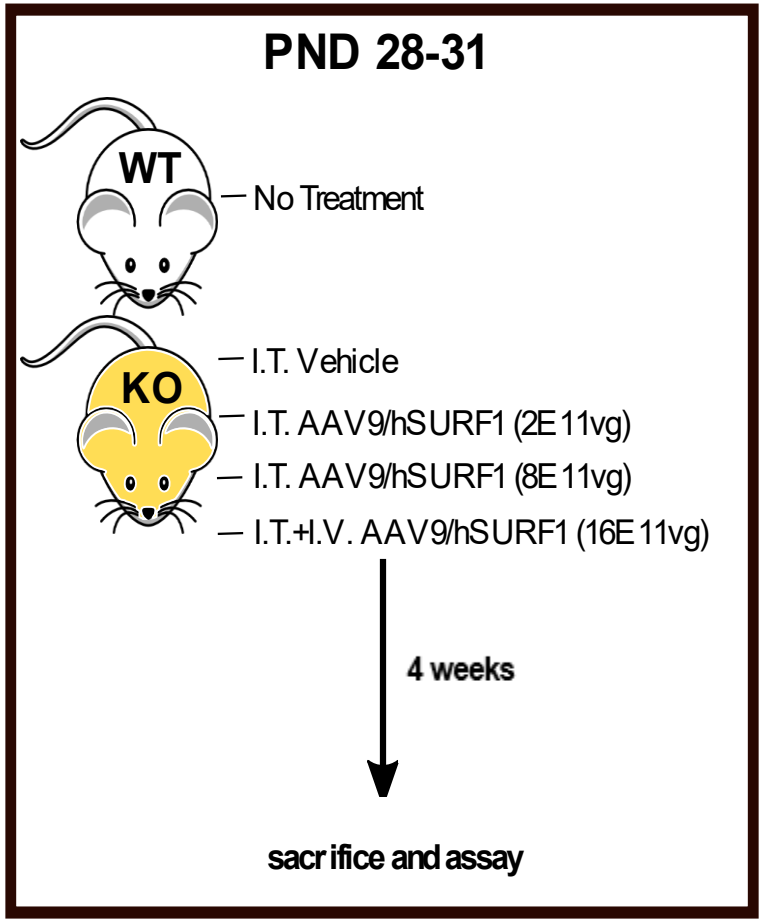


Reduction in COX activity correlated with disease worsening – Patient fibroblast data

TSHA-104
SURF1 deficiency

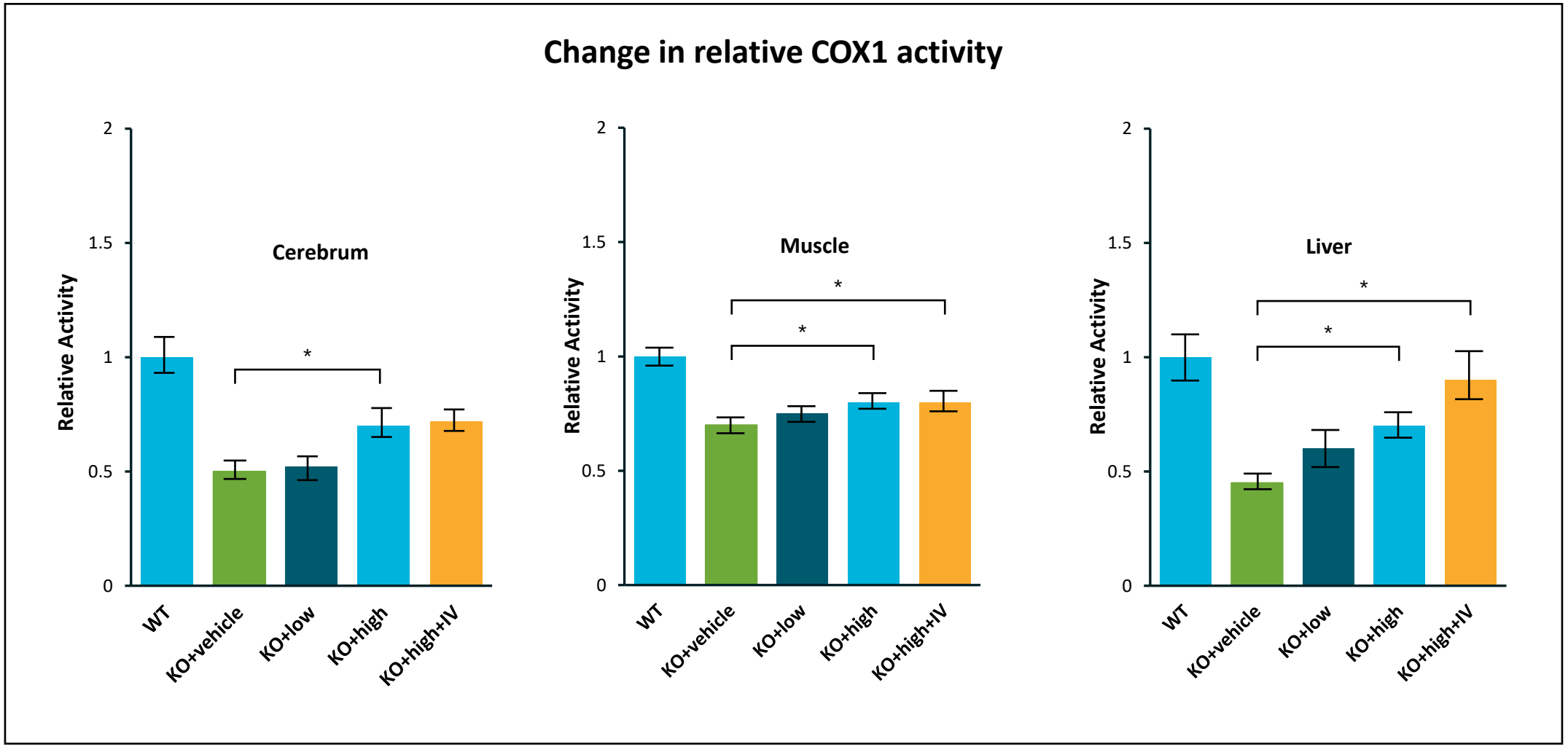


Vector transduction efficiency and efficacy – Part I

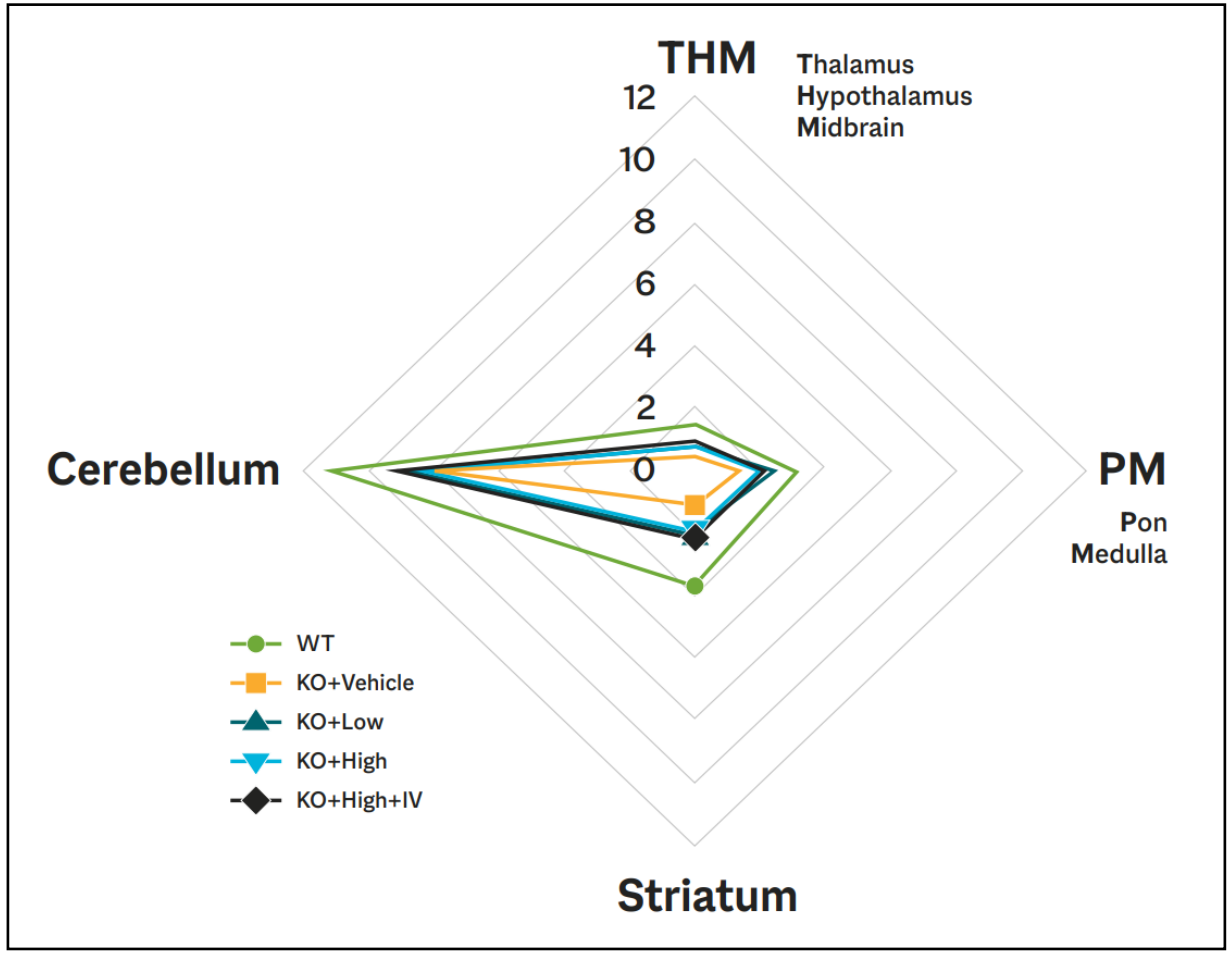


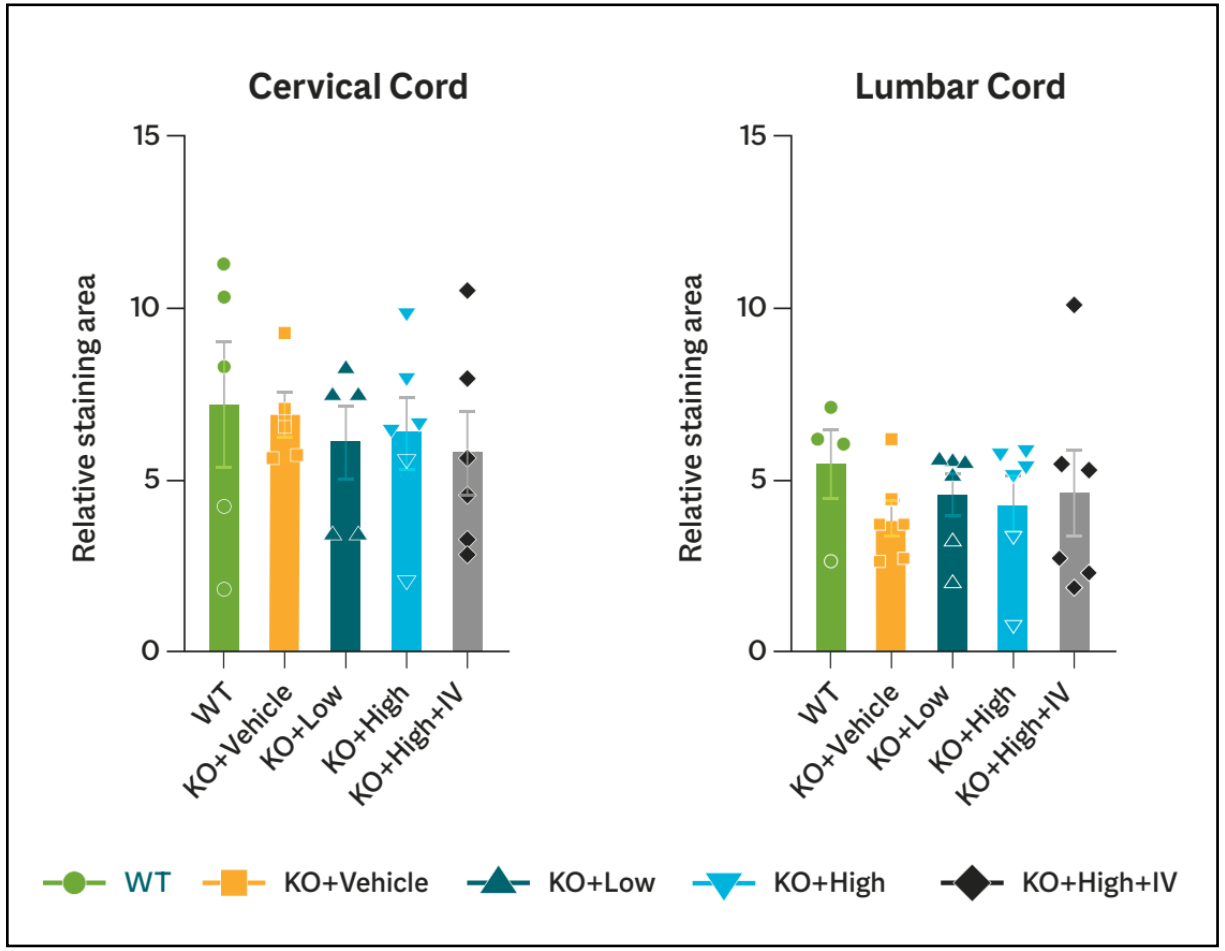
- COX activity assay in various tissues
- RNAScope for hSURF1opt mRNA expression
- COX content level using MT-CO1 protein as marker

TSHA-104 increased COX1 activity in brain and muscle in dose-dependent manner in SURF1 KO mice

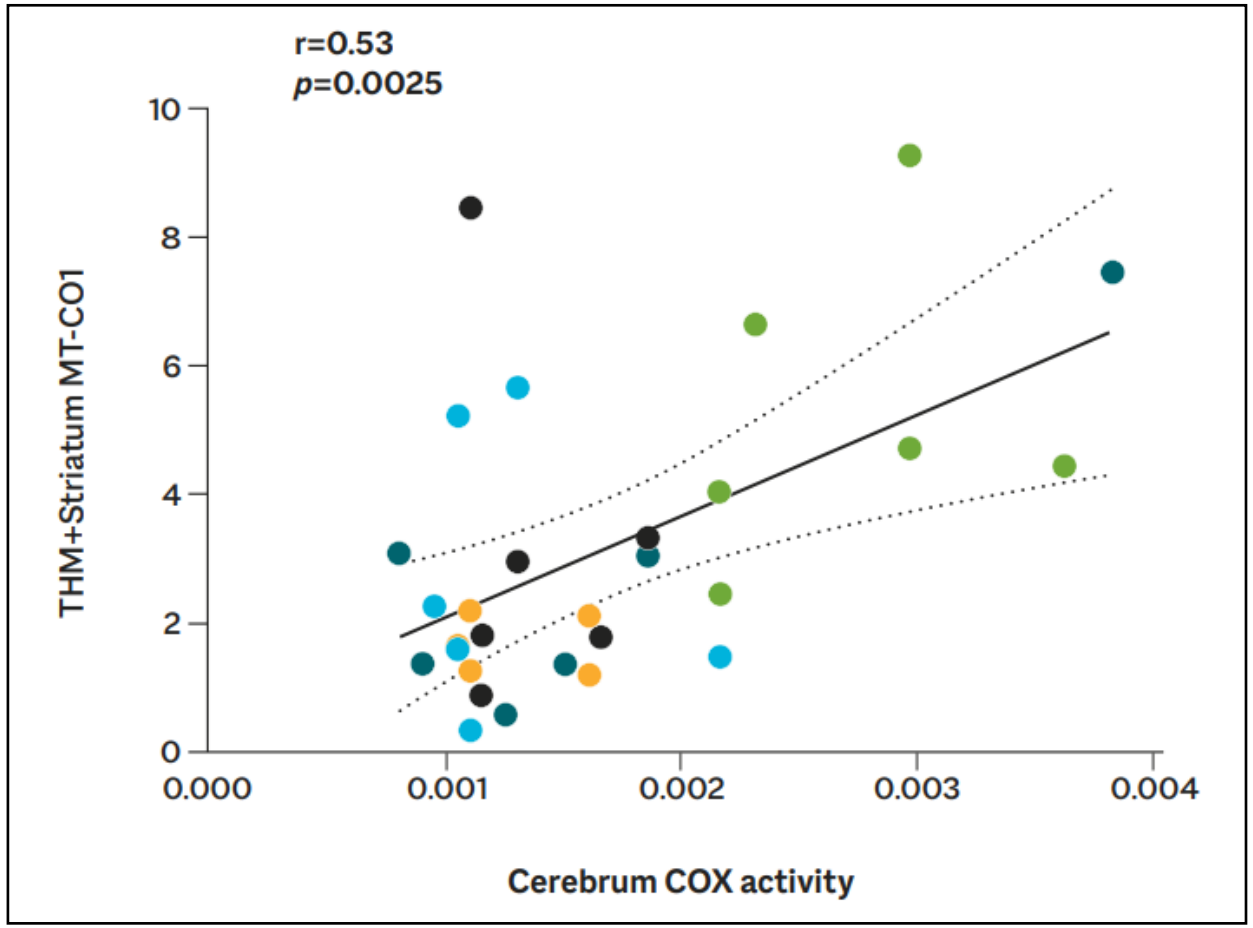


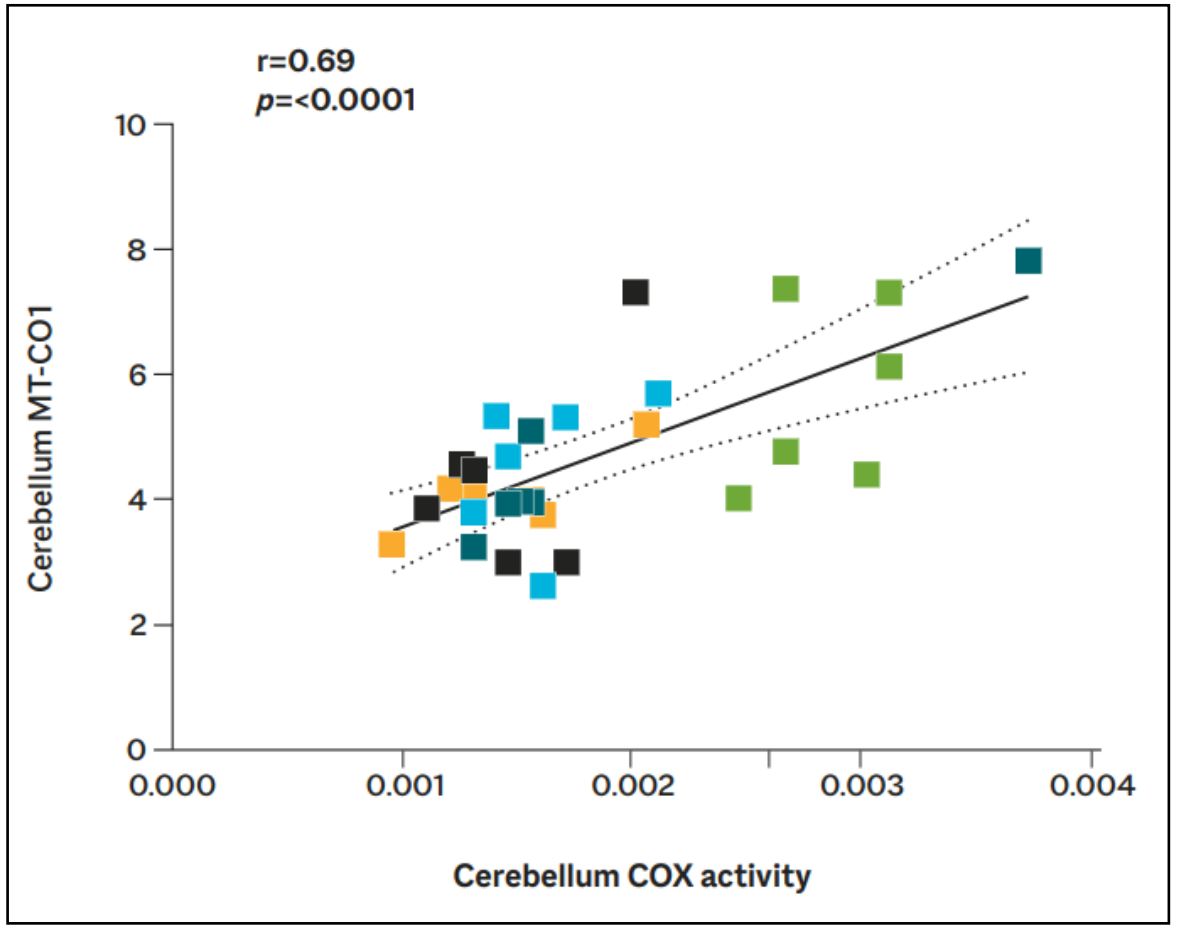
Improvement in MT-CO1 abundance 4 weeks post-injection



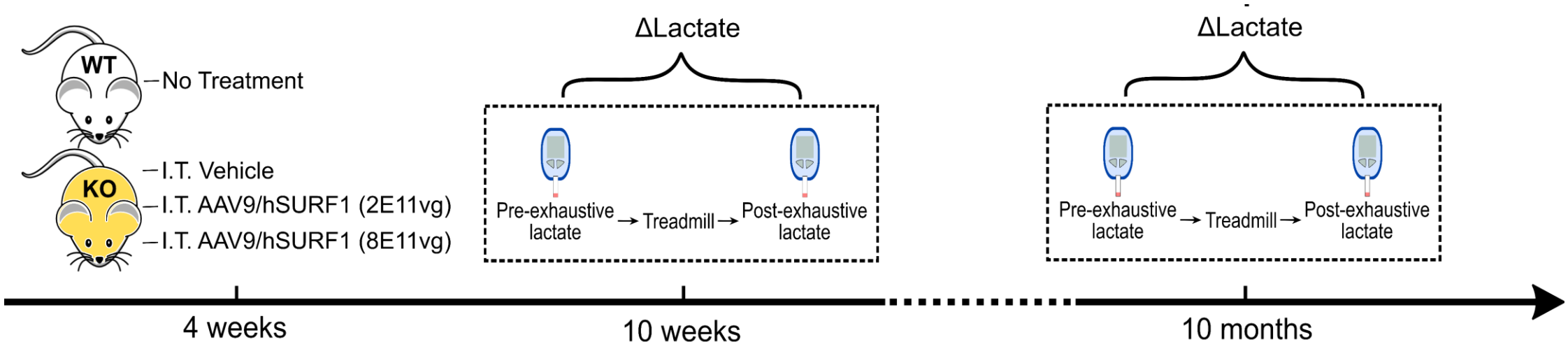


Biochemical COX activity correlated with histological COX content level

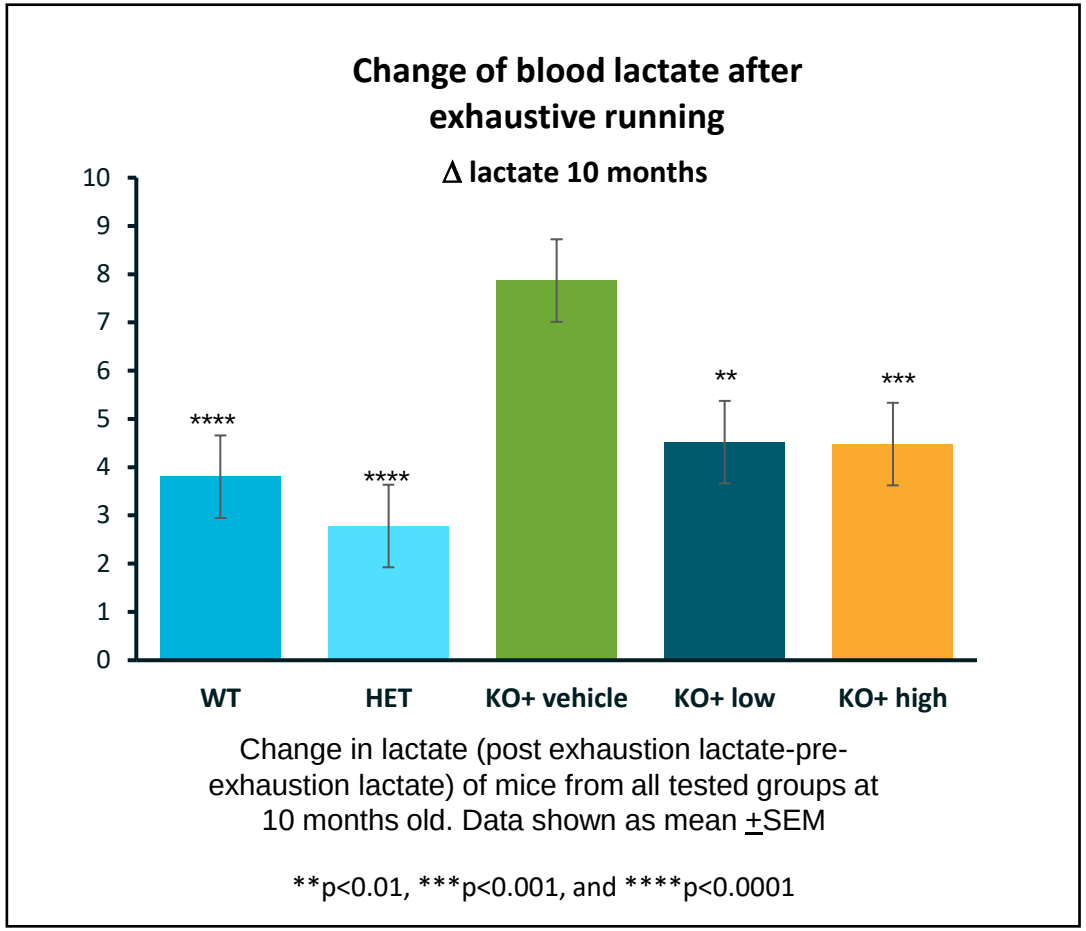




Efficacy Part II – Long-term rescue



TSHA-104 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

Summary

Efficacy in SURF1 KO Mice

- Effectively induced mRNA expression of h*SURF1*opt in various brain regions and spinal cord
- Diminished exhaustive exercise-induced lactic acidosis 9 months post-dosing
- Partially restored COX content in varies brain regions
- Partially restored COX activity in brain, liver and muscle
- IT administration demonstrated benefit

