TAYSHA GENE THERAPIES

Bringing New Cures to Life

Angelman Syndrome Investor Day

October 26, 2021 | 9:00 – 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, and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2021. 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.

Introduction

RA Session II

President, Founder & CEO

Agenda

Topic	Presenter
Introduction	RA Session II
Disease Overview	Kimberly Goodspeed, MD
Disease Burden **Patient and Family Perspective**	Allyson Berent, DVM, DACVIM
Novel Gene Replacement for Angelman Syndrome	Ben Philpot, PhD
RNAi Gene Therapy for Angelman Syndrome	Ryan Butler, PhD
Clinical Development Strategy	Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM
Closing Remarks	RA Session II

Speaker biographies

Kimberly Goodspeed, MD
Assistant Professor, Department of Pediatrics and Neurology at UTSW
- Child neurologist and neurodevelopmental specialist focused on autism spectrum disorder and intellectual disability
- Research focused on natural history and biomarker development in rare genetic variants of neurological disorders

Allyson Berent, DVM, DACVIM
Chief Science Officer, the Foundation for Angelman Therapeutics (FAST)
Director, Angelman Syndrome Biomarker and Outcome Measure Consortium (ABOM)
Co-Director, International Angelman Syndrome Research Council (INSYNC-AS)
- Allyson's daughter was diagnosed with Angelman syndrome at 5.5 months old
- Cofounder and chief operating officer of a biotech company focused on Angelman syndrome

Ben Philpot, PhD
Associate Director of the UNC Neuroscience Center
- A Kenan Distinguished Professor in the Neuroscience Center and Department of Cell Biology & Physiology at the University of North Carolina (UNC) at Chapel Hill; and member of the Carolina Institute for Developmental Disabilities for which he helps direct a cross-disciplinary postdoctoral training grant for neurodevelopmental disorders
- Research focuses on early-stage development of treatments for Pitt-Hopkins, Dup15q and Angelman syndromes

Ryan Butler, PhD
Assistant Professor, Department of Psychiatry and Pediatrics at UTSW
- Research focuses of his lab is gene therapy for genetic disorders, including Angelman syndrome; and determining the neural processes involved in adaptive pain, pain suppression, and the responses to pain threats to measure the neurobehavioral and molecular changes that occur with the reversal of these maladaptations

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM
Chief Medical Officer and Head of Research and Development at Taysha
- Expertise in international drug development, including preclinical, Phase I-IV trials, regulatory filings, commercial application
- Former CMO of Audentes Therapeutics; led XLMTM AAV8 program from preclinical to initial positive clinical data
- Prior roles include Medical Affairs and Clinical Development at BioMarin, Genzyme Therapeutics, and Eli Lilly and Company
- UK board certified with postgraduate qualifications in Pediatrics, Internal Medicine, Pharmaceutical Development, and Translational Science

Disease Overview

Kimberly Goodspeed, MD

Assistant Professor, Departments of Pediatrics and Neurology at UTSW

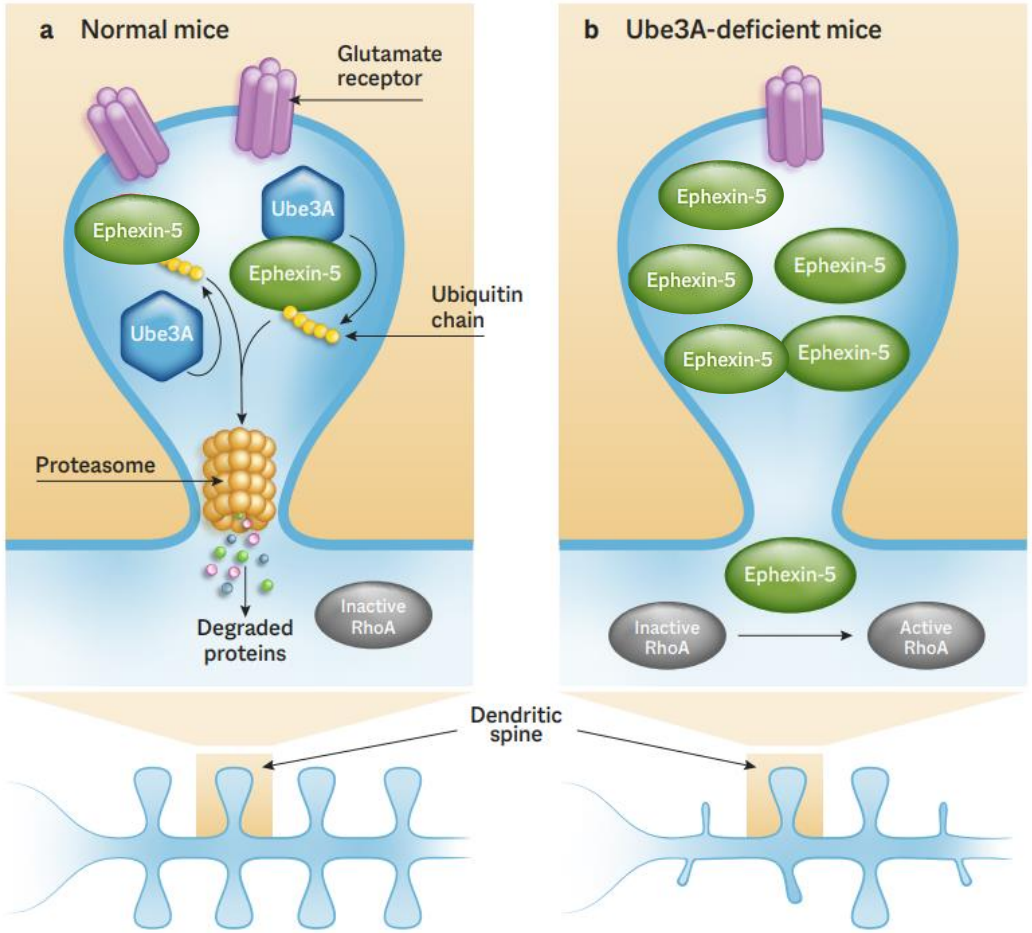
Angelman syndrome – Disclosures

- Kim Goodspeed, MD
  - Assistant Professor, Pediatrics | Neurology
  - Neurodevelopmental Disabilities
  - University of Texas Southwestern

- Disclosures
  - UTSW maintains a financial interest in Taysha due to Taysha's exclusive licensure of technology developed at UTSW
  - Taysha sponsors several research protects that I lead

Angelman syndrome – Genomic imprinting disorder

- Caused by a deletion or loss of function of the maternally inherited allele of the *UBE3A* gene
  - Maternal-specific inheritance pattern due to genomic imprinting of UBE3A in neurons
  - Maternal allele is expressed; paternal allele is silenced
- Absence of UBE3A leads to abnormal neuronal connectivity in the developing brain
  - UBE3A tags proteins for degradation
  - In the absence of UBE3A, the control of cell-signaling proteins responsible for synaptic formation and plasticity, including Ephexin-5, are unregulated and lead to a diminished number of synaptic connections