Non-GLP Toxicology in Mice

- No significant differences detected in viral vector-treated animals 4 weeks post-dosing
- No severe damages detected in tissue integrity 12 months post-injection, some mild abnormalities mostly due to aging

GLP Toxicology in Rats

- Ongoing IND-enabling toxicology study in normal rats

TSHA-104 Phase 1/2 study design plan

Goals and Targets of Trial

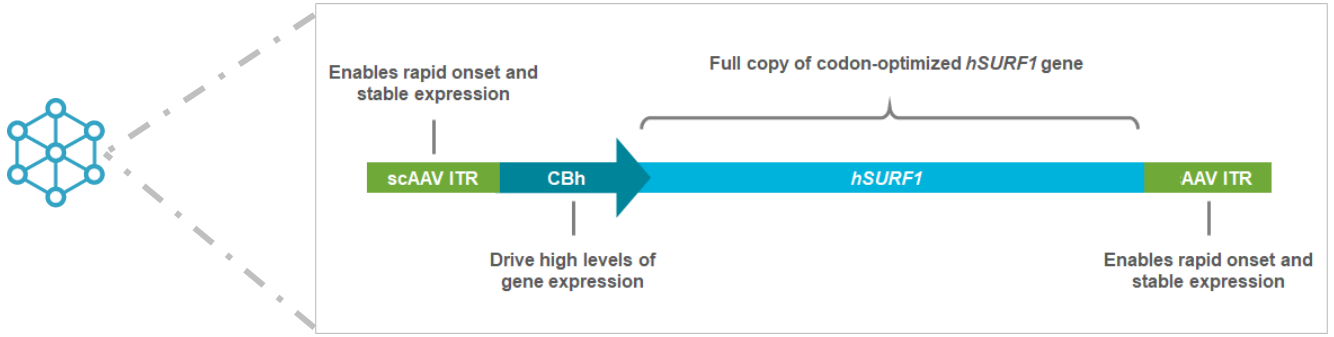
Goals

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

Target Recruitment

- Patients will roll in from ongoing prospective natural history study
- Up to 12 subjects, ages 1-18 years old
- Pathogenic confirmation of mutation in SURF1 gene
- All cohorts will be open for accrual concurrently

Product Details and Dose Cohorts



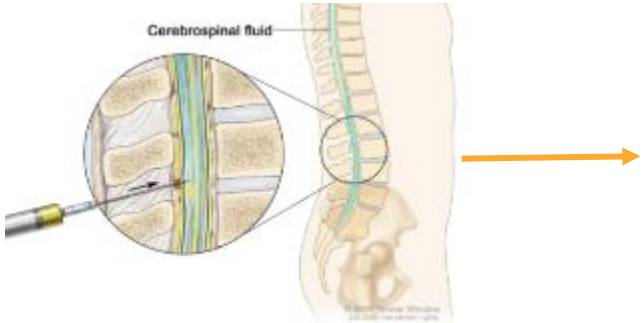
Dose Cohorts

- Participants below the age of 4 years will receive a calculated dose based on brain volume
- 5 x 10^{14} total vg (n=4)

Route and Method of Administration

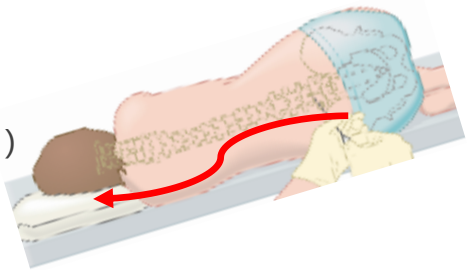
Administration

- Lumbar Intrathecal Infusion (IT)
- Amount and rate: 1 mL/min for total of 10-12 mL
- Immunosuppression regimen of prednisolone and sirolimus



Technique to Improve Transduction

- Trendelenburg position (15-30º)
- During infusion & 1 hour post infusion



TSHA-104 study clinical assessments

Disease-Specific/Global Assessments
- Newcastle Paediatric Mitochondrial Disease Scale (NPMDS)
- Gross Motor Function Measure (GMFM)
- Swallowing / Dysphagia Assessment
- Seizure Diary
- 100-Meter Walk Test
- Pediatric Balance Scale (PBS)
- Head Control Scale
- Scale for the Assessment and Rating of Ataxia (SARA)
- Vineland-3
- Bayley-III / WPPSI-IV / WISC-IV

Communication Assessments
- Expressive and Receptive One-Word Picture Vocabulary Test (ROWPVT-4, EOWPVT-4)
- Observer-Reported Communication Ability (ORCA)

Biomarkers
- COX activity
- COX expression
- Lactate
- Pyruvate

Quality of Life/Other Assessment
- Quality of Life Inventory Disability (QI-D)
- Infant Toddler Quality of Life Questionnaire (ITQOL)
- PedsQL Scales and Family Impact Module
- Study Participant Feedback Questionnaire
- Clinical Global Impression Scale (CGI)

Neurological Assessment
- EEG
- MRI/MRS

Anticipated next steps for TSHA-104

- Complete IND-enabling toxicology study
- Submit IND/CTA in 2H 2021
- Complete GMP manufacturing using commercial process
- Continue enrollment in natural history study
- Initiate Phase 1/2 interventional study by YE 2021

Q & A

TSHA-105 for SLC13A5 Deficiency

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

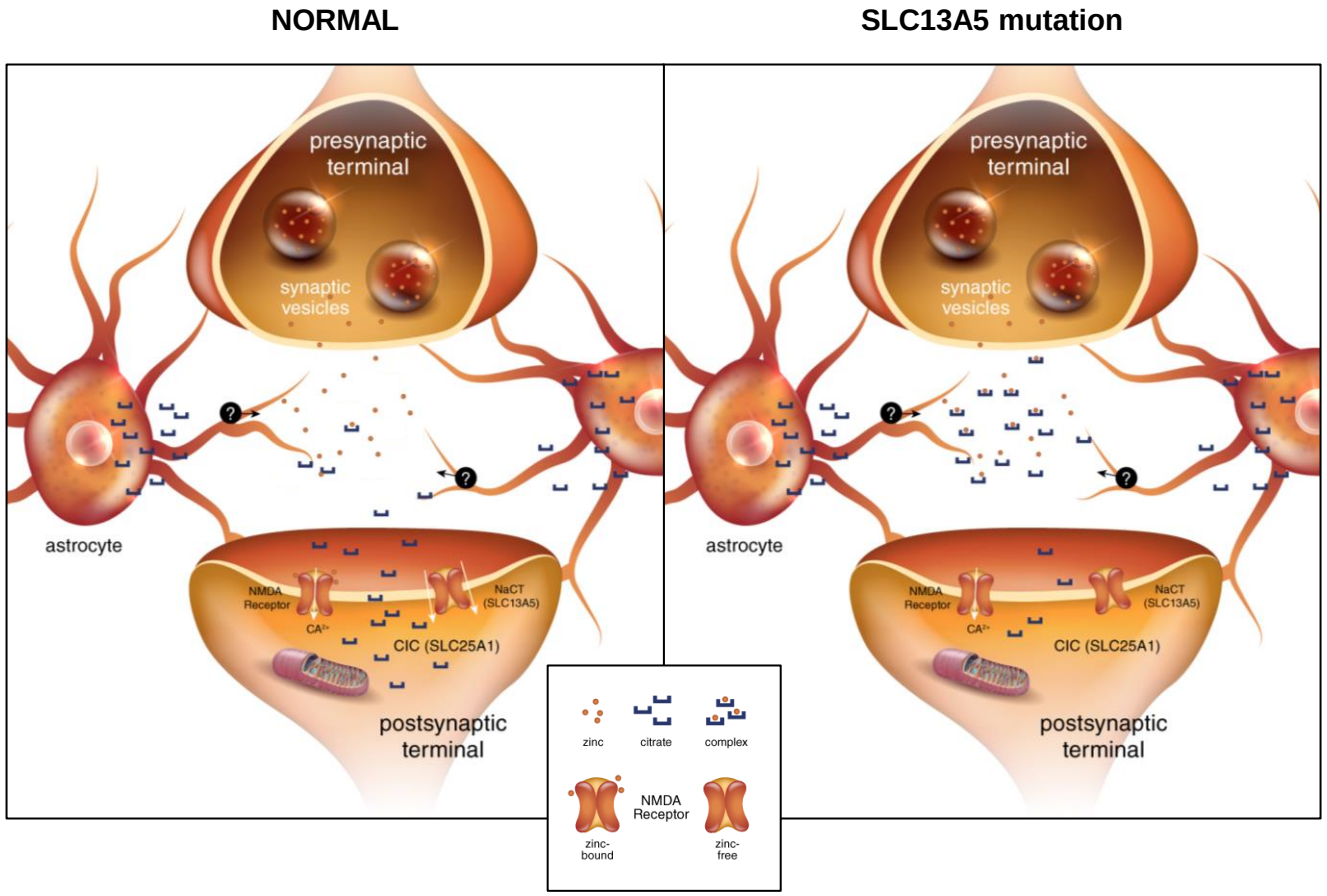
Chief Medical Officer and Head of R&D

Rachel Bailey, PhD

UTSW Gene Therapy Program

SLC13A5 deficiency is a rare autosomal recessive disorder

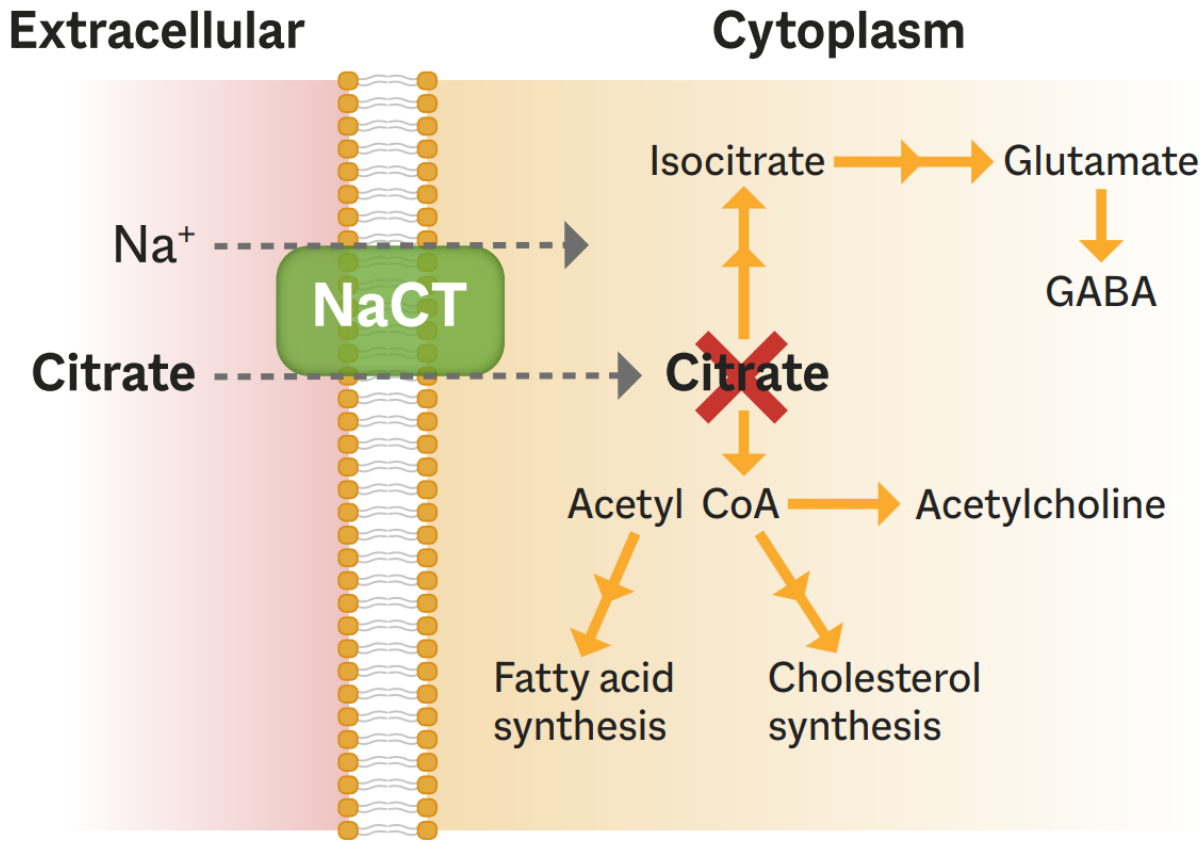
- Bi-allelic loss of function in the SLC13A5 gene, resulting in a loss or reduction in citrate transport and aberrant cellular metabolism
- Patients have impaired motor function, speech production and seizures
- Signs and symptoms include seizures within a few days of birth, persisting through life,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



Bhutia et al, *Molecules* 2017

SLC13A5 involvement in citrate transport

- Disorder caused by mutations in both copies of the *SLC13A5* gene which codes for a sodium dependent citrate transporter (NaCT)
- *SLC13A5* mutations greatly reduce or eliminate citrate transporter activity
- Citrate is a key metabolite and plays an important role in energy generation pathways in the cells
- NaCT expressed mainly in liver and brain
- NaCT can transport other molecules (succinate, alpha-ketoglutarate, and malate)
- SLC13A5 deficient patients have increased citrate levels in CSF and blood



SLC13A5 deficiency results in persistent seizures and developmental delays

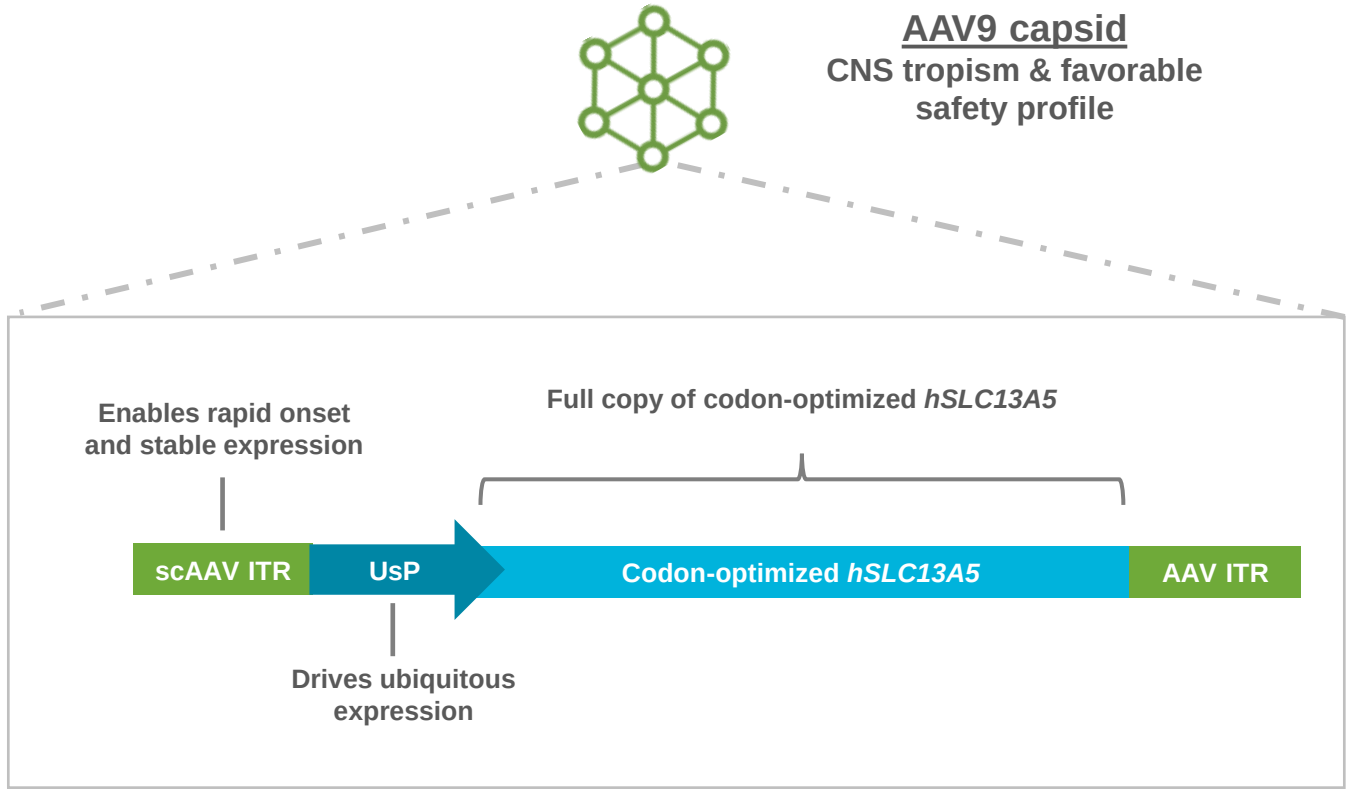
- **Seizures**
  - Affected children present with seizures within a few days of birth which persist throughout life
  - Multiple seizure types; anti-epileptic drugs (phenobarbital, valproate, and acetazolamide) have varying success in controlling seizures
  - Refractory to medication
  - Children can succumb to complications of the seizures
- **Movement Disorder**
  - Low muscle tone (hypotonia) and a lack of muscle control or coordination of voluntary movements, such as walking or picking up an object (ataxia)
  - Episodes of body stiffening or weakness (minutes to a few hours)
  - Dystonia & chorea
- **Developmental Delay**
  - Intellectual disability and global developmental delay
  - Limited to no speech production, but have receptive language
  - Limited and slow motor progress with problems standing or walking independently
- **Biomarkers**
  - Nearly all children have abnormal tooth enamel
  - Brain MRIs appear normal or have subtle changes in the white matter
  - EEGs have a relatively well-preserved background for age, even in the face of frequent seizures
  - Elevated citrate levels in blood, urine and CSF

No currently approved therapies
Patients require constant supervision and care

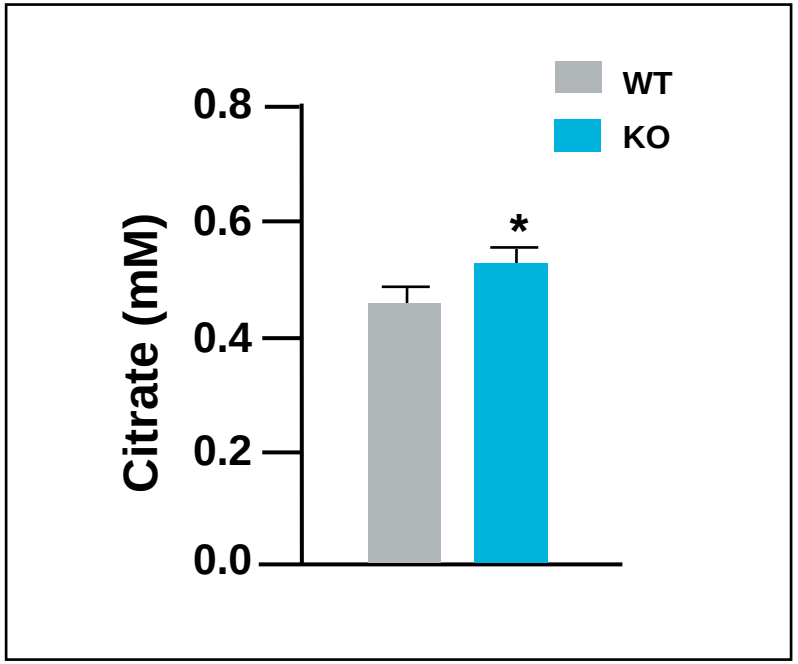
Yang et al. *Child Neurology Open* 2020

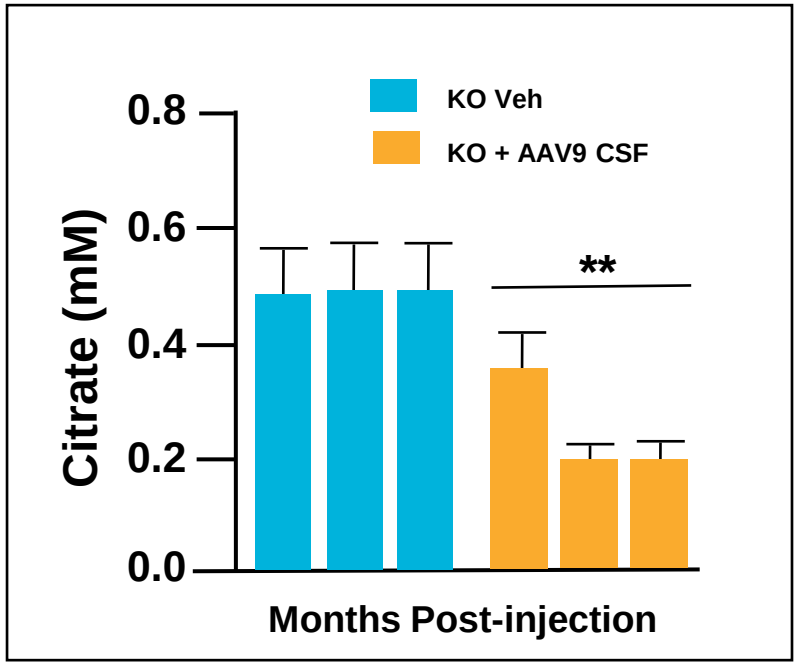
TSHA-105 currently in IND/CTA-enabling studies

- Self-complementary AAV9 expressing human SLC13A5 protein under the control of a ubiquitous promoter
- Delivered intrathecally
- Currently in IND/CTA-enabling studies

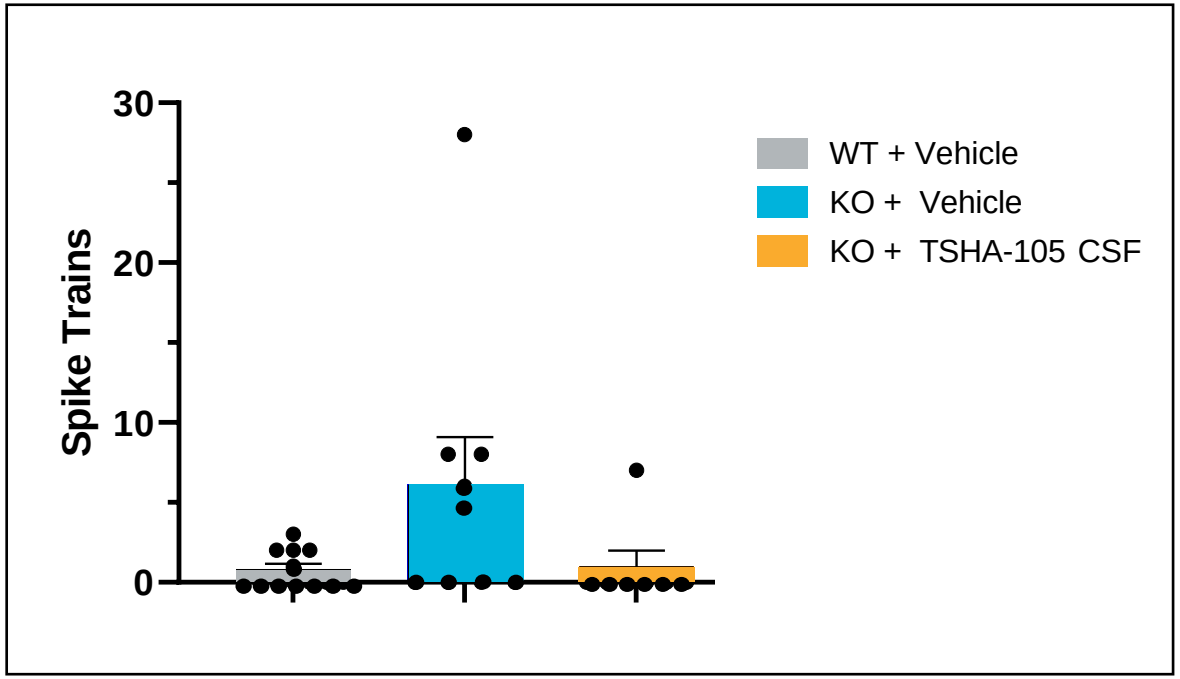


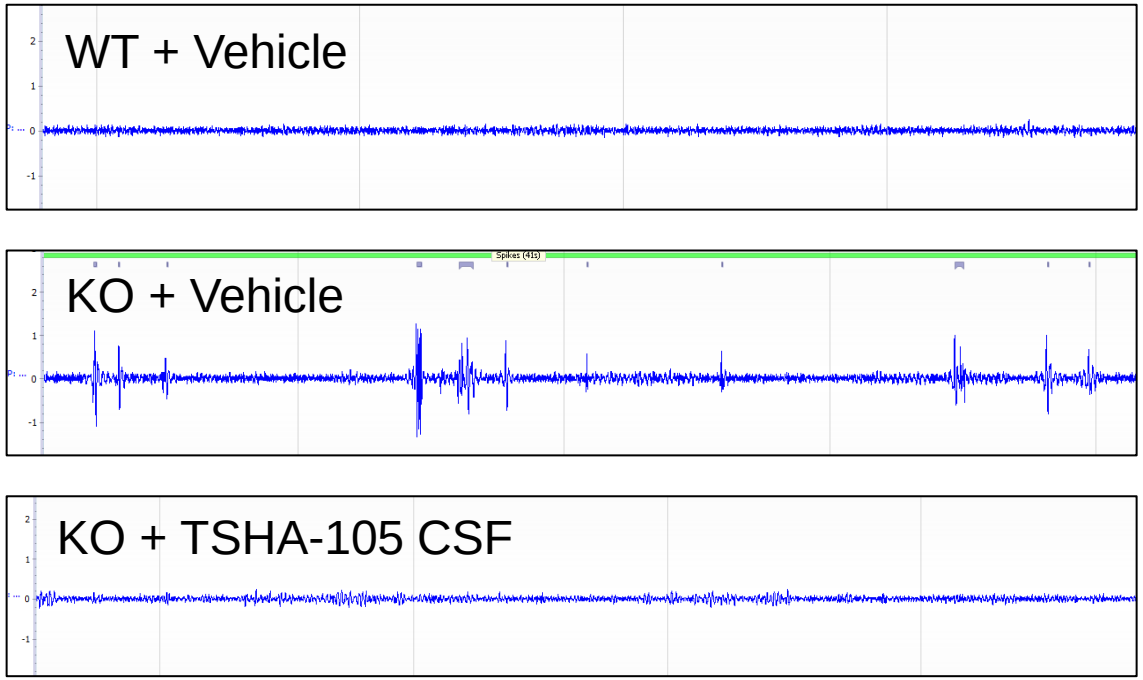
TSHA-105 decreased plasma citrate levels in 3-month old SLC13A5 KO mice





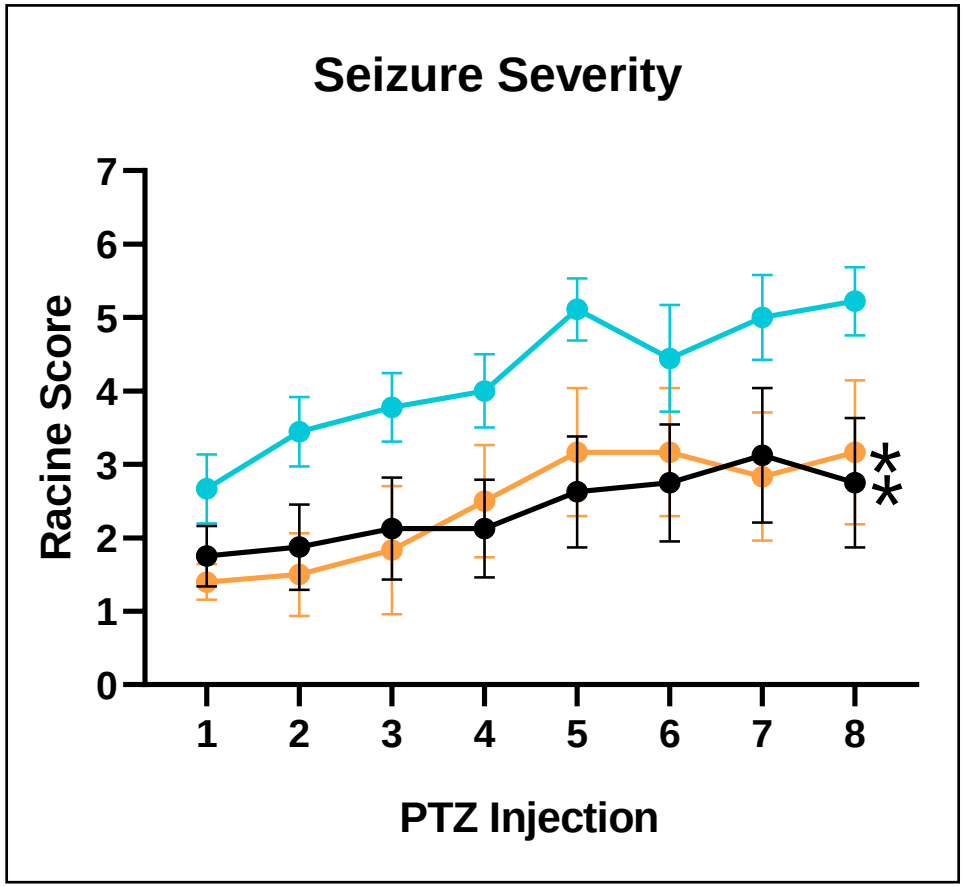
TSHA-105 improved EEG activity in 3-month old SLC13A5 KO mice

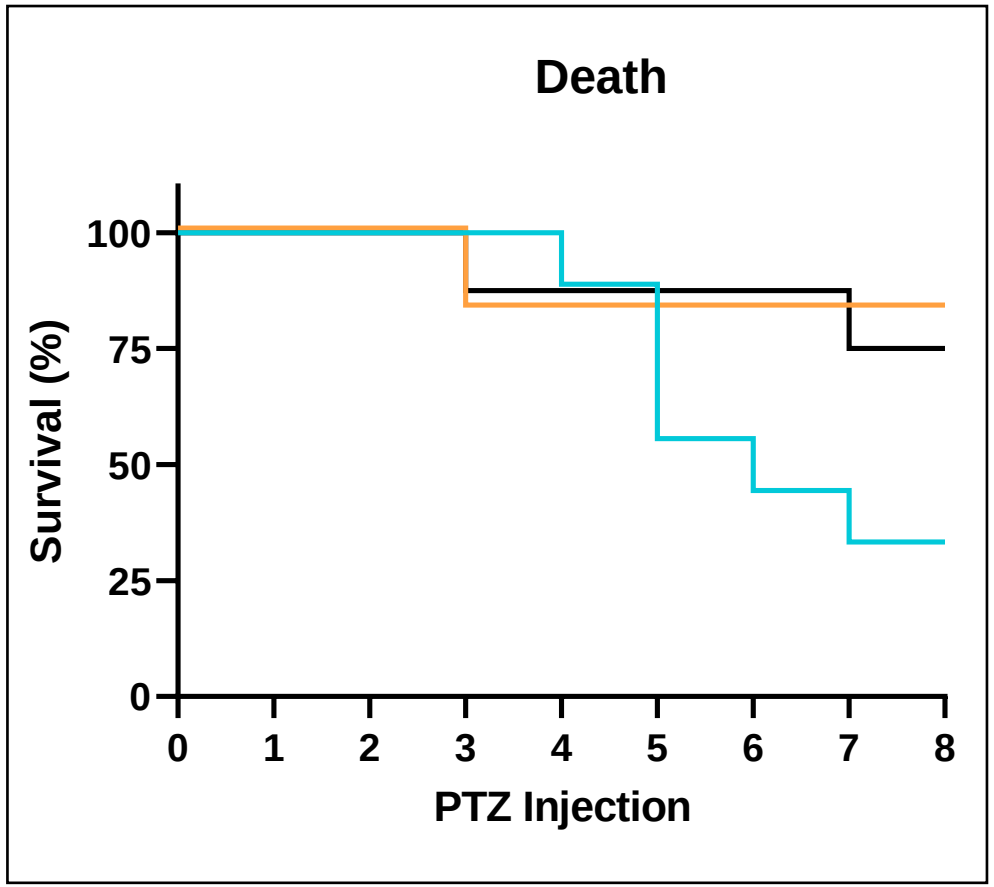




Bailey, R. 2020

TSHA-105 reduced seizures and associated deaths in SLC13A5 KO mice





WT + Vehicle (n=8)
KO + Vehicle (n=9)
KO + TSHA-105 CSF (n=6)

PTZ - pentylenetetrazol

Bailey, R. 2020

Moving TSHA-105 towards clinical study – Clinical considerations

- Ongoing IND/CTA-enabling studies for TSHA-105
- Patients will roll in from ongoing prospective natural history study
- Current clinical trial considerations:

Considerations for the TSHA-105 Phase 1/2 first-in-human study		
Study design	• Open-label, randomized, dose-escalation study of the safety, tolerability and preliminary efficacy of TSHA-105 for the treatment of epileptic encephalopathy caused by SLC13A5 deficiency • CSF dosing in children	
Clinical assessments	**Disease-Specific/Global Assessments** • CHOP-INTEND • Peabody Developmental Motor Scale • Bayley Scales of Infant Development • Developmental quotient score • Clinical global impression of improvement (CGI-I) • Quality of Life scales **Communication Assessments** • Observer-reported communication ability (ORCA) **Imaging** • MRI of Brain	**Biomarkers** • Citrate levels in plasma, urine, and CSF **Seizure Monitoring** • Seizure frequency • Incidence of status epilepticus • EEG • Ratio of slow wave activity (SWA) during first hour of non rapid eye movement (NREM) sleep (measured by interictal EEG)

Anticipated next steps for TSHA-105

Complete IND/CTA-enabling preclinical work

Continue enrollment in natural history study

Pre-IND/CTA meeting anticipated 2H 2021

Complete GMP manufacturing using commercial process

Q & A

TSHA-103 for SLC6A1 Haploinsufficiency Disorder

Kim Goodspeed, MD

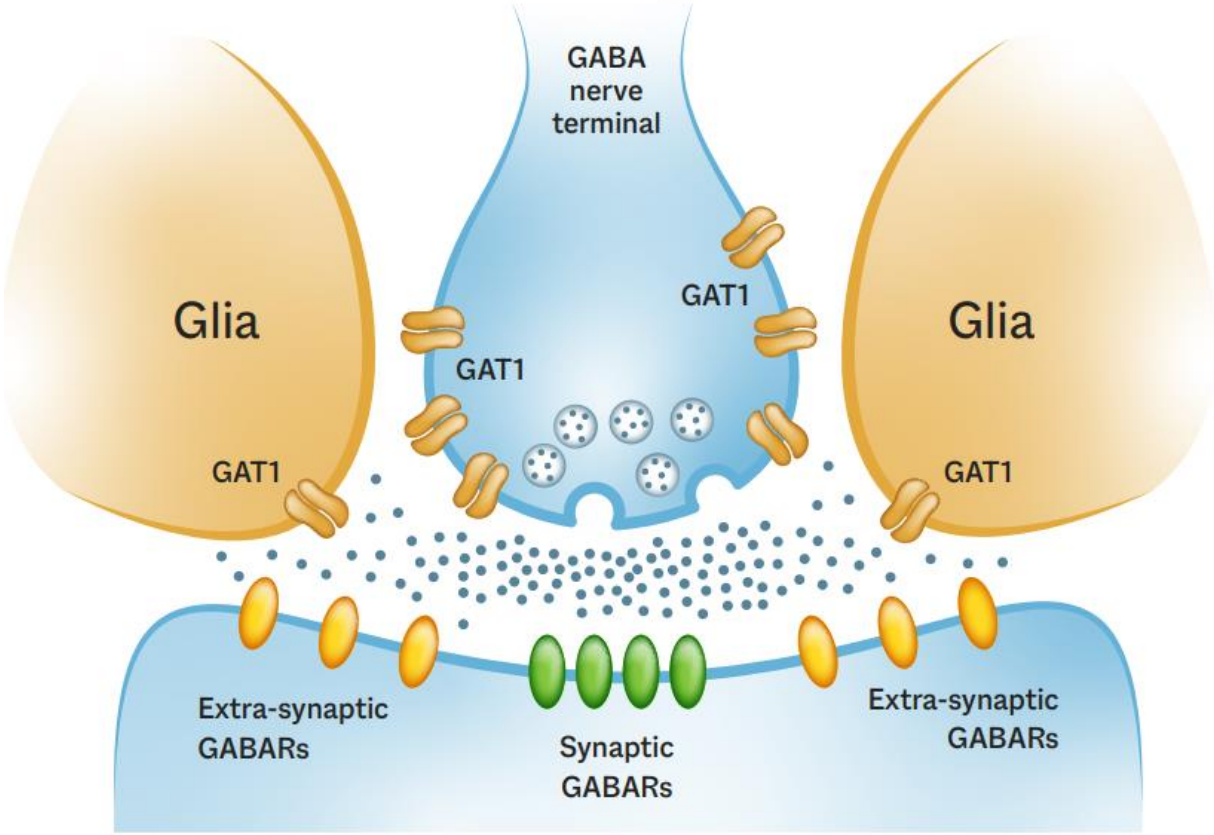
UTSW Gene Therapy Program

Steven Gray, PhD

Chief Scientific Advisor, UTSW Gene Therapy Program

SLC6A1 haploinsufficiency disorder results in persistent seizures and developmental delays

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

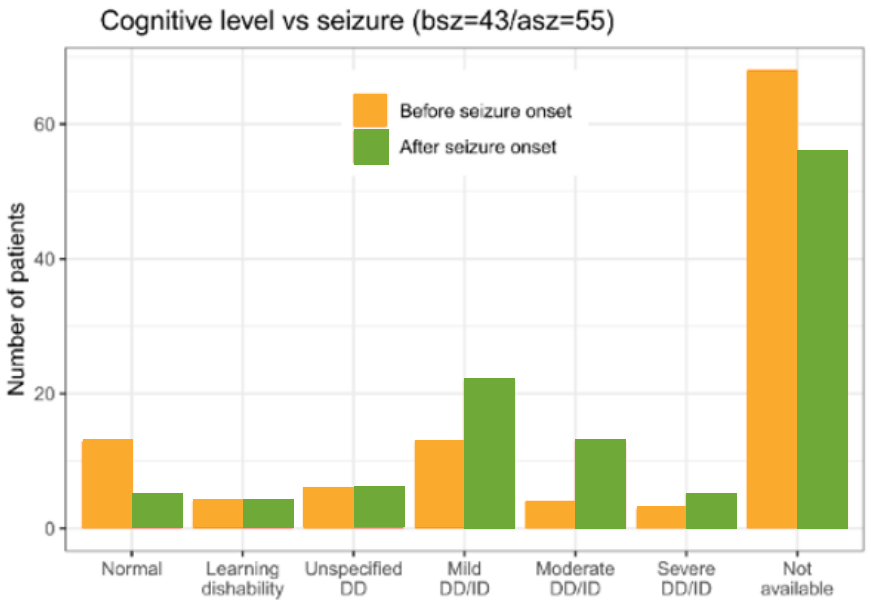


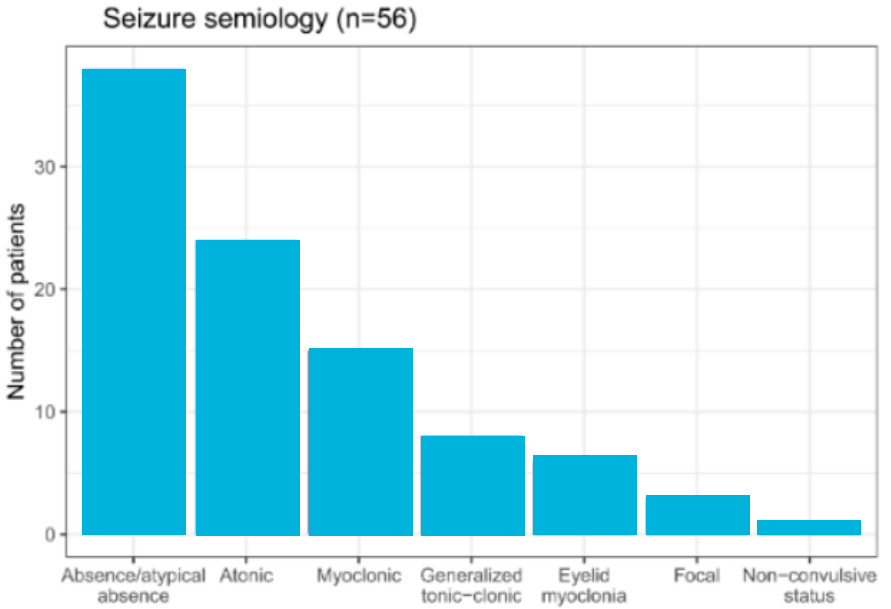
SLC6A1 Patient Video

SLC6A1 Patient Video

SLC6A1 haploinsufficiency disorder results in persistent seizures and developmental delays

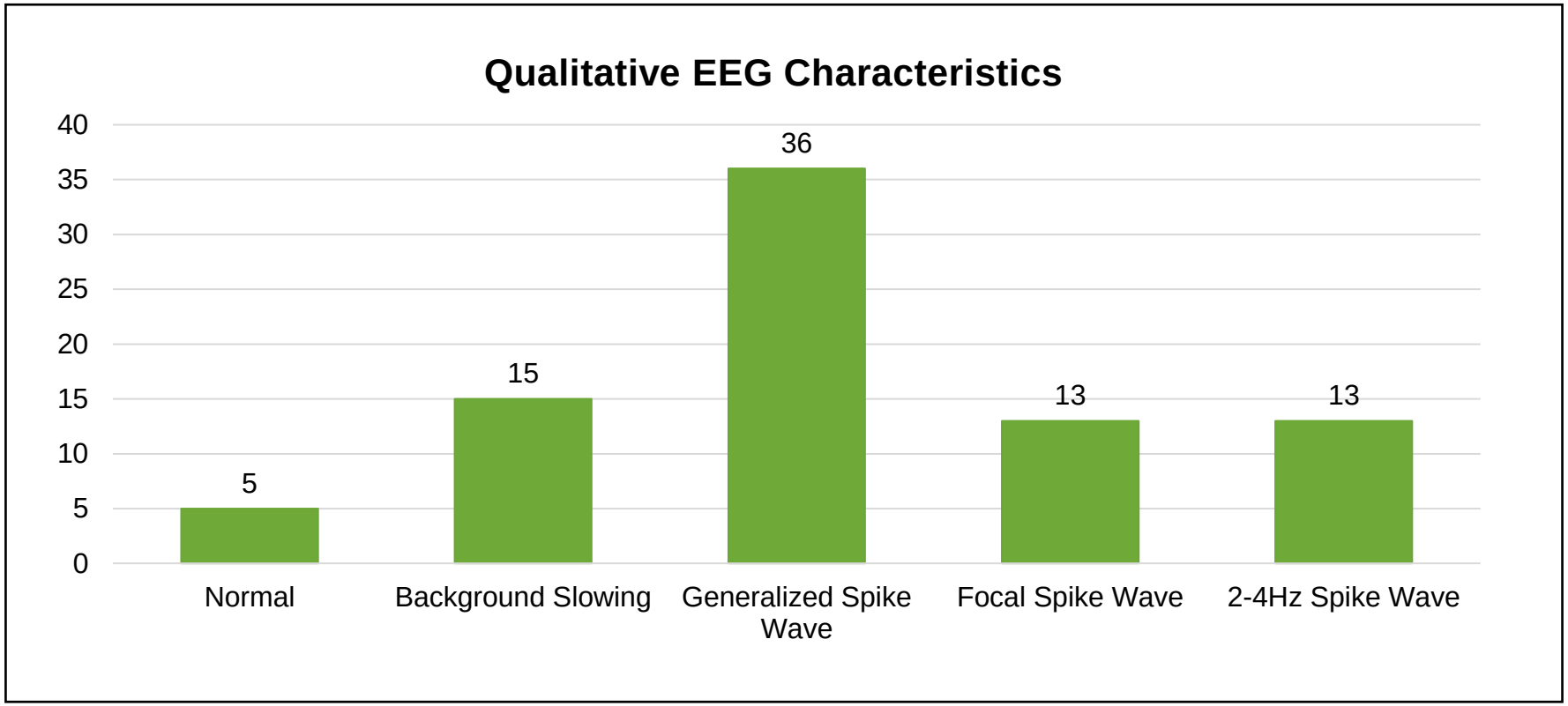
- Based on review of 116 cases, developmental abilities are variable from mild learning disability to severe developmental delay or intellectual disability
- Initial cases highlighted myoclonic-atonic seizures; however, absence or atypical absence seizures were the most prevalent seizure semiology





Goodspeed K et al. *Brain Comm* 2020

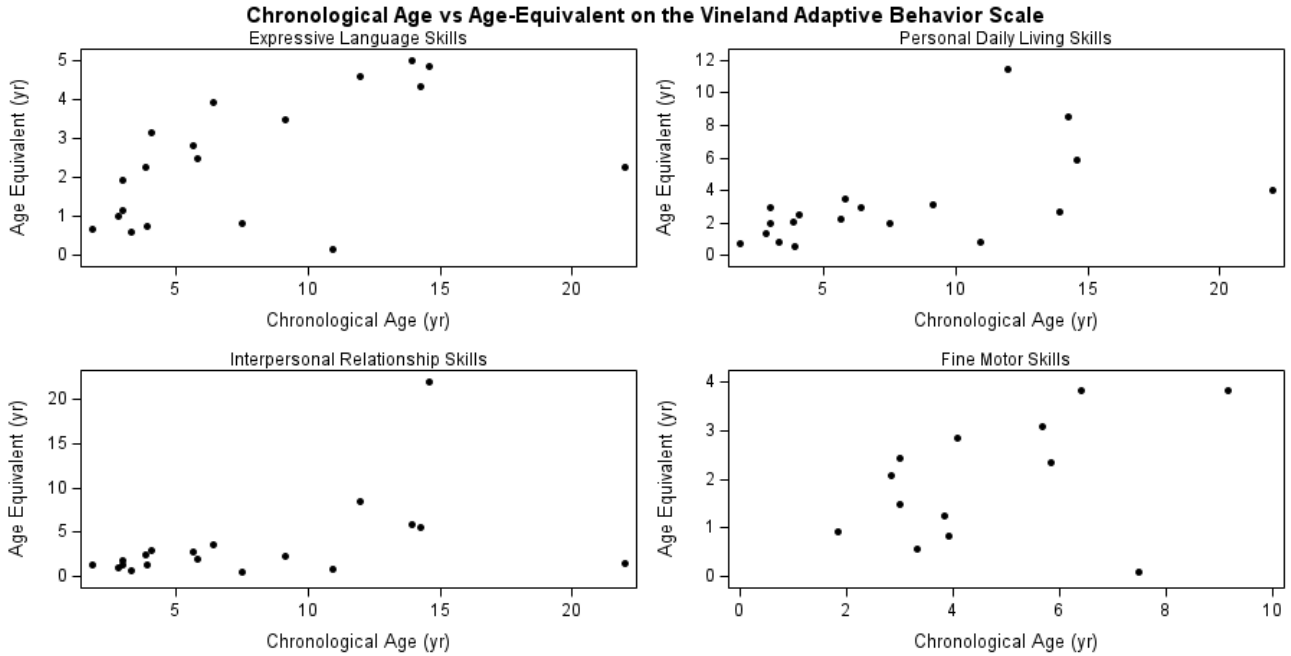
Qualitative EEG findings demonstrated abnormalities with generalized epileptiform discharges being the most prevalent