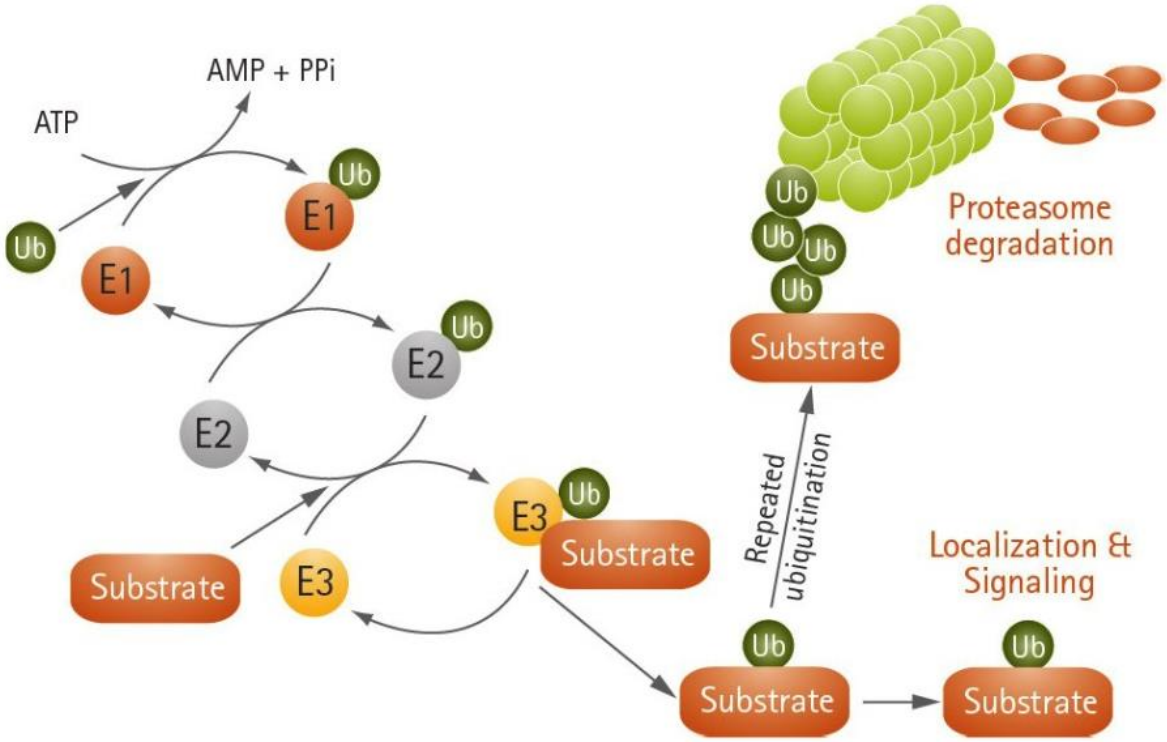


UPD – Uniparental disomy

Scheiffele, P. et al. *Nature* 2010

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

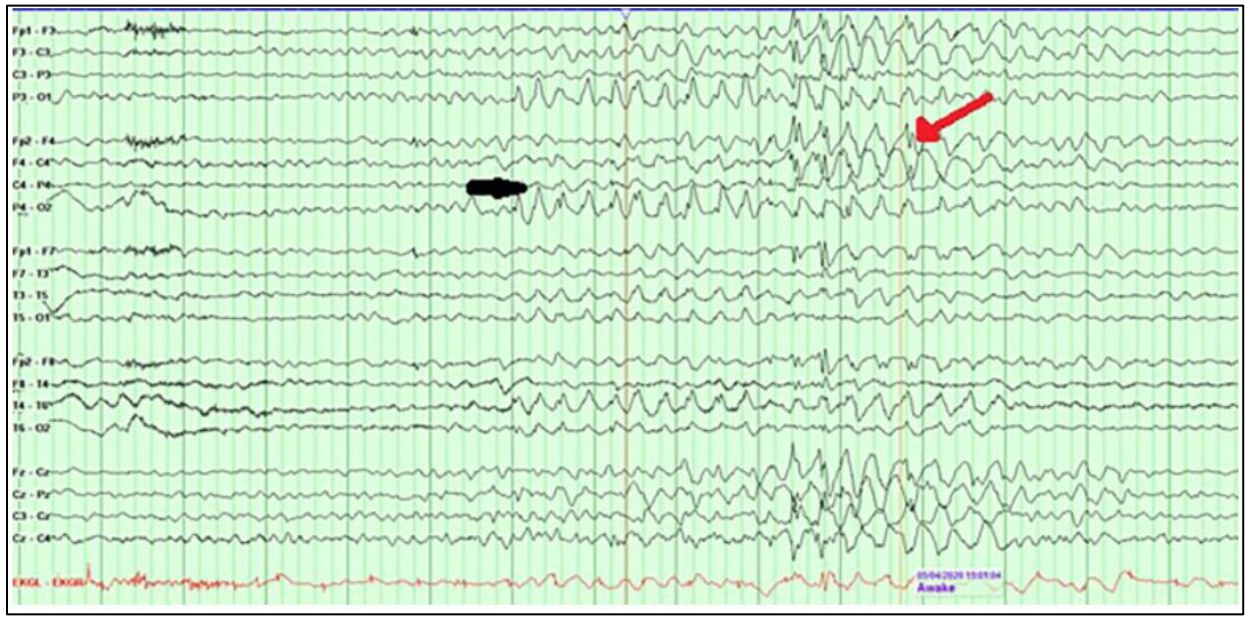
Angelman syndrome – Clinical overview

- Estimated incidence rates of approximately 1:15,000 with ~500,000 individuals diagnosed worldwide
- Present with delayed developmental milestones within the first year of life
  - Global developmental delay and intellectual disability
    - Language skills are more delayed than motor skills
    - Most have no spoken language, but receptive is relatively stronger
    - 10% never gain the ability to walk independently
  - Happy demeanor though some have maladaptive behaviors
  - Stereotypies and hyperkinetic movements or ataxia
  - Sleep disorders are common
  - Most have seizures (onset in toddler years)
  - Resting and intention tremors onset in adolescence or adulthood

Scheiffele, P. et al. *Nature* 2010, Tan & Bird *AJMG* 2016, Wheeler AC et. Al. Orphanet J Rare Dis, 2017
Photos copied from: https://cureangelman.org/about-as#about

Angelman syndrome – Epilepsy

- 80-90% of individuals with AS will develop epilepsy by 3 years of age
  - Early-onset epilepsy is associated with autistic traits
  - Deletion subtype has the most severe epilepsy
  - Variable seizure types
    - Atypical absence
    - Myoclonic
    - Tonic-clonic
    - Infantile spasms
    - Atonic
    - Non-convulsive Status Epilepticus
- EEG may serve as a biomarker
  - High-voltage rhythmic 4-6 Hz
  - Anterior-dominant rhythmic 2-3 Hz
  - Posterior-dominant 3-4 Hz notched delta & theta with eye closure



Diagnostic testing for Angelman syndrome

Methods:

- **Standard Chromosome Analysis or Cytogenetics Analysis** to examine the size, shape and number of chromosomes in a cell
- **The DNA methylation test** to see if both copies of a gene are active
- **The FISH Test** to see if any chromosomes are missing