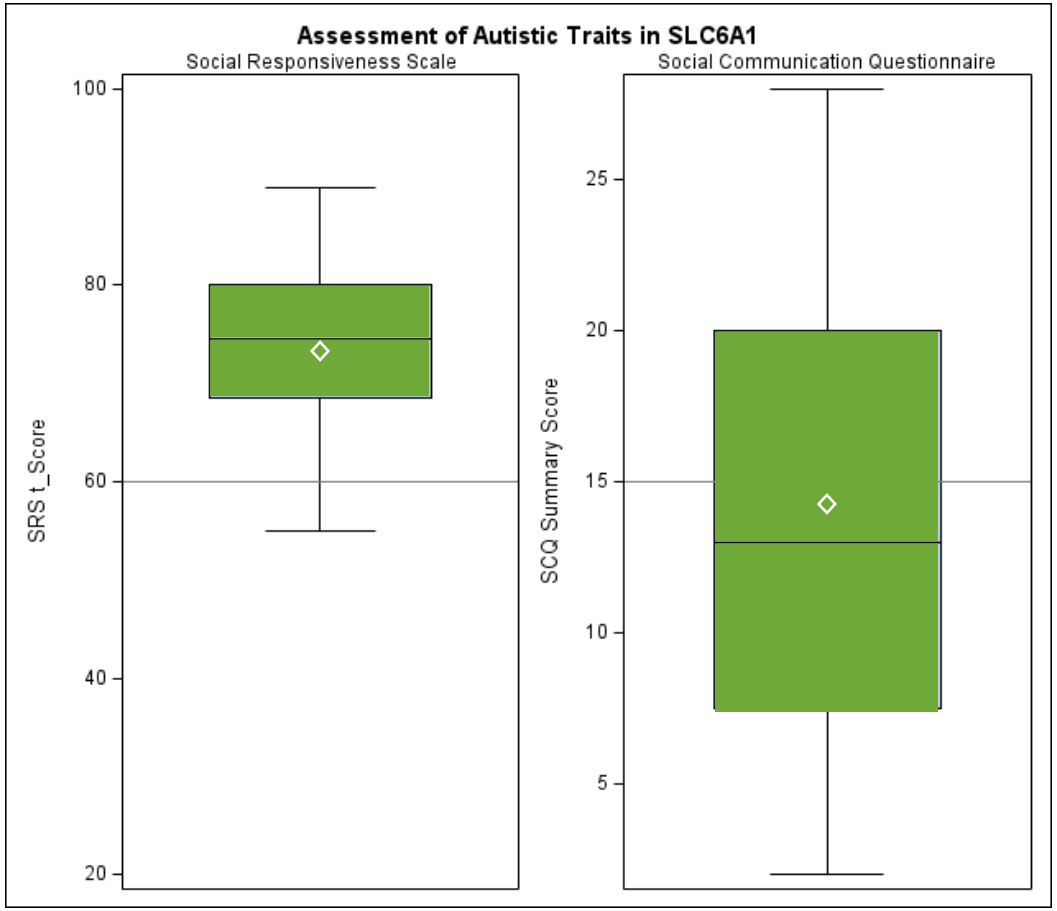


Goodspeed K et al. *Brain Comm* 2020

SLC6A1 haploinsufficiency disorder results in persistent seizures and developmental delays

- Vineland Adaptive Behavior Scale demonstrated deficits across all four domains
- Autism spectrum disorder questionnaires demonstrated elevated scores, with higher scores on the Social Responsiveness Scale

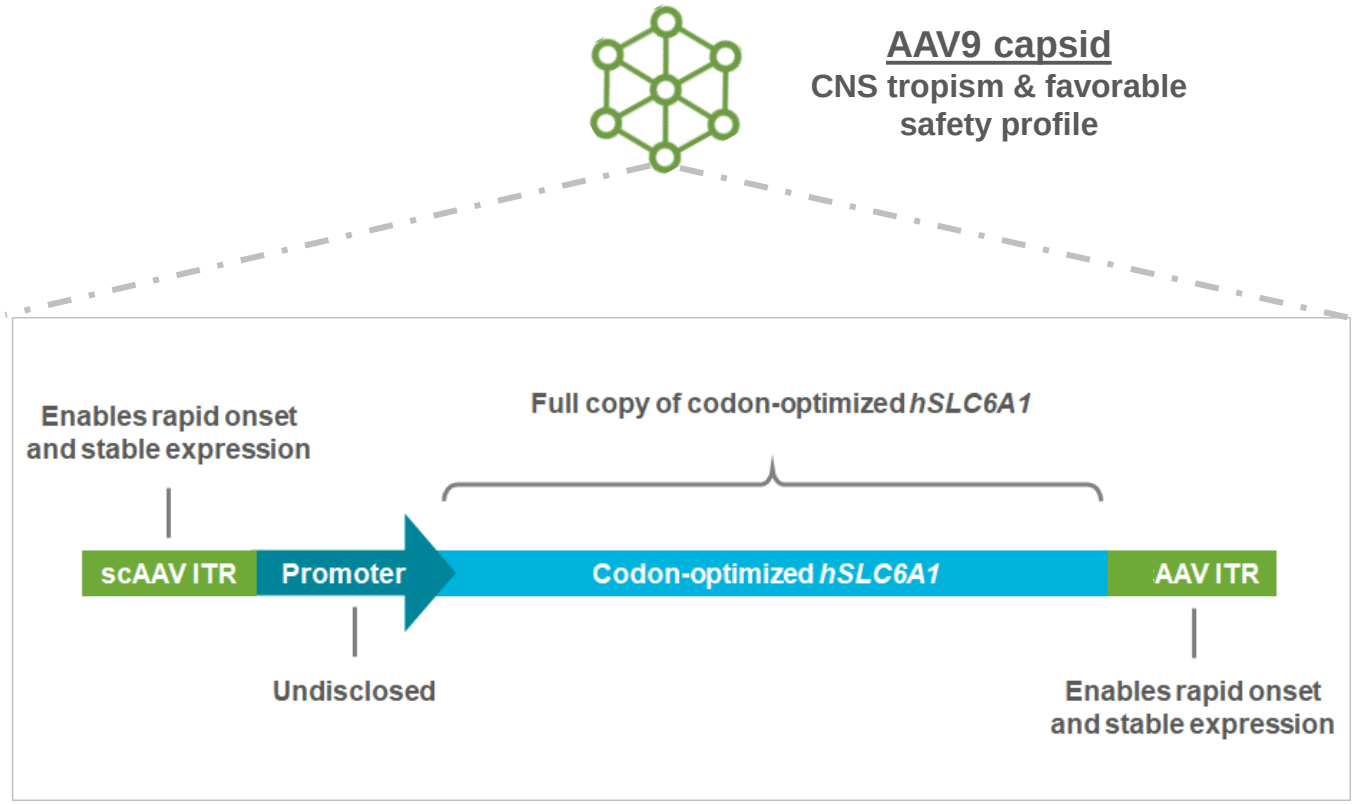




Manuscript in review, 2021

TSHA-103 in IND/CTA-enabling studies

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



SLC6A1 KO mouse phenotype

Decreased body weight

Tremor

Hindlimb clasping

Rotarod
- Poor motor coordination

Open Field
- Anxious behavior

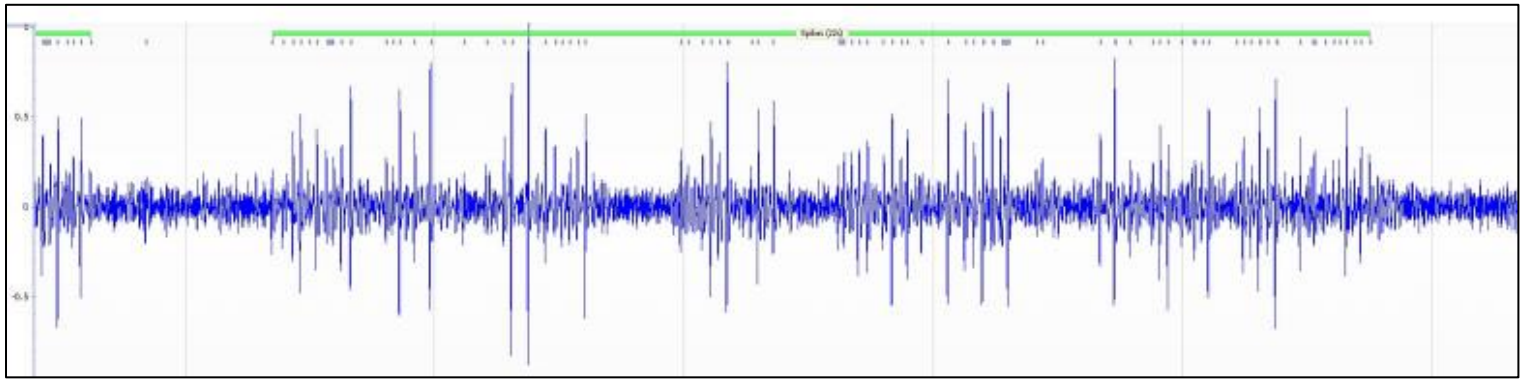
Nest building
- Decreased nest building score = autism-like phenotype

Context fear conditioning
- Poor learning and memory

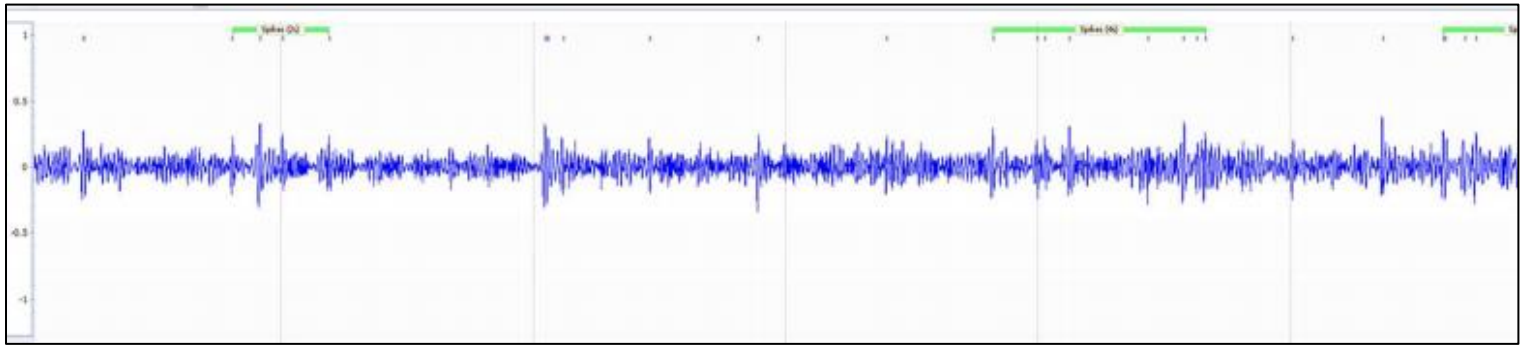
Abnormal EEG
- Absence seizure-like activity

Neonatal ICV administration of TSHA-103 rescued abnormal EEG in SLC6A1 KO and heterozygous mouse models

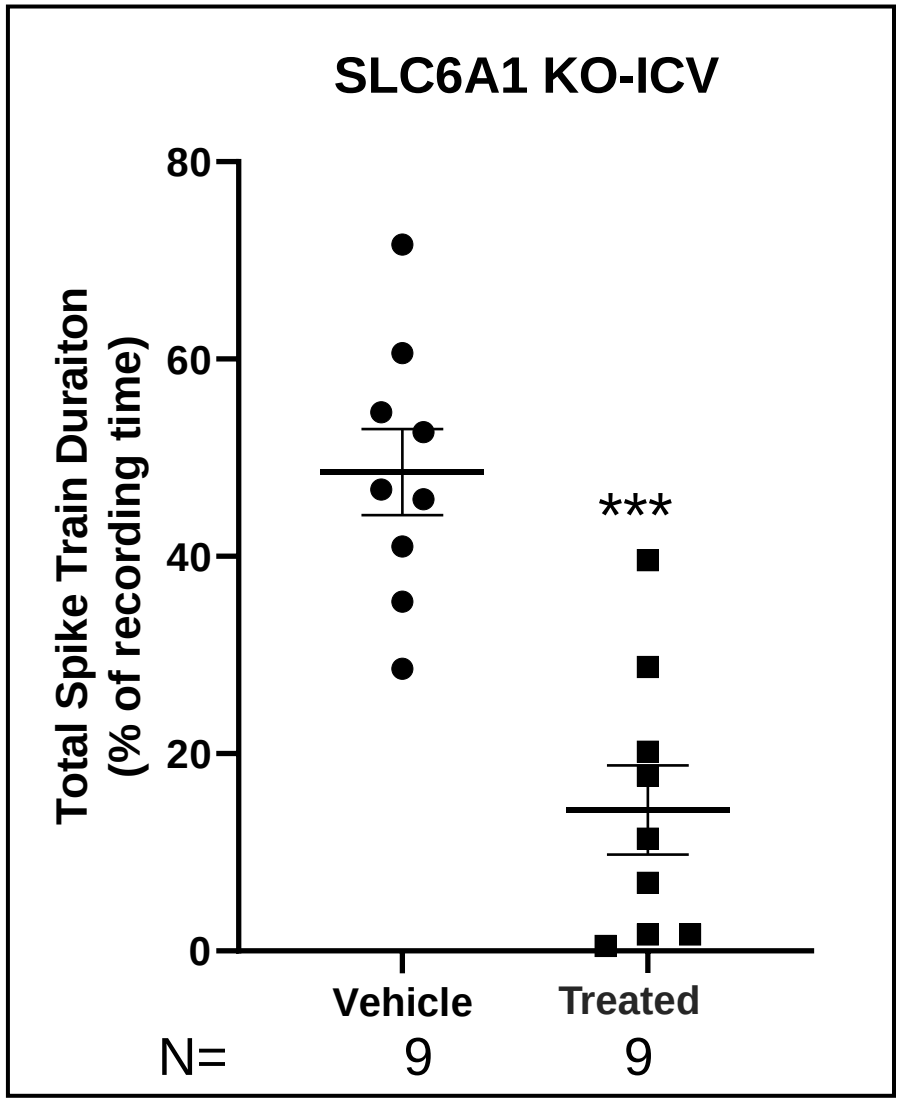
KO + vehicle

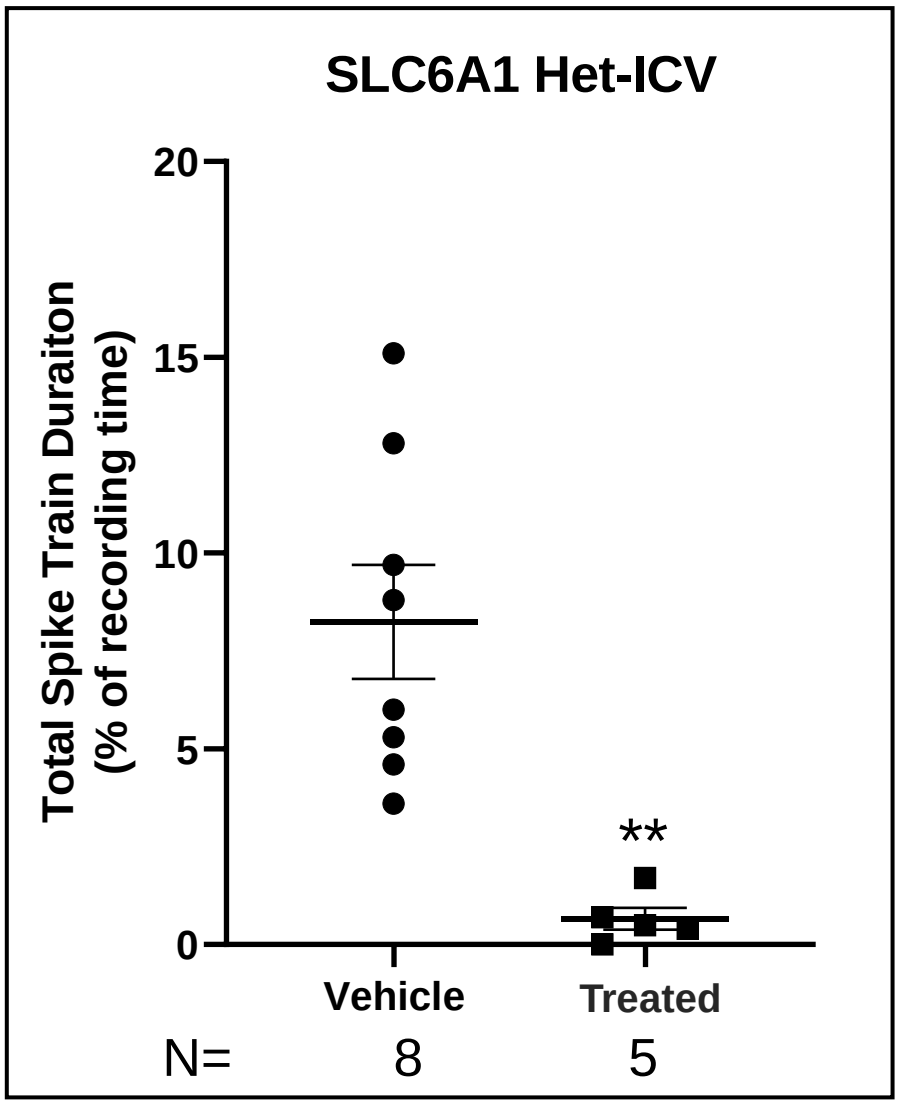


KO + TSHA-103



Neonatal ICV administration of TSHA-103 rescued abnormal EEG in SLC6A1 KO and heterozygous mouse models





Anticipated next steps for TSHA-103

Animal proof-of-concept achieved in KO mouse model

Evaluate dose response and age response and finalize dose from pharmacology

Natural history study initiated by patient advocacy foundation

Interventional trial protocol development underway

Q & A

TSHA-112 for Adult Polyglucosan Body Disease

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

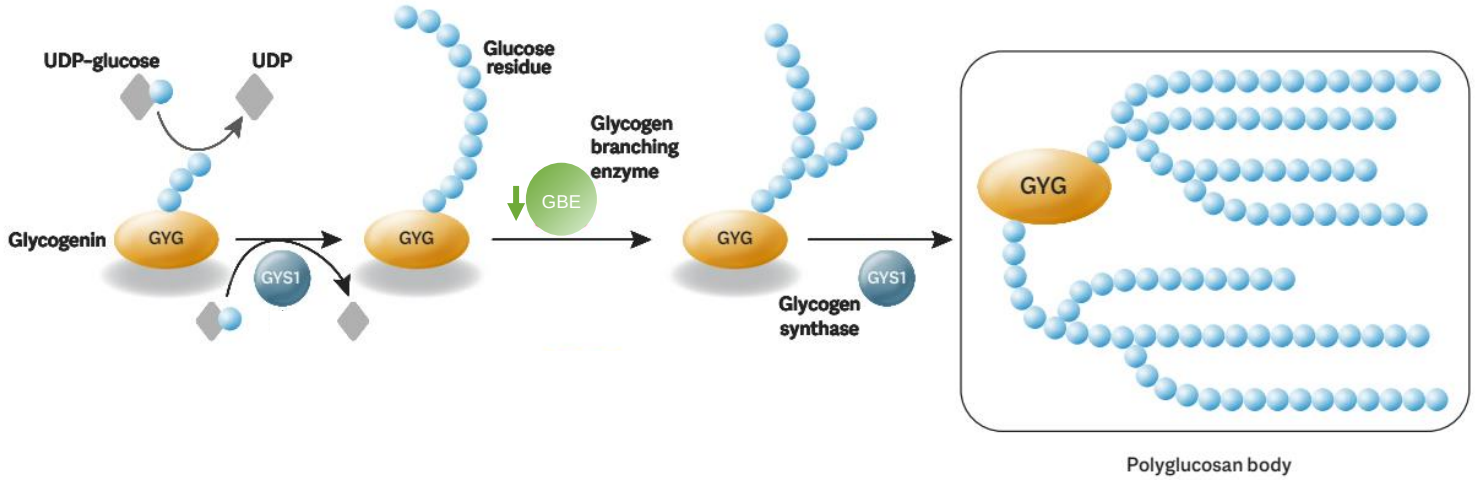
Chief Medical Officer and Head of R&D

Berge Minassian, MD

Chief Medical Advisor, UTSW Gene Therapy Program

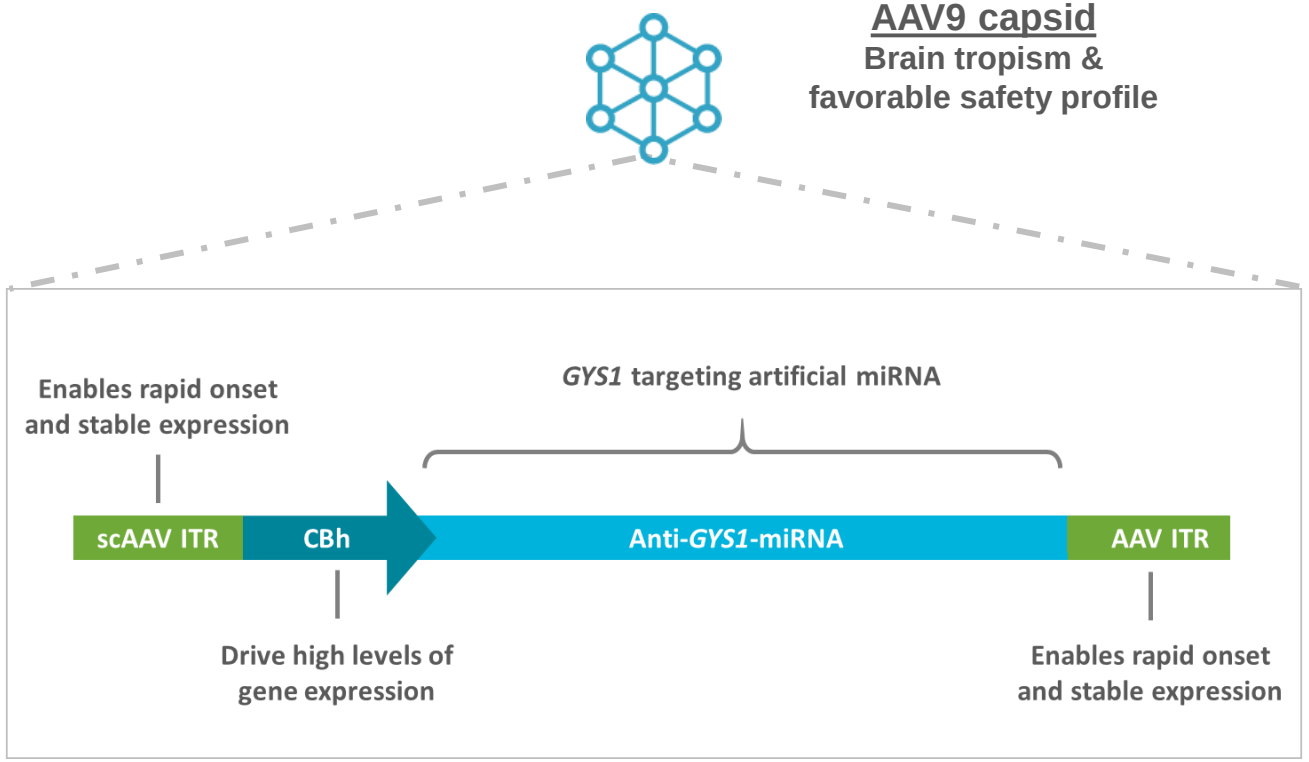
Adult polyglucosan body disease (APBD)

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

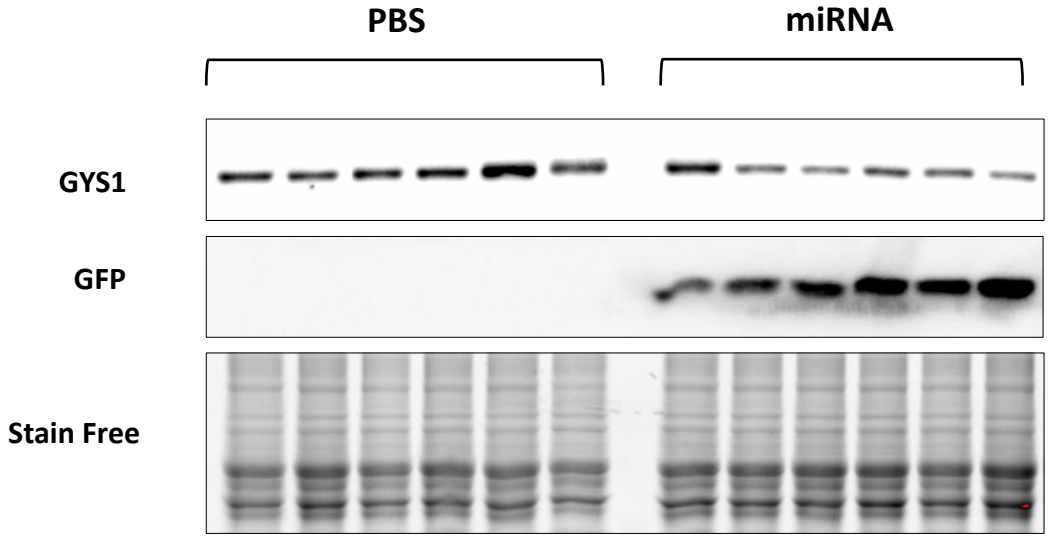


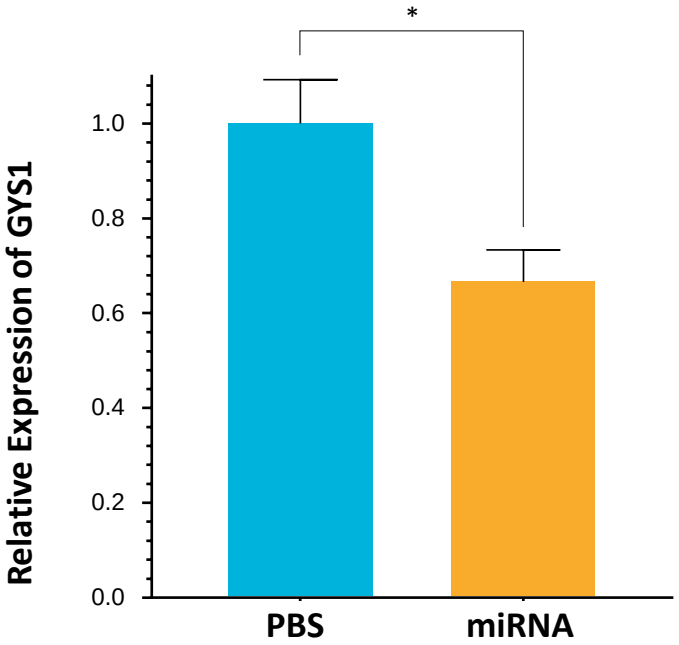
TSHA-112 expected to advance in IND/CTA-enabling studies in 2021

- 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

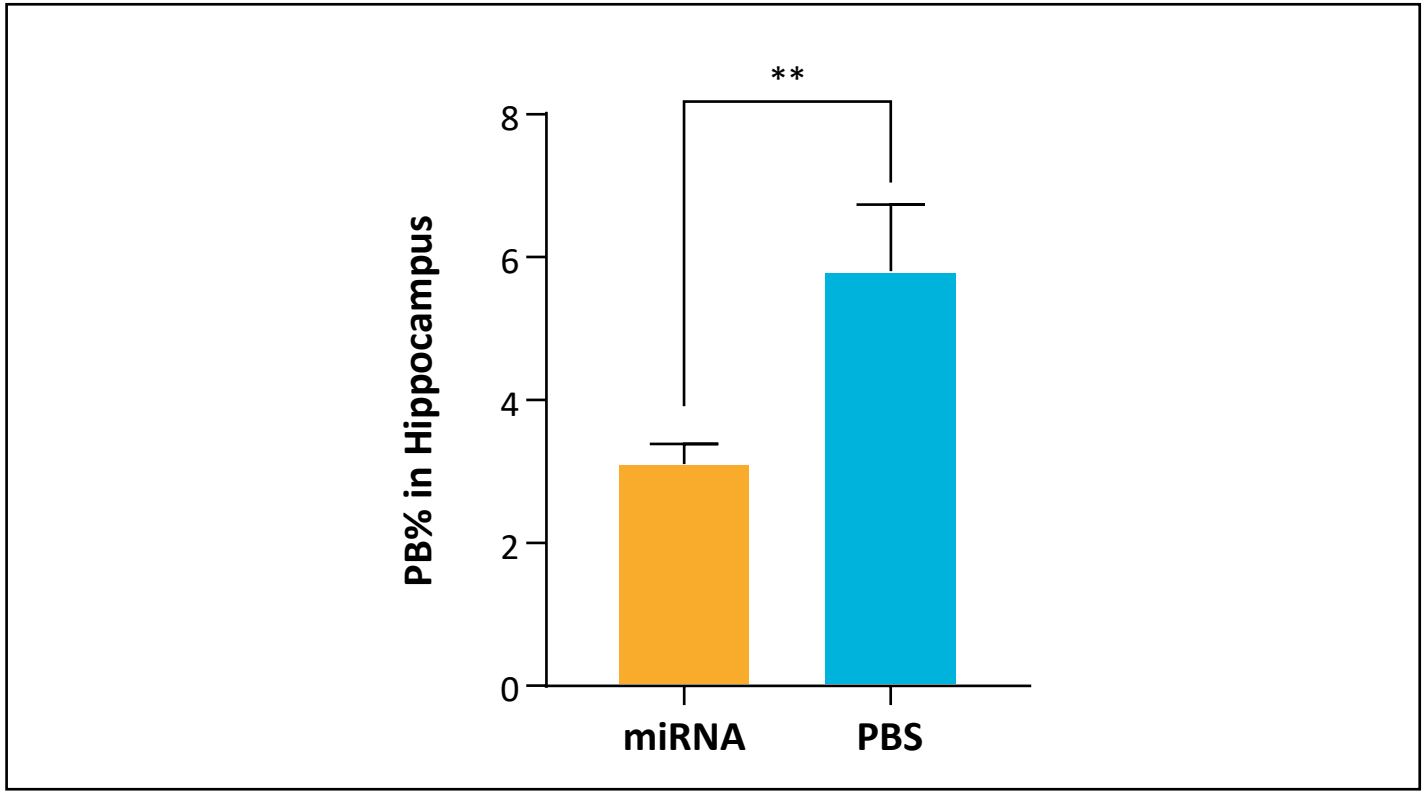


TSHA-112 reduced GYS1 expression in the APBD KO model





TSHA-112 decreased polyglucosan body formation in mice hippocampus



TSHA-112 decreased polyglucosan body formation in the hippocampus

Anticipated next steps for TSHA-112

Animal proof-of-concept achieved in KO mouse model

Evaluate dose response and age response and finalize dose from pharmacology

Interventional trial protocol development underway

Q & A

TSHA-111 for Lafora Disease

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

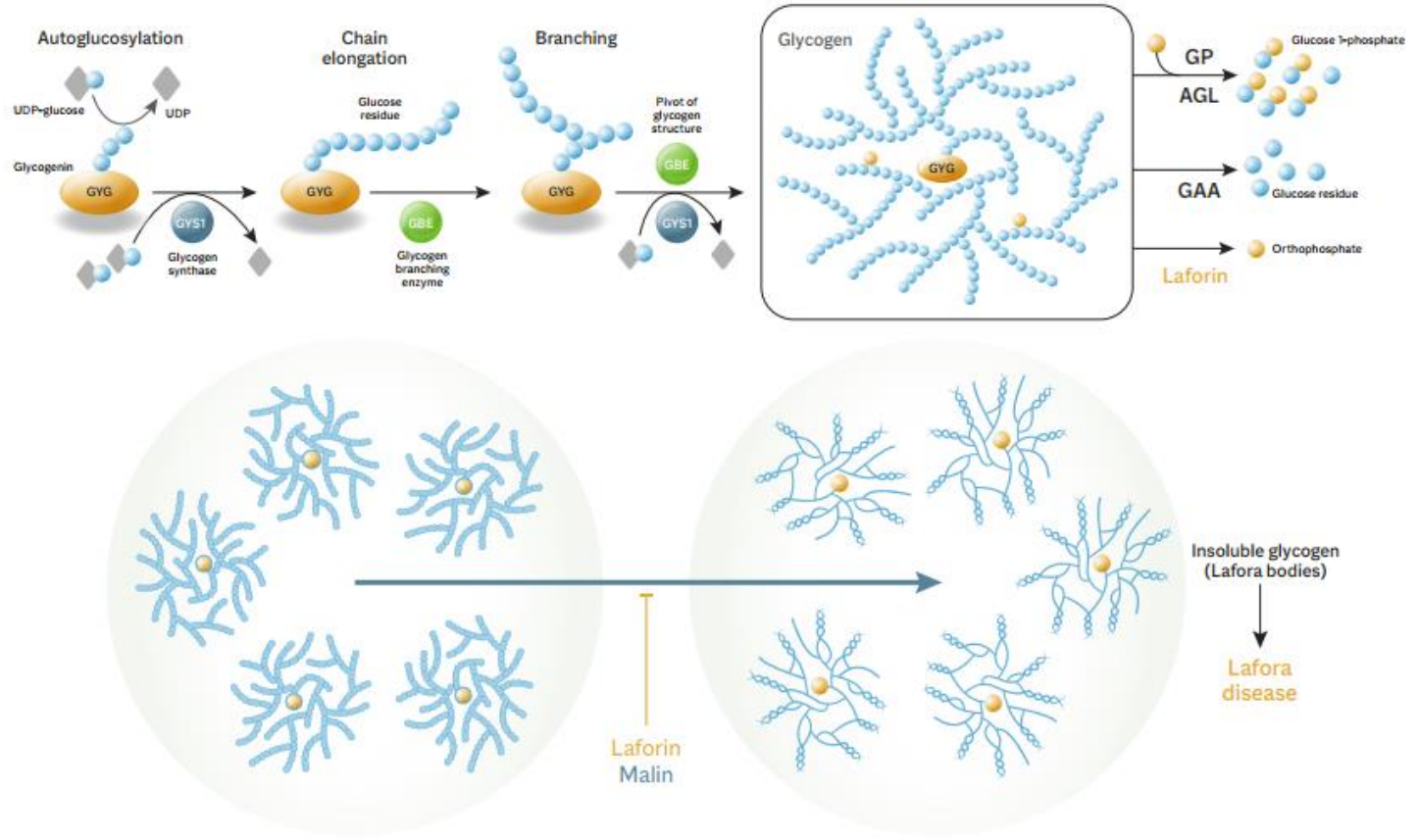
Chief Medical Officer and Head of R&D

Berge Minassian, MD

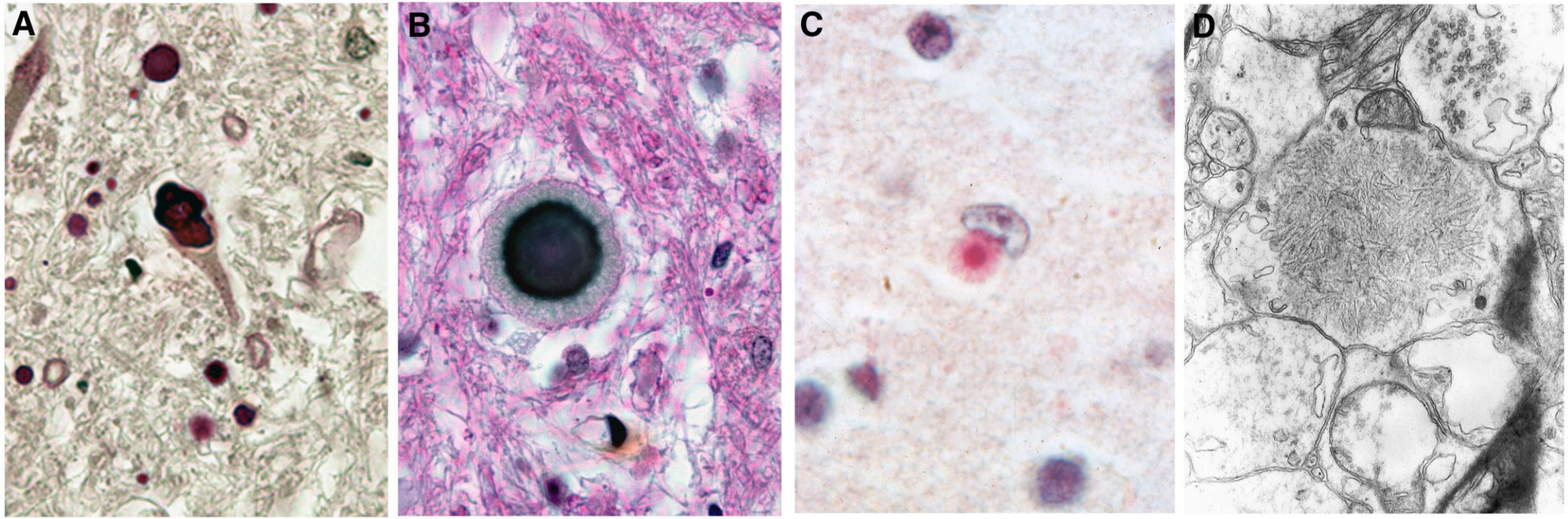
Chief Medical Advisor, UTSW Gene Therapy Program

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)



Examples of polyglucosan bodies



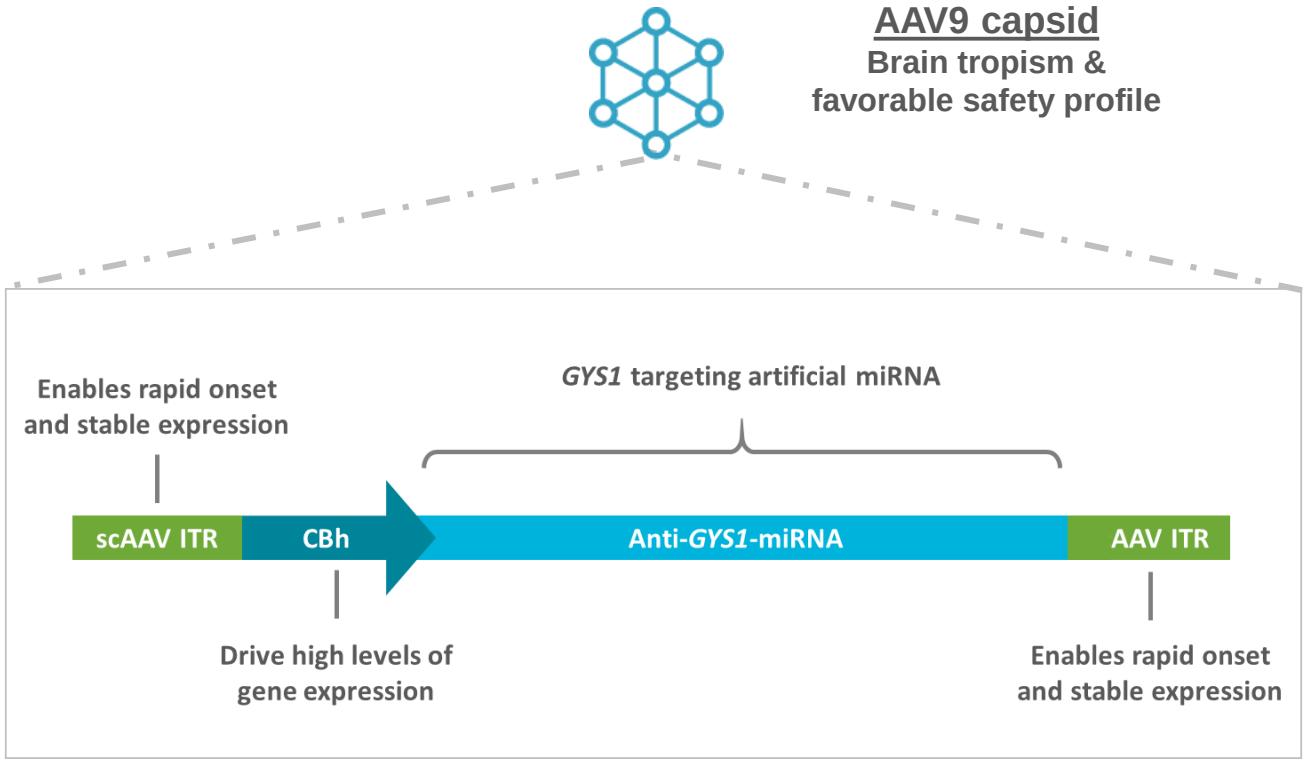
Chelsea, healthy at 14.

Chelsea after Lafora disease diagnosis

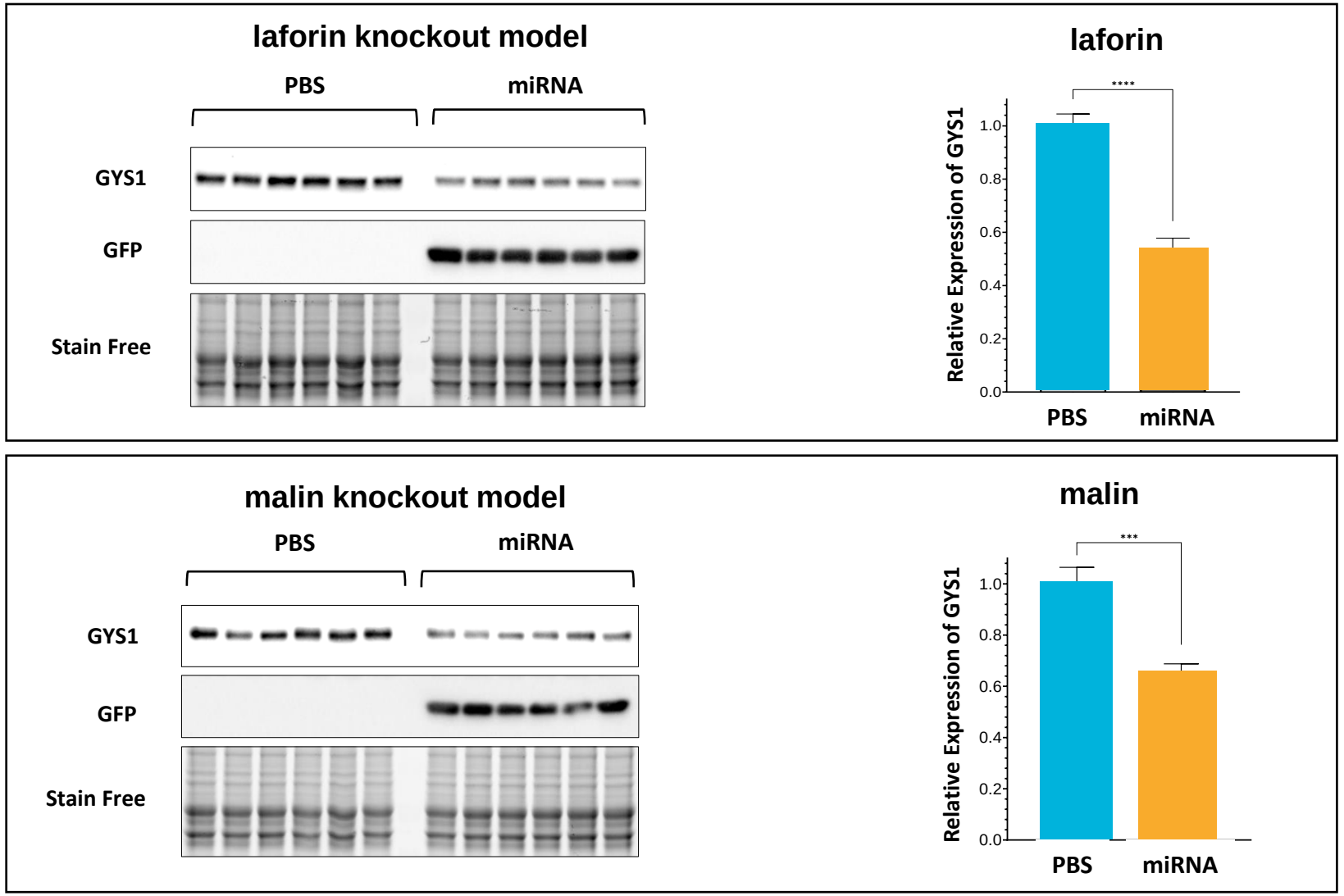
Lafora Patient Video

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

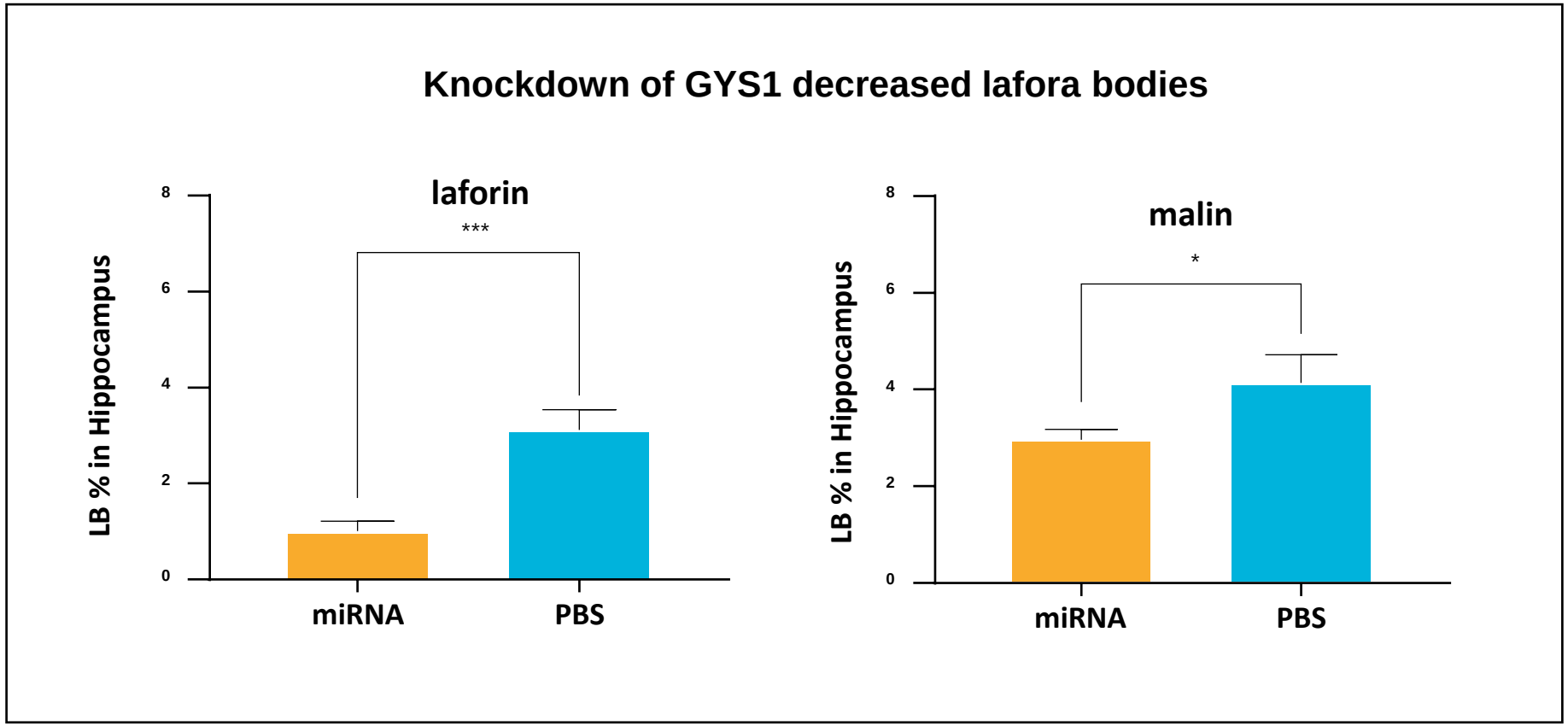
- Recombinant AAV9 viral vector designed for miRNA-mediated knockdown of the *GYS1* gene
- GYS1 knockdown designed to reduce Lafora bodies and improve clinical condition
- Self-complementary AAV capsid (scAAV) for rapid activation and stable expression
- CBh promoter drives high levels of expression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