- **PCR Assay** to detect uniparental disomy (UPD) and imprinting center defects (ICD)
- **UBE3A Sequencing** to look for a mutation in the maternal allele of this gene
- **Prenatal Test**: method is limited because of the type of AS; It looks like they only can detect large or microdeletion in AS

Angelman syndrome – Genotype-phenotype correlation

- Comparison of major phenotypes of different subtypes

Major Aspects	AS Due to Maternal del15q11–13	AS Due to Non-Deletion		
		Paternal Uniparental Disomy for Chromosome 15q11–q13 (UPD)	Imprinting Defect	Pathogenic UBE3A Mutation
Development	• More delayed across all development domains than other types • Cognitive skills lower than other types • Delayed gross and fine motor skills more severe • Reduced developmental age regarding visual perception, receptive language, and expressive language	• Higher overall age equivalent scores and growth score equivalents than deletion type but lower than UBE3A mutation subtype • Better development and expressive language ability in patients with UPD and imprinting defect • Higher scores and greater rates of skill attainment in all development domains in patients UBE3A mutation		
Seizures	• More common and severe in the deletion group	• Lower prevalence of epilepsy, and more with late-onset seizures • UPD subtype has the lowest frequency of epilepsy and exhibits the least severe epilepsy phenotype • The severity of epilepsy in the UBE3A mutation subtype ranks second after the deletion subtype		
Behavior	• Lower response rates to the social reinforcement paradigm than other types	• The imprinting defect a high rate of reinforcement by social stimuli. Patients with UBE3A mutations		
Sleep	• Common in all subtypes but Sleep problems are more prevalent in children with UPD and UBE3A mutations			
Others	• Higher rate of hypopigmentation	• UPD and imprinting defects have a higher risk of obesity than deletion type		