Anticipated next steps for TSHA-111-LAFORIN and TSHA-111-MALIN

Animal proof-of-concept achieved in KO mouse model

Evaluate dose response and age response and finalize dose from pharmacology

Interventional trial protocol development underway

Q & A

TSHA-113 for Tauopathies

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

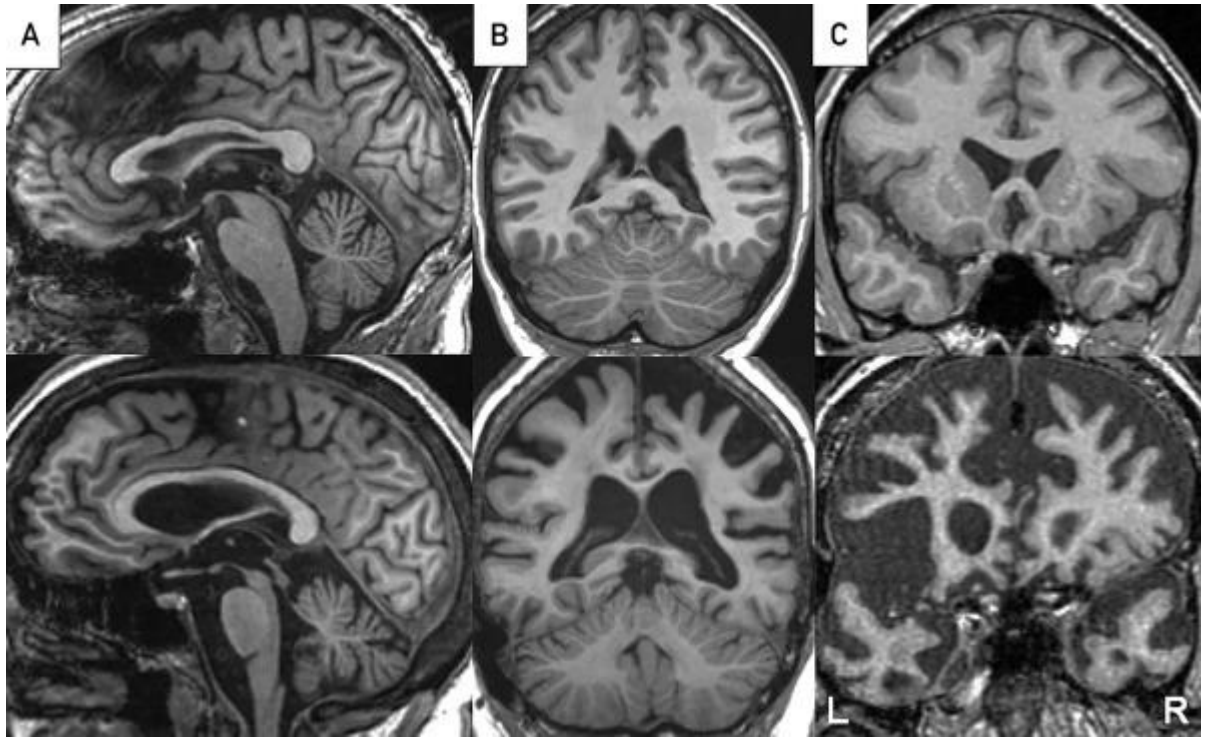
Chief Medical Officer and Head of R&D

Rachel Bailey, PhD

UTSW Gene Therapy Program

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
- 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

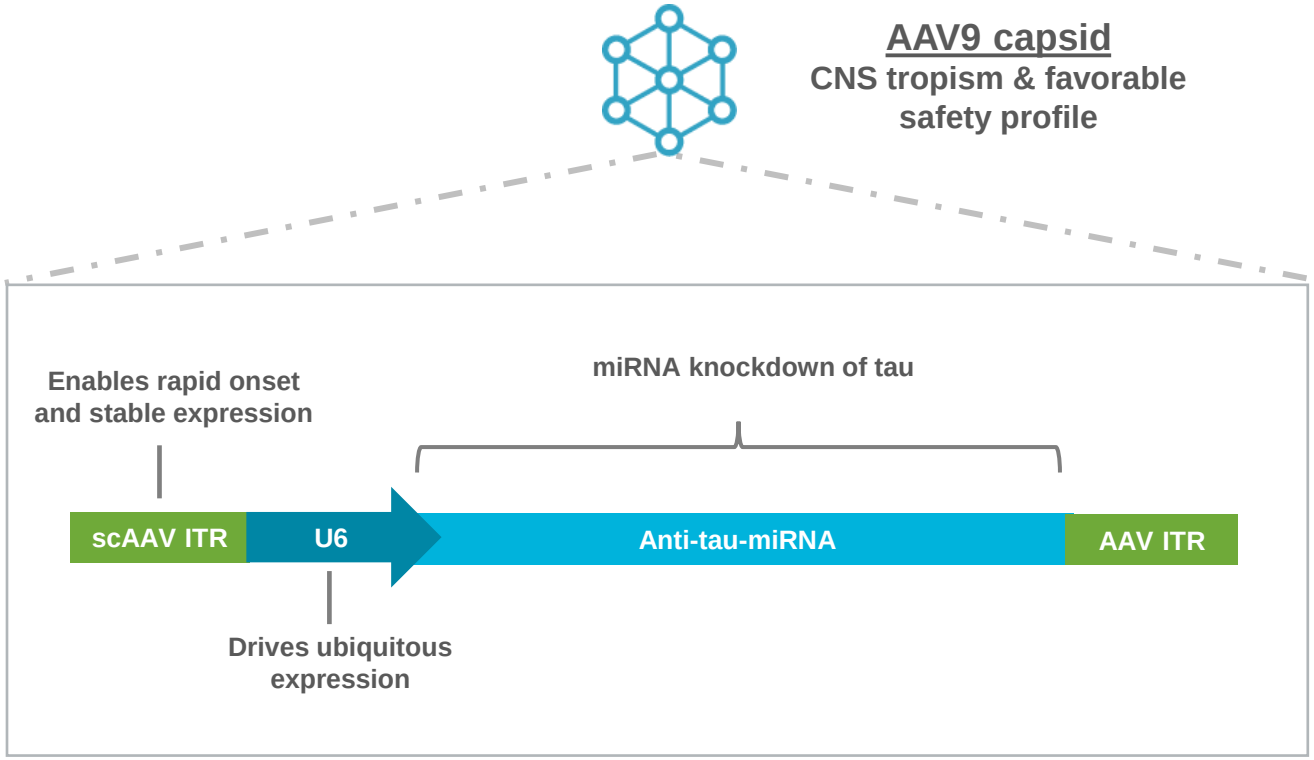


Mayo Clinic Proceedings 2017 921291-1303DOI: (10.1016/j.mayocp.2017.04.016)

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

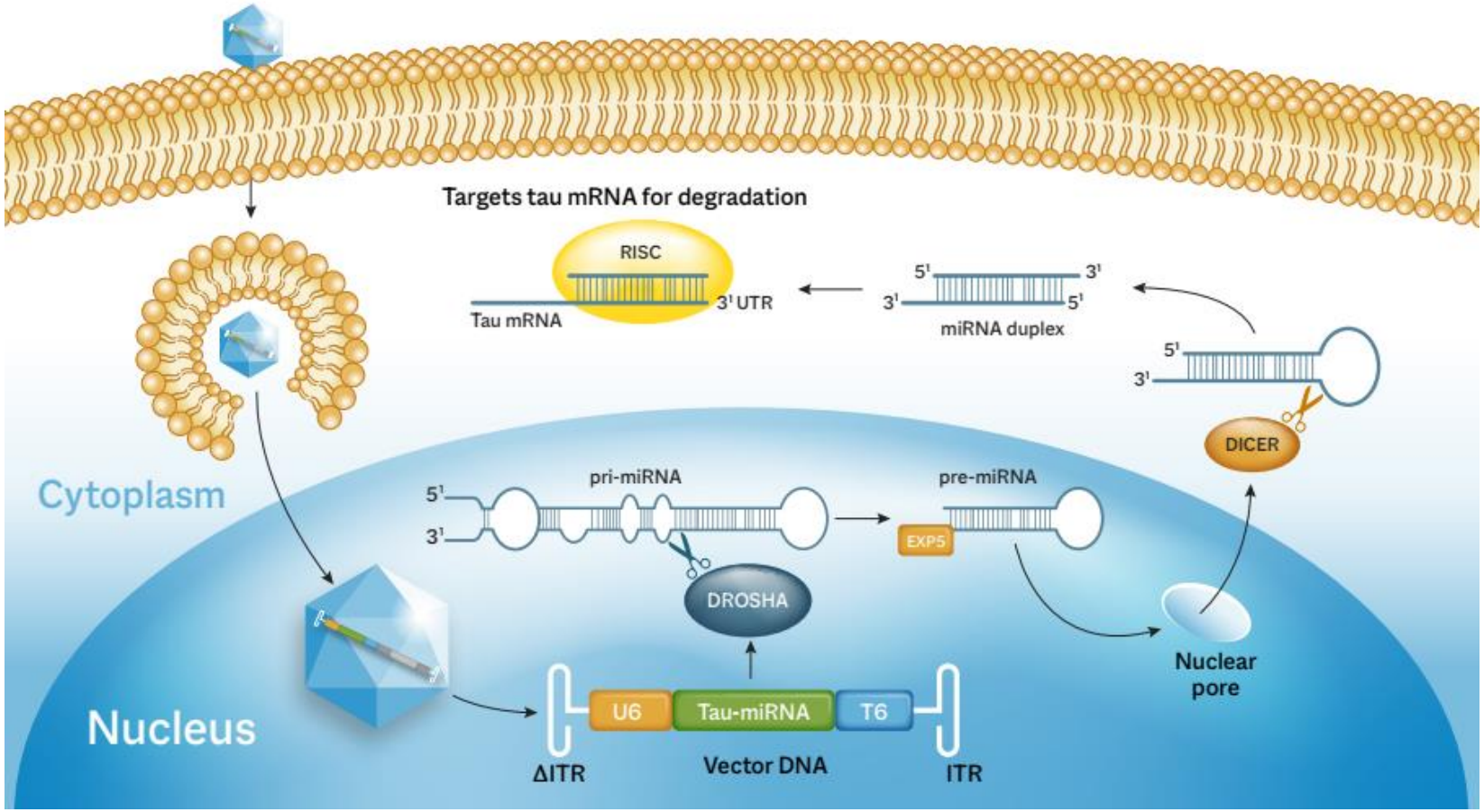
TSHA-113 in preclinical development

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

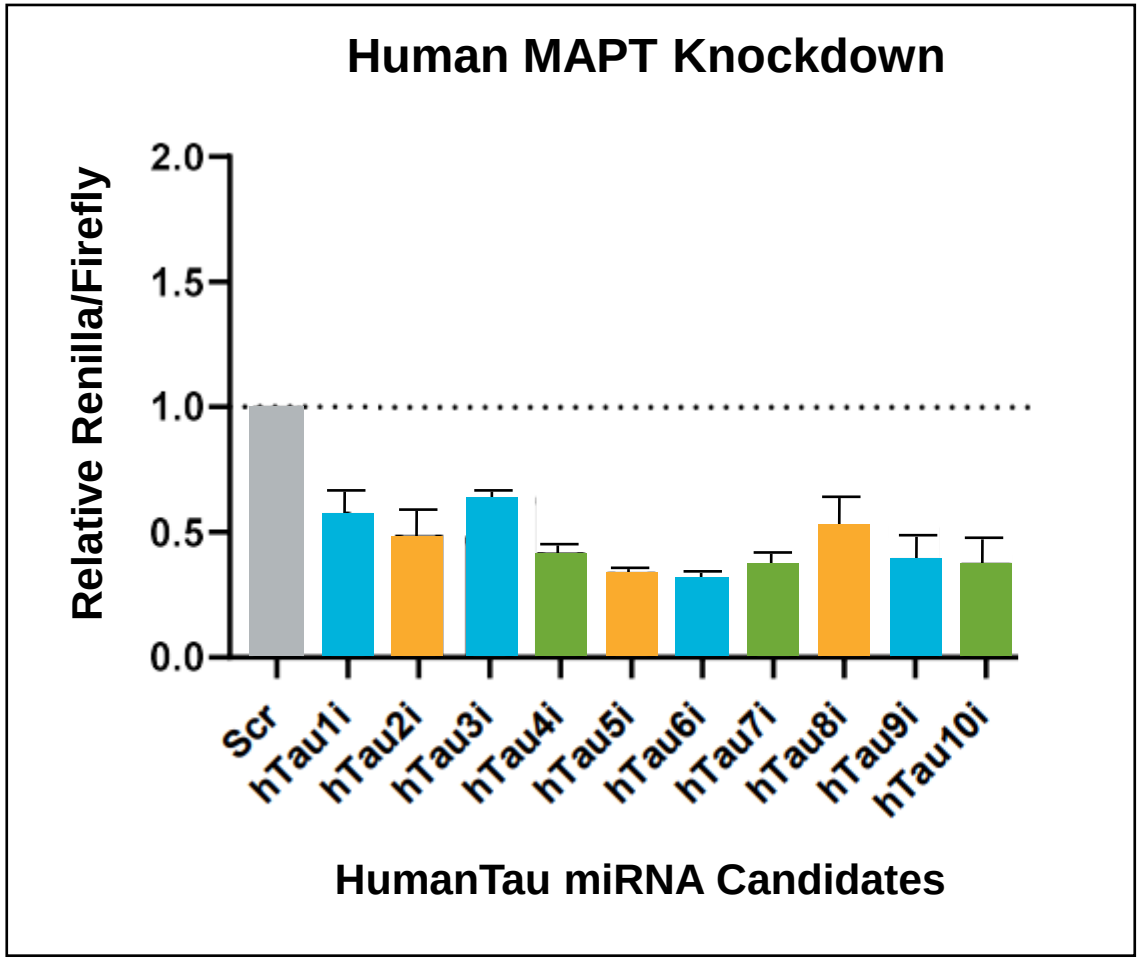


Our approach to treat MAPT

- 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



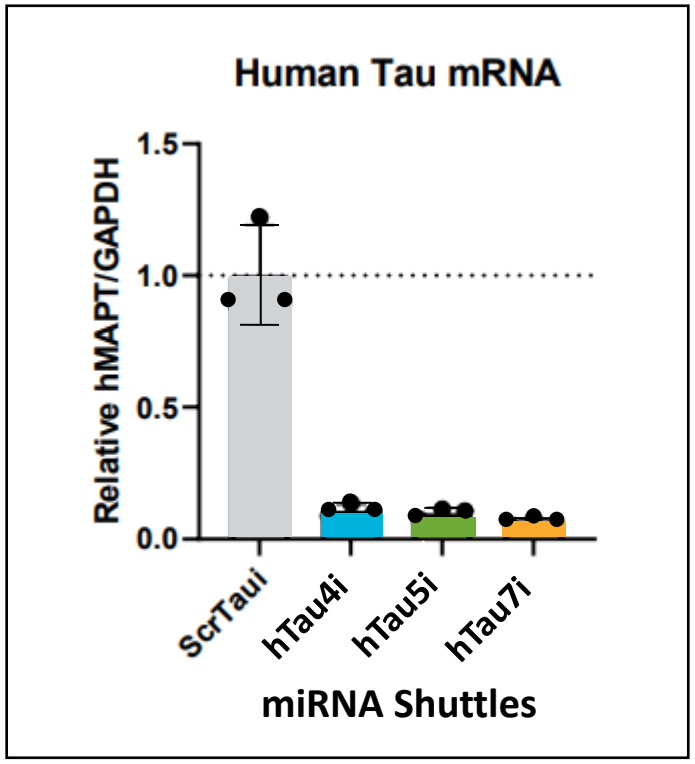
Primary screen of human tau miRNA candidates

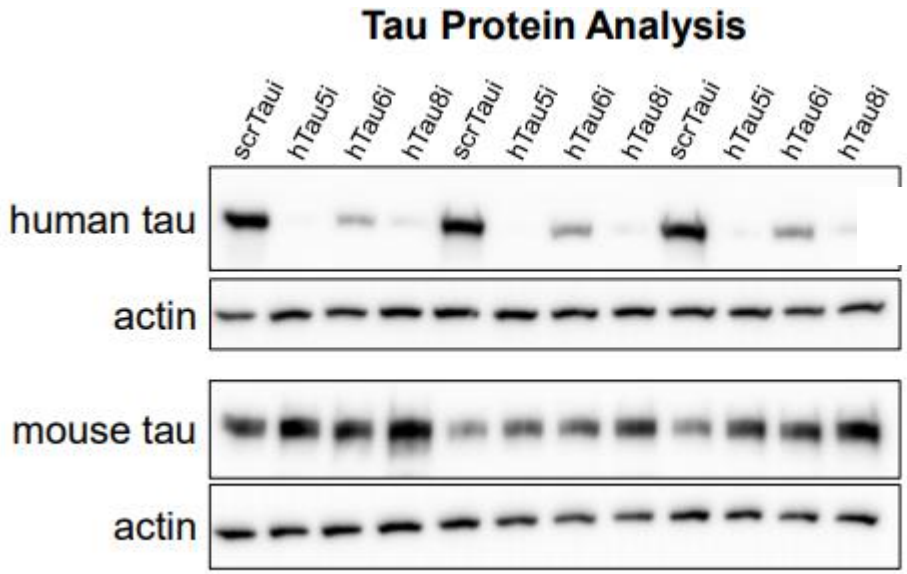


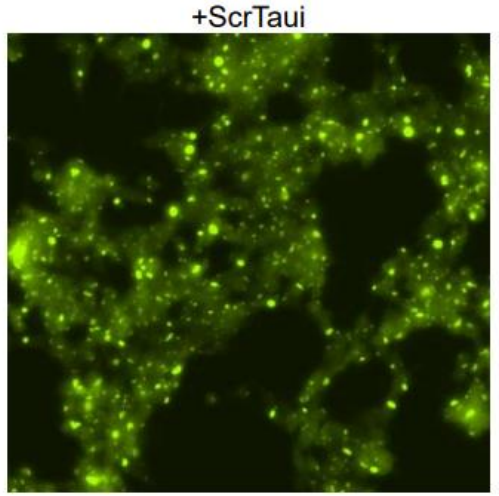
Secondary screening of top candidates:
hTau4i, hTau5i, and hTau7i

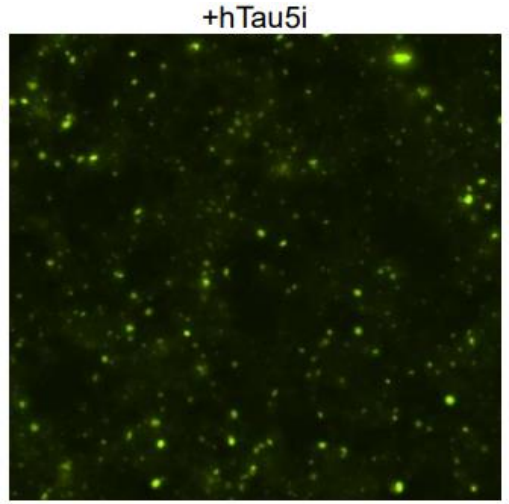
Scr = scrambled tau miRNA; hTau = human-specific tau miRNA

TSHA-113 reduced tau expression

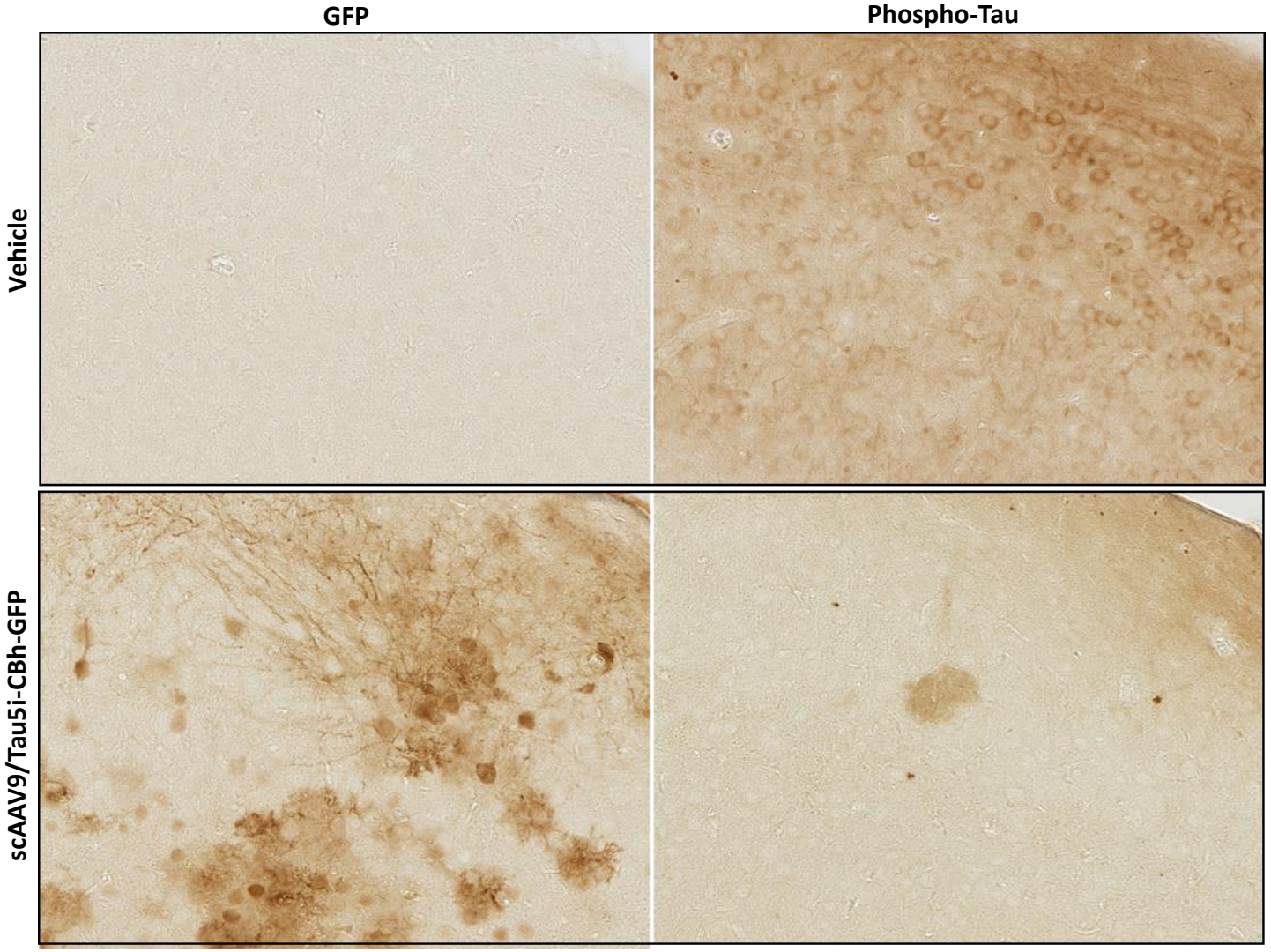


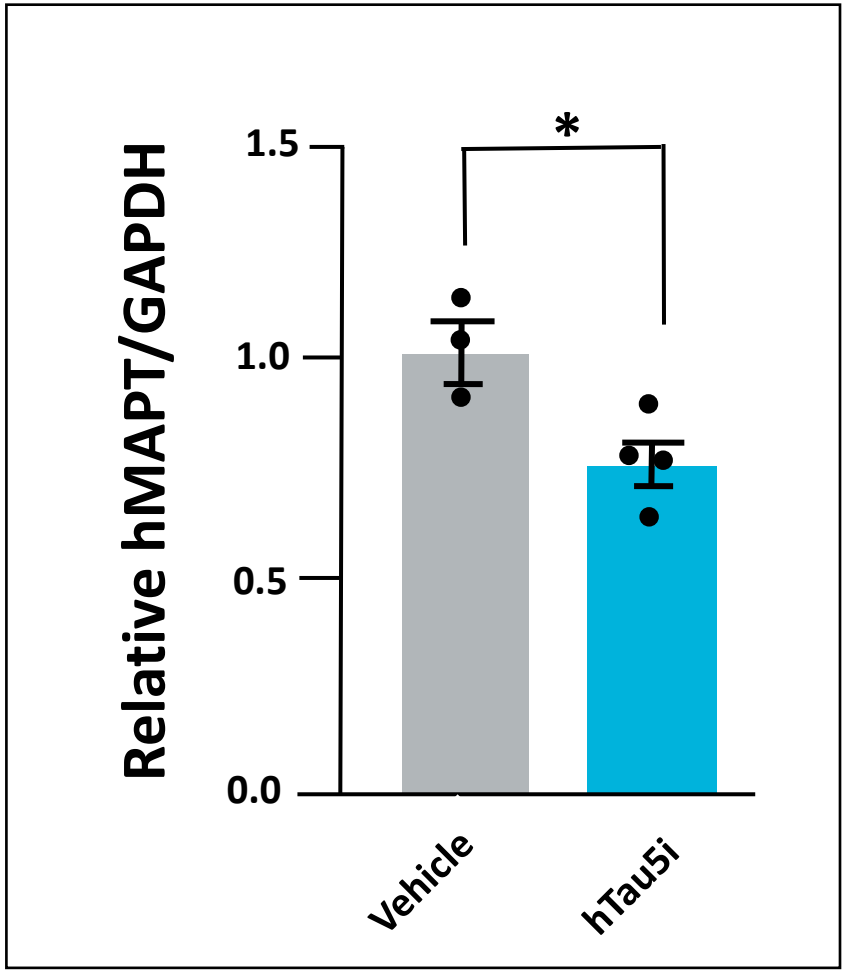






Tau mice dosed with TSHA-113 demonstrated function and GFP expression in neurons and glia





Anticipated next steps for TSHA-113

Animal proof-of-concept achieved in KO mouse model

Evaluate dose response and age response and finalize dose from pharmacology

Interventional trial protocol development underway

Q & A

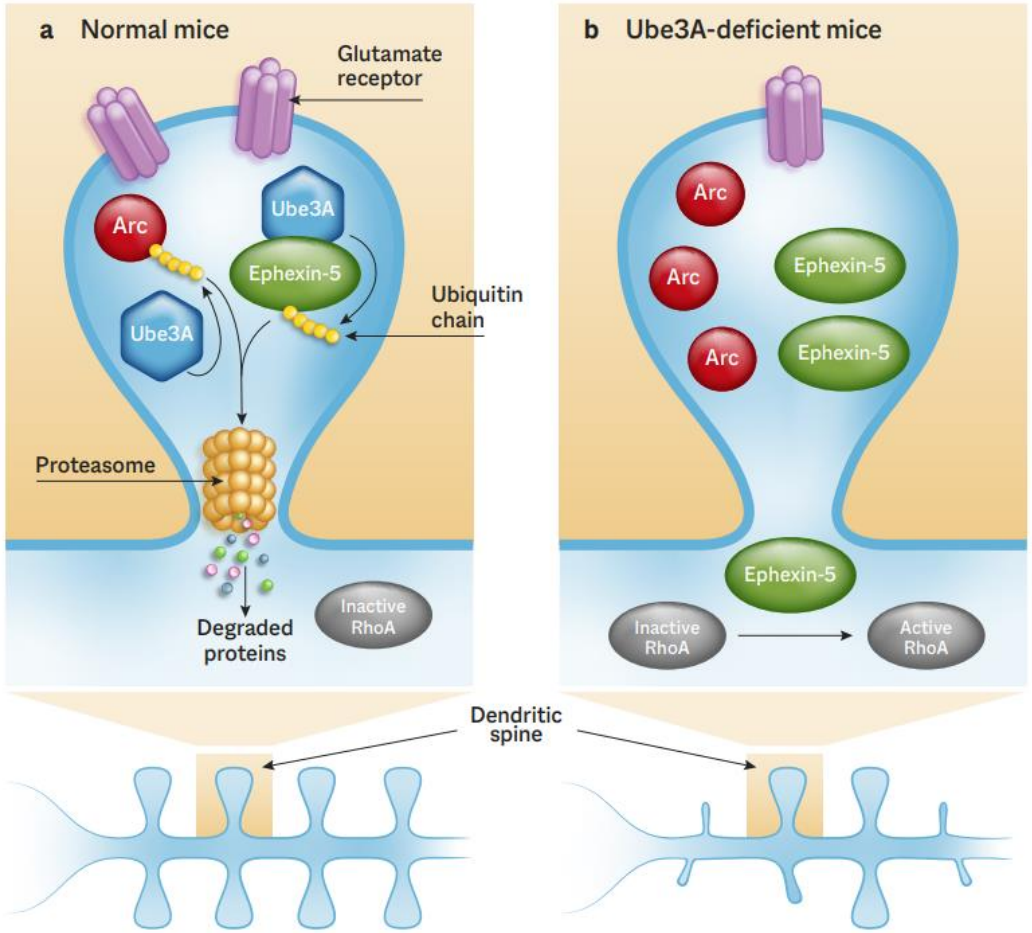
TSHA-106 for Angelman Syndrome

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

Chief Medical Officer and Head of R&D

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
- No signs of Angelman syndrome at birth. Disorder usually diagnosed at 6-12 mo
- Signs and symptoms include developmental delay, severe impairments in behavior, motor function, communication and sleep, as well as intellectual disability, debilitating seizures and ataxia
  - Frequent smiling and laughter (happy puppet syndrome)
  - Feeding issues, no speech or minimal speech
  - Abnormal sleep-cycles and diminished need for sleep
  - Seizures may begin at 2 to 3 years
- Normal lifespan but unable to live independently
- Estimated prevalence of Angelman syndrome is 55,000 patients (US+EU)



UPD – Uniparental disomy

Scheiffele, P. et al. *Nature* 2010

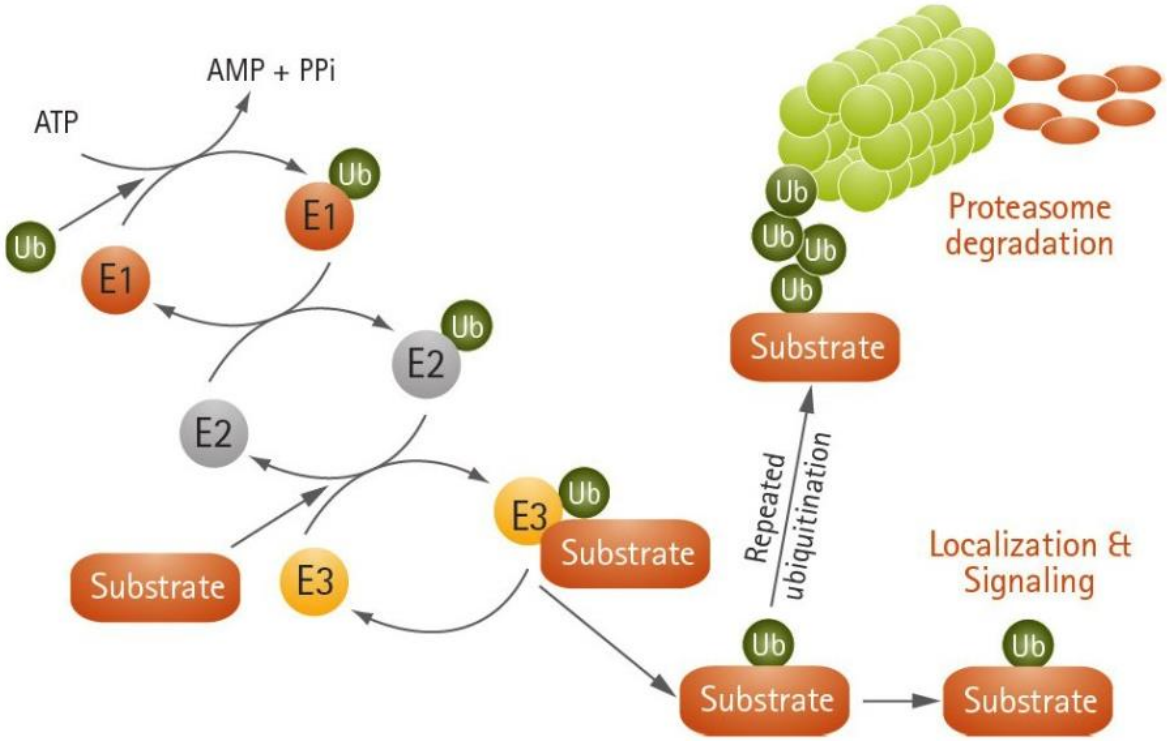
Current treatment for Angelman syndrome

There is no cure for Angelman syndrome.
Current treatment focuses on managing the medical and developmental issues.

- **Anti-seizure medication** to control seizures
- **Physical therapy** to assist with walking and movement problems
- **Communication therapy,** which may include sign language and picture communication
- **Behavior therapy** to help overcome hyperactivity and a short attention span and to aid in development

Molecular pathology of Angelman syndrome

- UBE3A, an E3 ligase in the ubiquitin-proteasomal system, plays important roles in brain development and normal function
- UBE3A conjugates polyubiquitin chains to specific lysine residues in its substrates, regulating the expression and function of these proteins
- Deletion or loss-of-function mutations of the maternally inherited allele of UBE3A result in Angelman syndrome while maternal duplication or triplication of the chromosome 15q11–13 region is associated with autism spectrum disorder
- Impairments in ubiquitin-mediated protein degradation can lead to deficits in neuronal development and the maintenance of synaptic connections



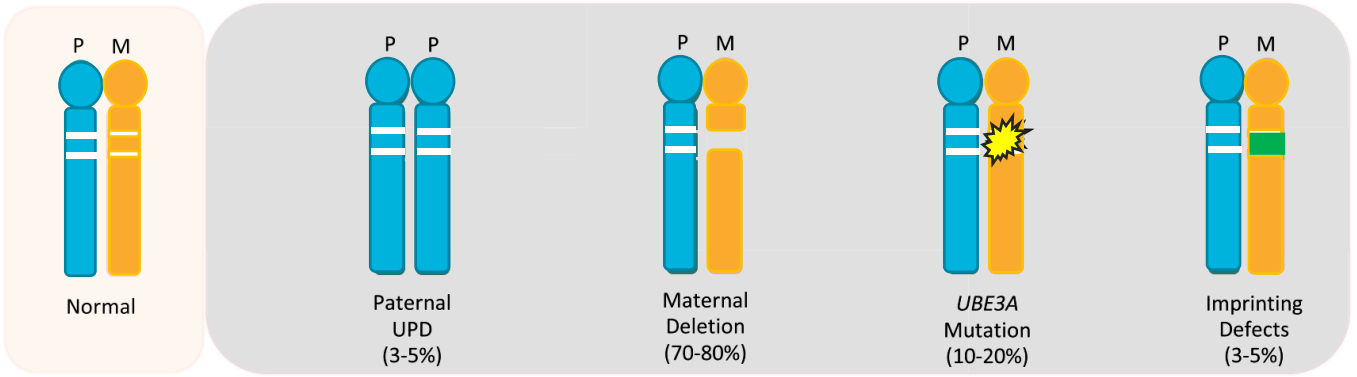
The ubiquitination process

Role of UBE3A in brain development

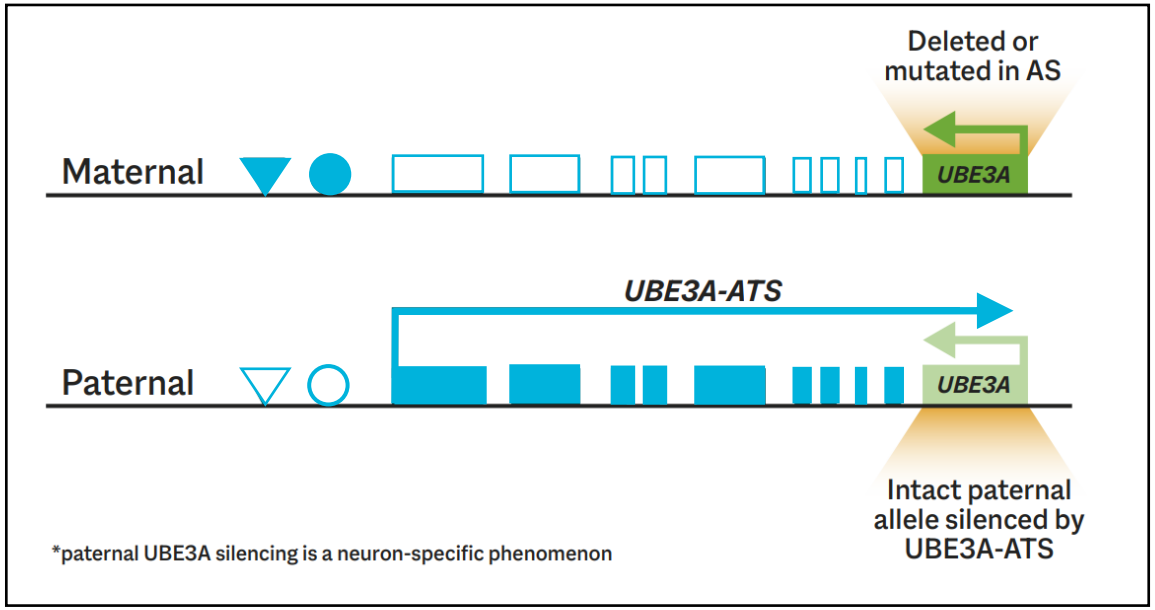
Function of UBE3A	Target of UBE3A	Function of Target	(Expected) Phenotypes
Coactivator of the estrogen receptor (ER)	Cyp26b1 ↓	Cytochrome P450 26B1	Involved in learning and memory process
Ubiquitin-protein ligase	Arc ↑	Activity-regulatory cytoskeleton-associated protein	Synaptic plasticity ↓
	p18 ↑	Regulator of mTOR	Synaptic plasticity↓, impaired actin filament remodeling, disrupted PSD95-TrkB signaling in Hipp. Neuron
	Synaptic SK2 ↑	Synaptic small-conductance potassium channel 2	Impaired LTP, neuroplasticity and learning performance
	Alpha-synuclein ↑	A main component of the inclusions	Synaptic plasticity ↓
	PTPA ↑	Activator of protein phosphatase 2A (pp2A)	Defects in dendritic spine maturation, reduction in excitatory synaptic transmission and motor impairment
	Ephexin ↑	A RhoA guanine nucleotide exchange factor, brake on excitatory synapse formation	UBE3A-dependent hippocampal dysfunction
	p27 ↑	Cyclin-dependent kinase (CDK) inhibitor	Cell cycle alteration / could decrease neuronal cell proliferation and inappropriate cell death during development in AS brain
	p53 ↑	Tumor suppressor	-
Dendritic spine malformation and mitochondrial dysfunction	-	Probably related to mTOR pathway	Abnormal dendritic spine dynamics; small CAI hippocampal neurons, dense mitochondria with altered cristae, impaired mitochondrial oxidative phosphorylation (OXPHOS) complex Ill activity, and reduced synaptic vesicle density, increased mitochondrial superoxide levels, affecting hippocampal LTP and contextual fear memory, excessive free radical production

Two novel approaches to treat Angelman syndrome

- Targeting entire Angelman syndrome population using two approaches
  - Knockdown of UBE3A-ATS to unsilence paternal allele
  - Gene replacement strategy on *UBE3A* to mimic maternal UBE3Q allele expression
- Currently developing both approaches



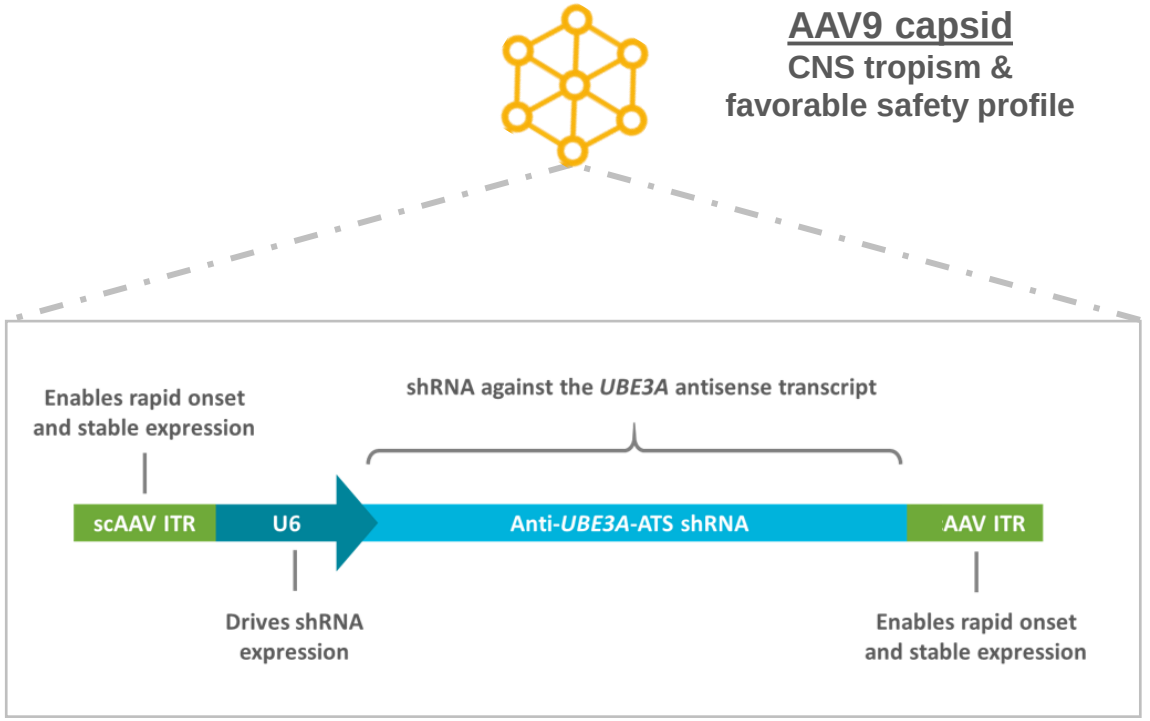
In neurons, the **maternally inherited UBE3A allele is the only active allele**, since the **paternally inherited UBE3A allele is silenced through cell type–specific imprinting**



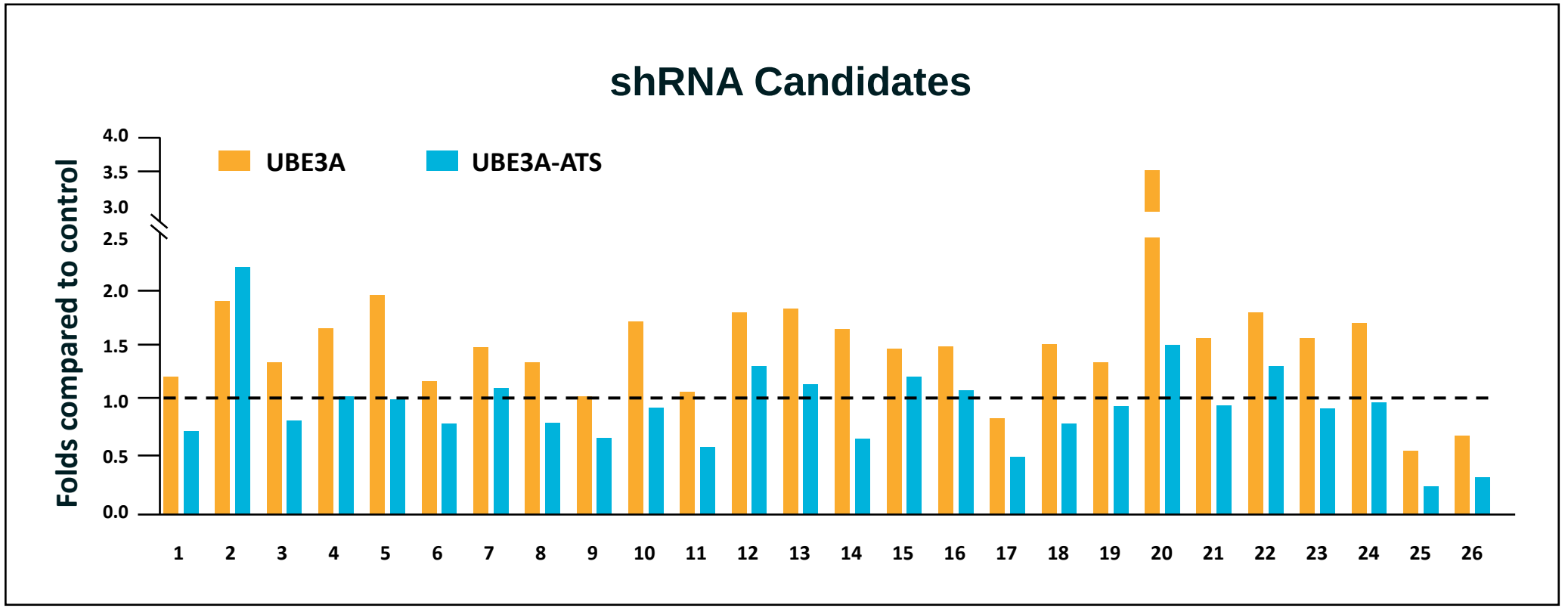
UPD – Uniparental disomy

Knockdown of UBE3A-ATS established, placing TSHA-106 in a competitive position to advance rapidly

- AAV9 viral vector designed for shRNA-mediated knockdown of UBE3A-ATS, the antisense transcript governing the expression of UBE3A through the paternal allele
- First-in-human study in Angelman syndrome demonstrated that knockdown of UBE3A-ATS to unsilence the paternal allele led to meaningful clinical improvement
  - Five patients treated with an antisense oligonucleotide (ASO) therapy had significant improvement in the Clinical Global Impression (CGI) scale of change in Angelman syndrome after 128 days of treatment
  - CGI-I-AS measures several domains of function, including global, fine motor, gross motor, communication, behavior, and sleep
  - Treatment with the ASO was generally well tolerated but led to SAEs, including transient lower extremity weakness in all 5 patients treated
- Gene therapy to unsilence the paternal allele offers a unique profile of advantages
  - One-time dosing
  - Widespread transduction through the CNS using an AAV9 vector
  - Established safety as seen with other intrathecal clinical trials



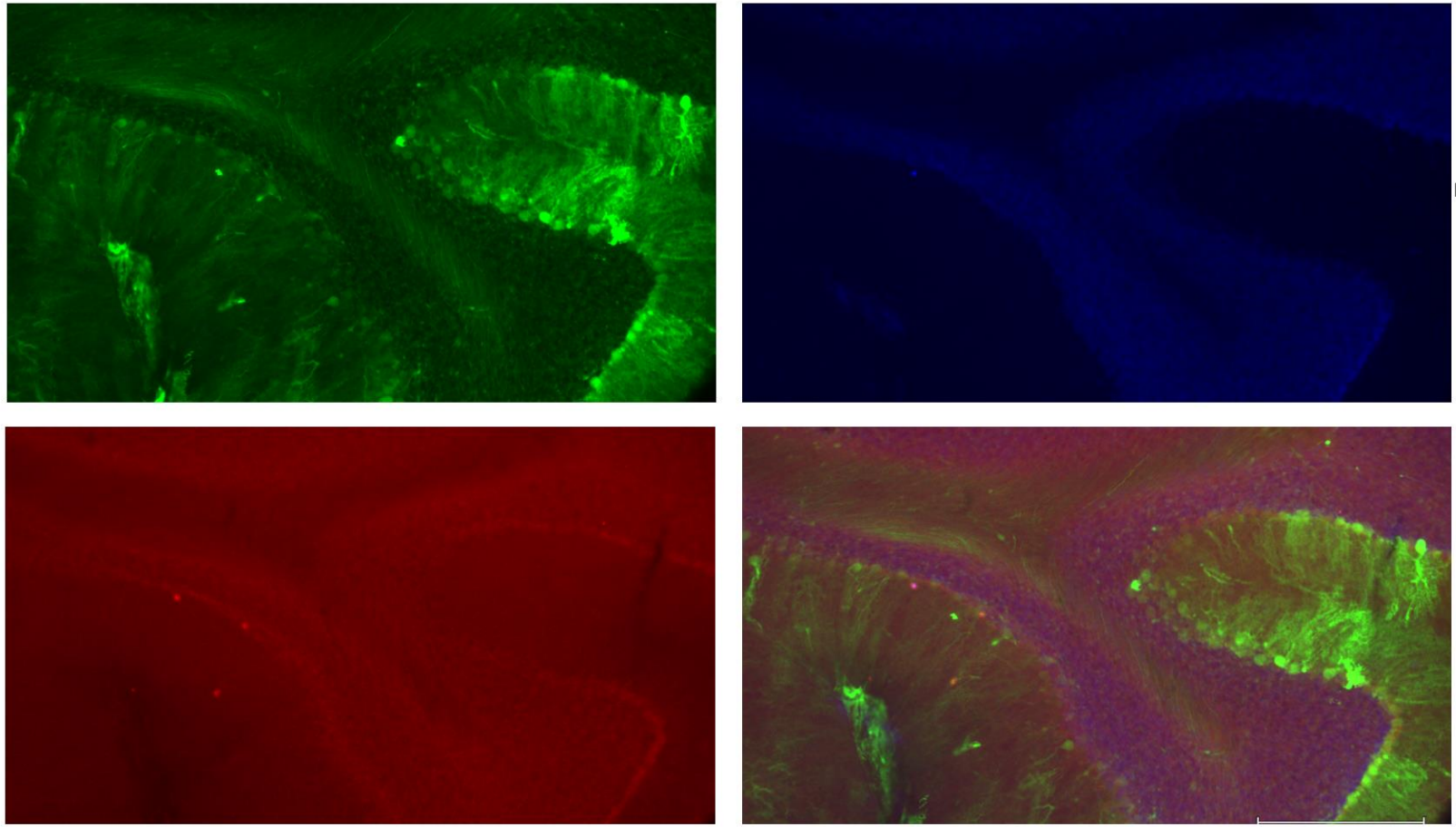
TSHA-106 targets UBE3A-ATS transcript through shRNA knockdown



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

UBE3A expression following administration of shRNA candidate

Cerebellum



Anticipated next steps for TSHA-106

Interim expression and safety data from confirmatory NHP studies

Evaluate dose response and age response and finalize dose from pharmacology

Interventional trial protocol development underway

Q & A

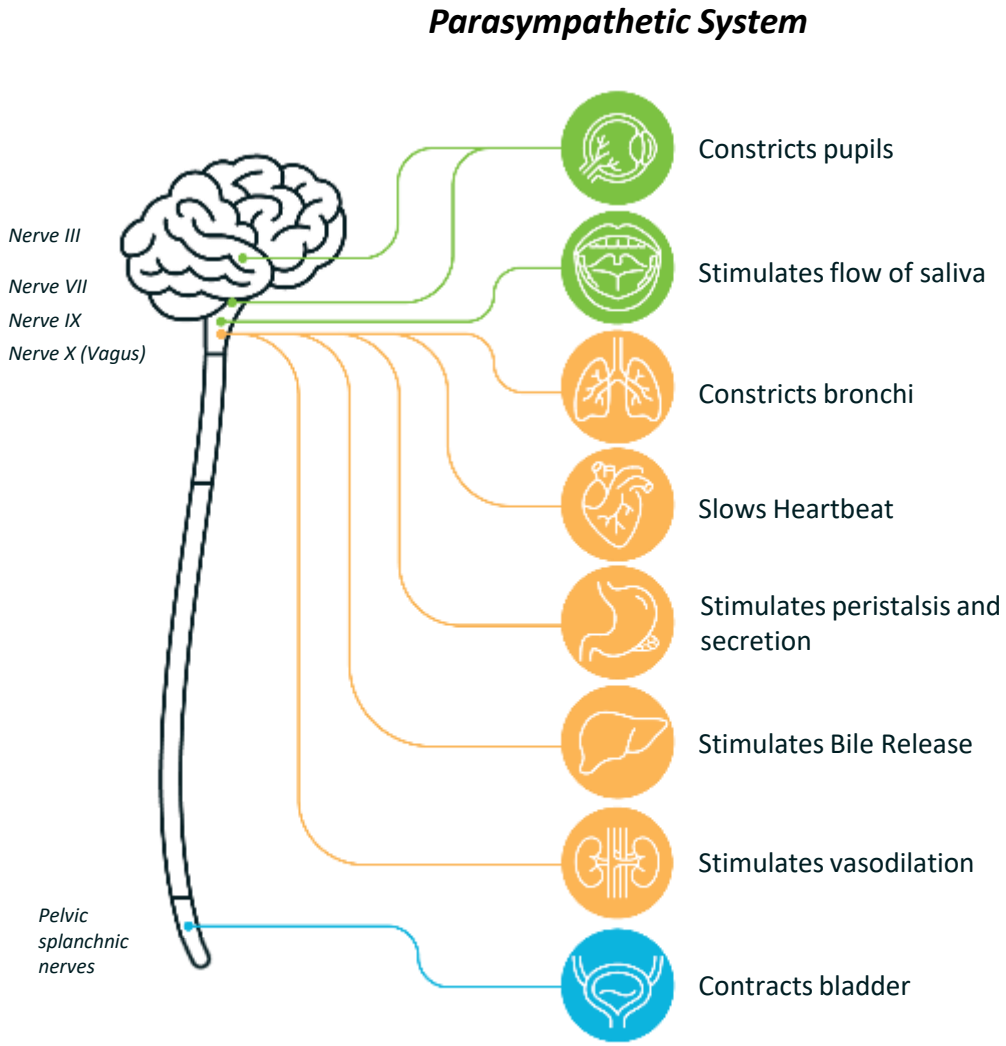
Redosing Platform

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

Chief Medical Officer and Head of R&D

Opportunity to achieve human POC for vagus nerve redosing

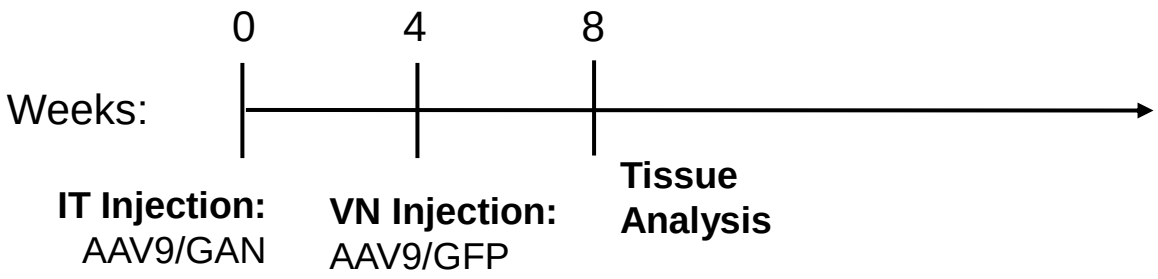
- The vagus nerve represents the main component of the autonomic nervous system
- Direct delivery to the vagus nerve may provide broad coverage of the autonomic nervous system and enable redosing by subverting the humoral immune response
- Proof-of-concept established in rodent and canine models; oral 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



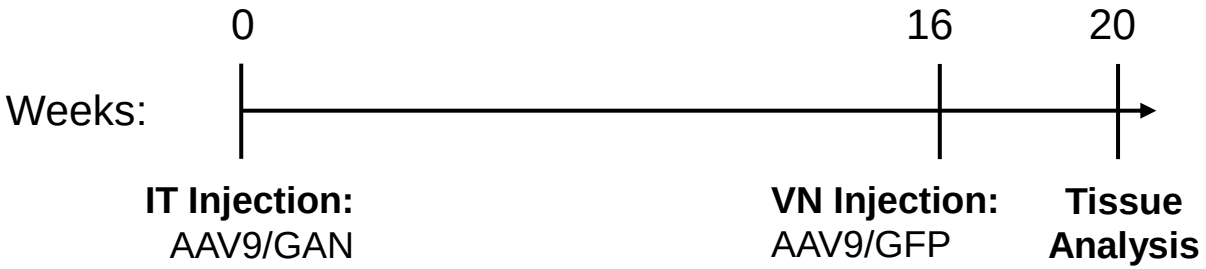
Robust expression of GFP in the vagus nerve and associated nodose ganglia in rats support redosing via vagus nerve injection

TSHA-120
GAN

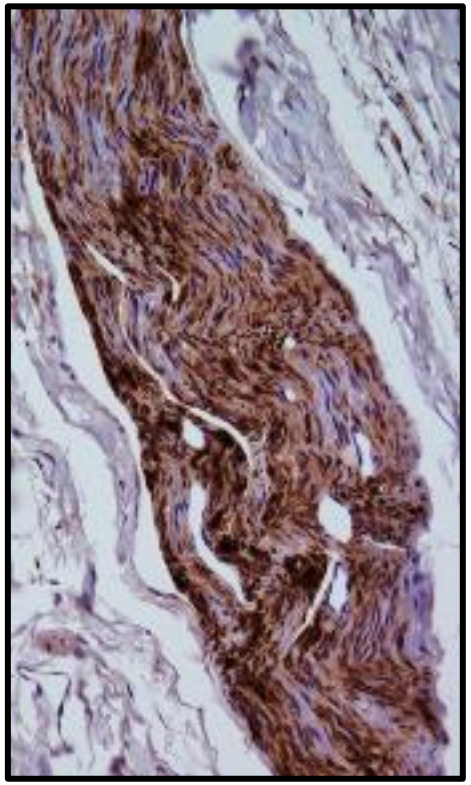
Study 1



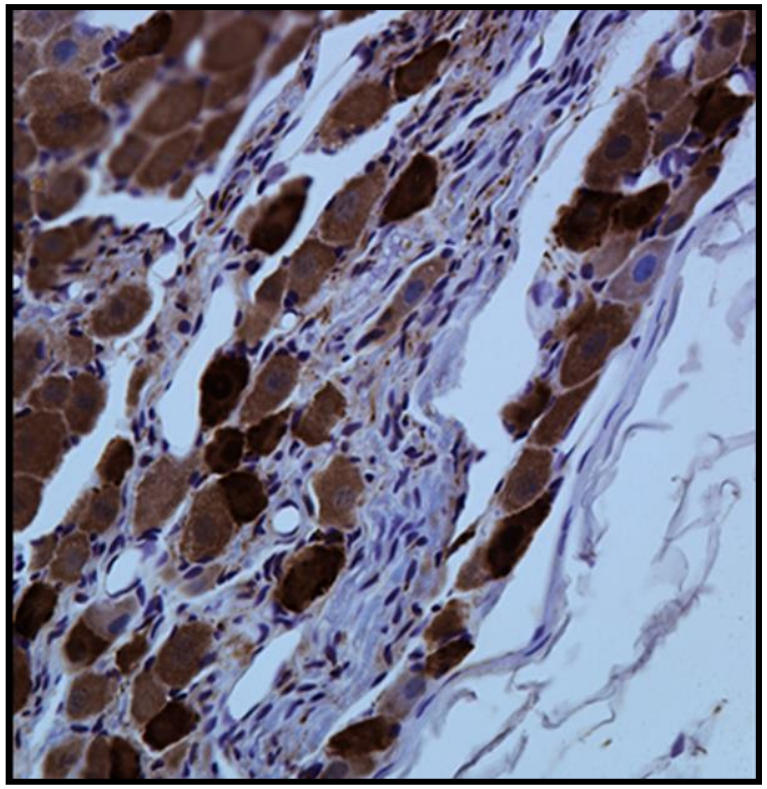
Study 2



Vagus Nerve



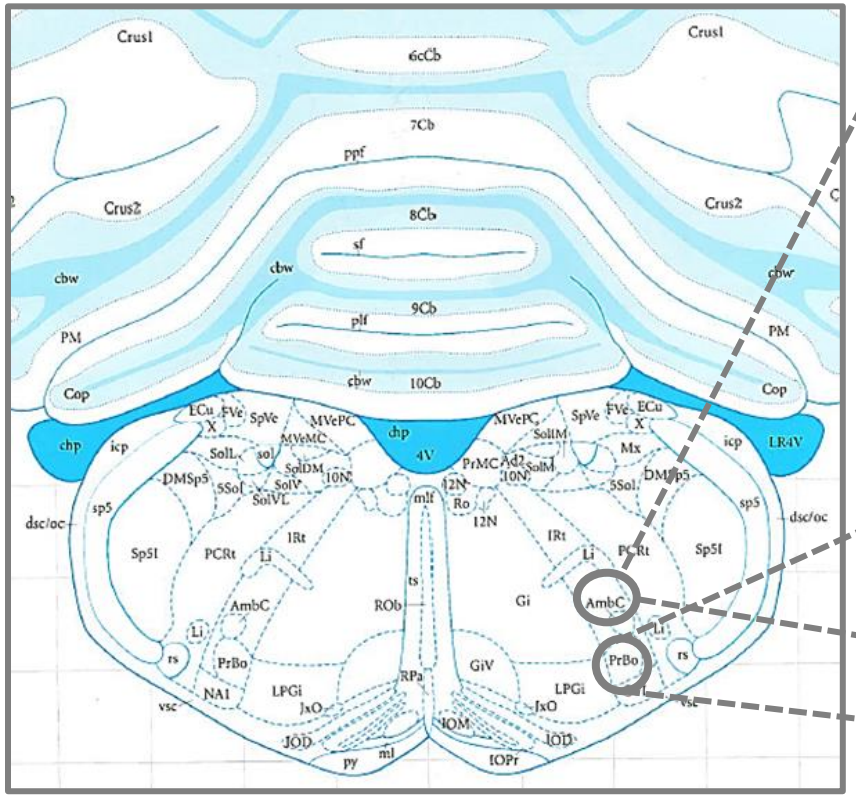
Nodose Ganglia



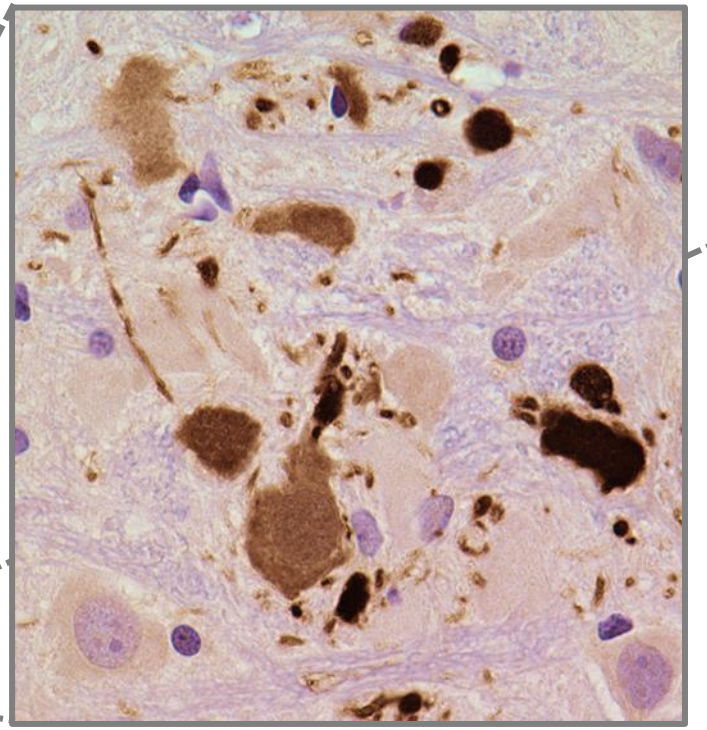
GFP – green fluorescent protein
Courtesy of Dr. Diane Armao

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

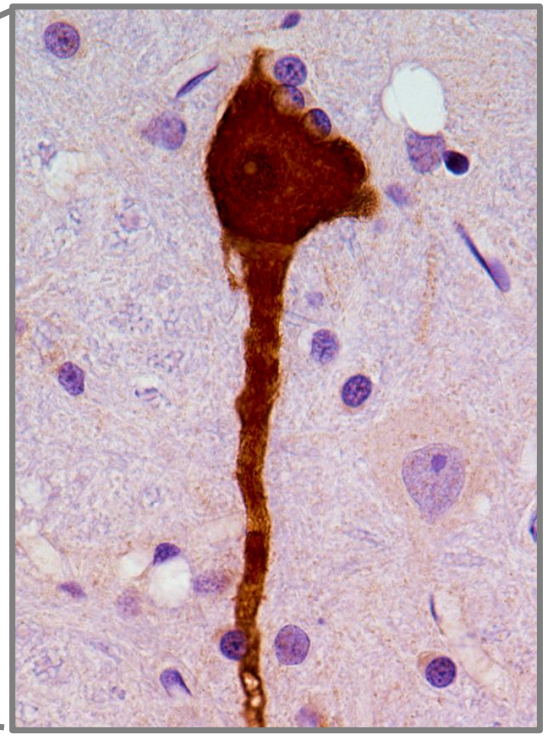
TSHA-120
GAN



Medulla



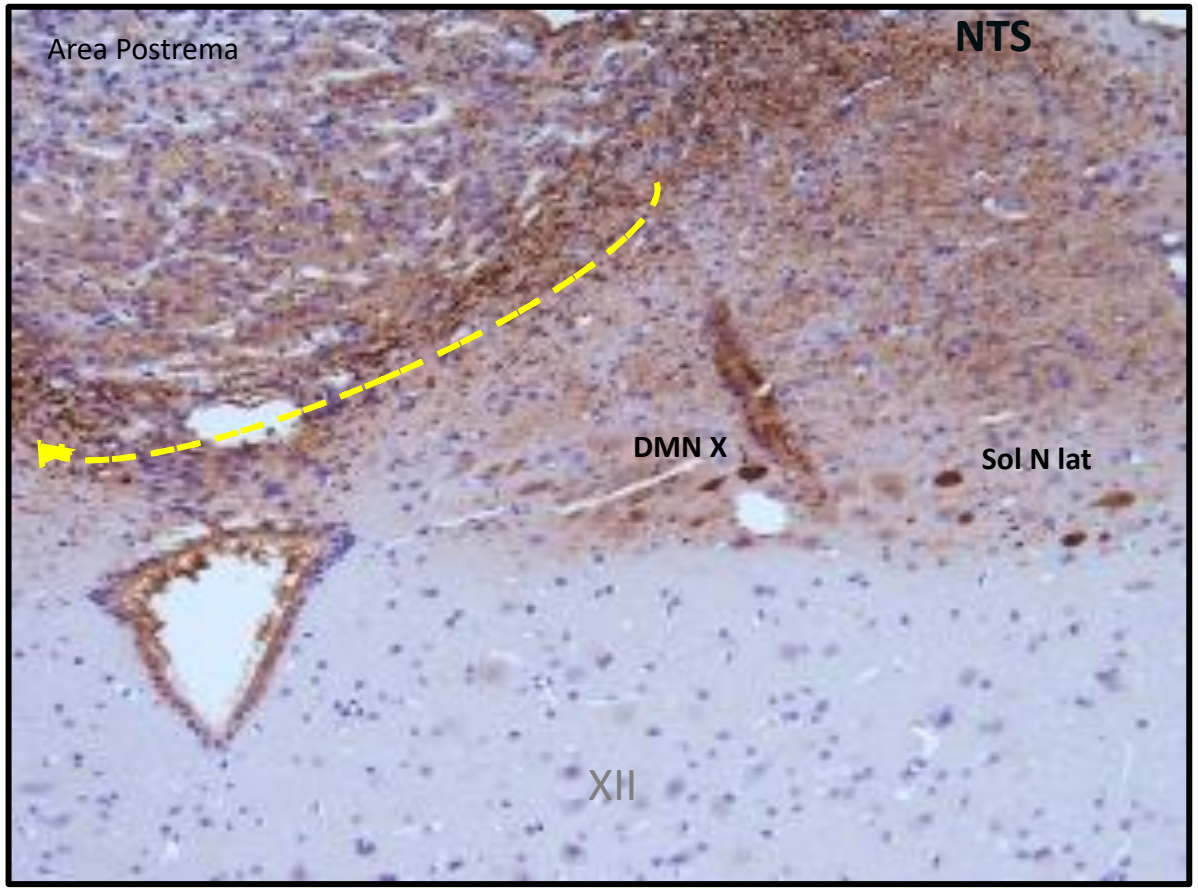
Nucleus Ambiguous



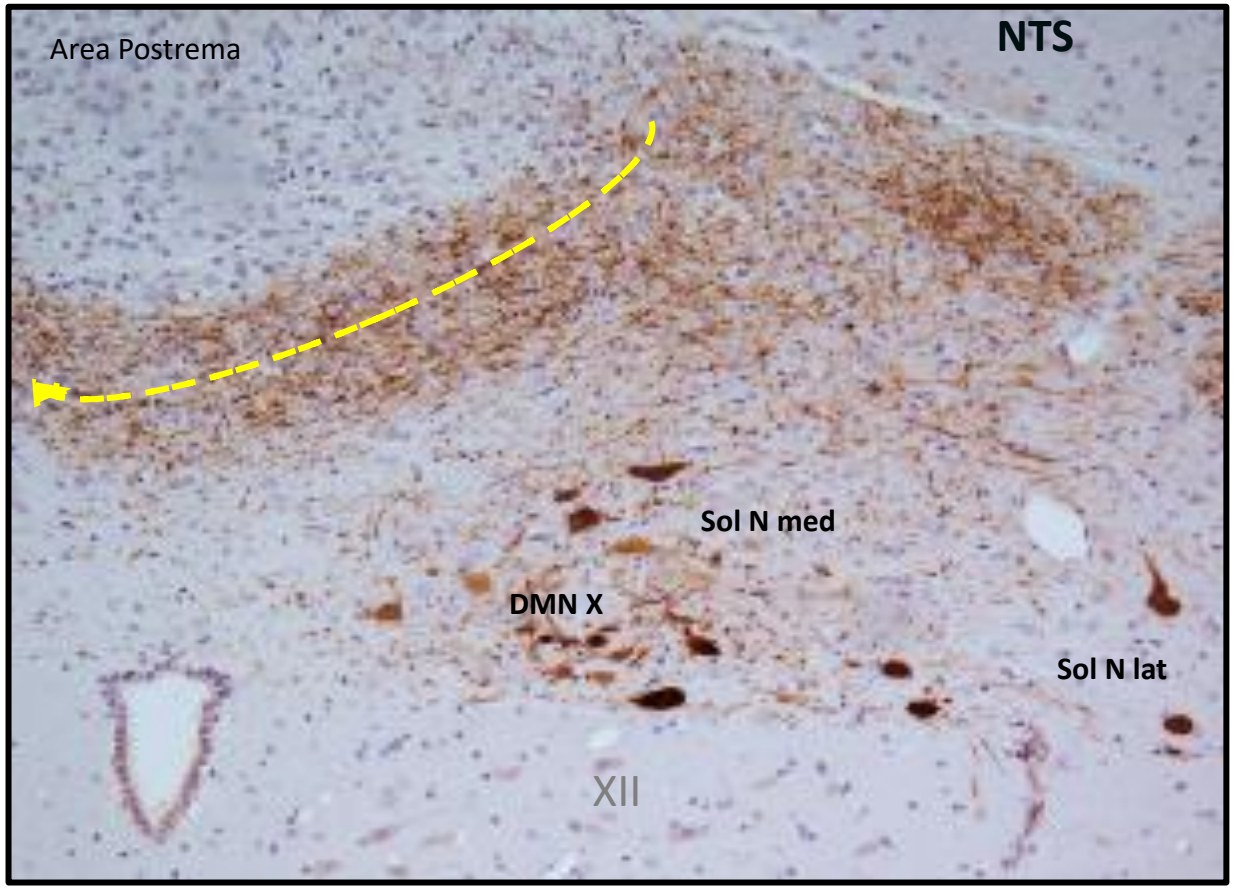
Pre-Botzinger Complex

Courtesy of Dr. Diane Armao

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



Naive



AAV9 Pre-immunized

Courtesy of Dr. Diane Armao

Q & A

Closing Remarks

RA Session II

President, Founder & CEO

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

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

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

Initiated construction of internal cGMP facility in 1H 2021

5 additional programs currently in IND-enabling studies
Manufacturing Investor Day July 27, 2021
TSHA-118 CLN1 Investor Day August 2021
TSHA-102 Rett syndrome Investor Day September 2021
Numerous value generating catalysts over the next 18 months

Upcoming Investor Mini-Series

Manufacturing Investor Day	**July 27, 2021**
TSHA-118 CLN1 Investor Day	**August 2021**
TSHA-102 Rett syndrome Investor Day	**September 2021**

TAYSHA GENE THERAPIES

Thank you