Yang et al. Genes 2021

Angelman syndrome – Management

- Normal lifespan but individuals with AS are unable to live independently
- Economic burden has not been studied, but is likely to be high over the lifetime of an individual with AS
- There are no approved therapies for AS
- Current treatment focused on managing medical and developmental issues
  - Physical, occupation, speech therapy
  - Applied behavioral analysis therapy
  - Medications to manage
    - Seizures
    - Behavior problems
    - Sleep problems
    - Movement disorder
- There are significant unmet needs in AS
  - Motor impairment
  - Speech/Communication impairment
  - Maladaptive behavior
  - Sleep problems
  - Cognitive impairment

Tan & Bird AJMG 2016, Wheeler AC et. Al. Orphanet J Rare Dis, 2017, Samanta D. Brain & Dev, 2021

References

1. Scheiffele P, Beg AA. Neuroscience: Angelman syndrome connections. Nature. 2010 Dec 16;468(7326):907-8. doi: 10.1038/468907a. PMID: 21164477.
2. Tan WH, Bird LM. Angelman syndrome: Current and emerging therapies in 2016. Am J Med Genet C Semin Med Genet. 2016 Dec;172(4):384-401. doi: 10.1002/ajmg.c.31536. Epub 2016 Nov 8. PMID: 27860204.
3. Wheeler AC, Sacco P, Cabo R. Unmet clinical needs and burden in Angelman syndrome: a review of the literature. Orphanet J Rare Dis. 2017 Oct 16;12(1):164. doi: 10.1186/s13023-017-0716-z. PMID: 29037196; PMCID: PMC5644259.
4. Samanta D. Epilepsy in Angelman syndrome: A scoping review. Brain Dev. 2021 Jan;43(1):32-44. doi: 10.1016/j.braindev.2020.08.014. Epub 2020 Sep 4. PMID: 32893075; PMCID: PMC7688500.
5. Pearson E, Wilde L, Heald M, Royston R, Oliver C. Communication in Angelman syndrome: a scoping review. Dev Med Child Neurol. 2019 Nov;61(11):1266-1274. doi: 10.1111/dmcn.14257. Epub 2019 May 10. PMID: 31074506.

Q & A

Disease Burden – Patient and Family Perspective

Allyson Berent, DVM, DACVIM

Chief Science Officer, the Foundation for Angelman Therapeutics (FAST)

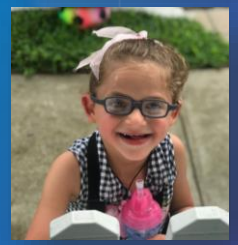
Director, Angelman Syndrome Biomarker and Outcome Measure Consortium (ABOM)

Co-Director, International Angelman Syndrome Research Council (INSYNC-AS)

A Parent's Journey Through Translational Research for Angelman Syndrome

Allyson Berent, DVM, DACVIM

- Chief Science Officer: **Foundation for Angelman Syndrome Therapeutics**
- Chief Operating Officer: **GeneTx Biotherapeutics**
- Director: **Angelman Syndrome Biomarker and Outcome Measure Consortium**
- Co-Director: **INSYNC-AS:** International Angelman Syndrome Research Council
- Veterinary Internal Medicine **Clinician:** Director Interventional Endoscopy
- **MOTHER OF QUINCY:** 7-year-old living with Angelman syndrome

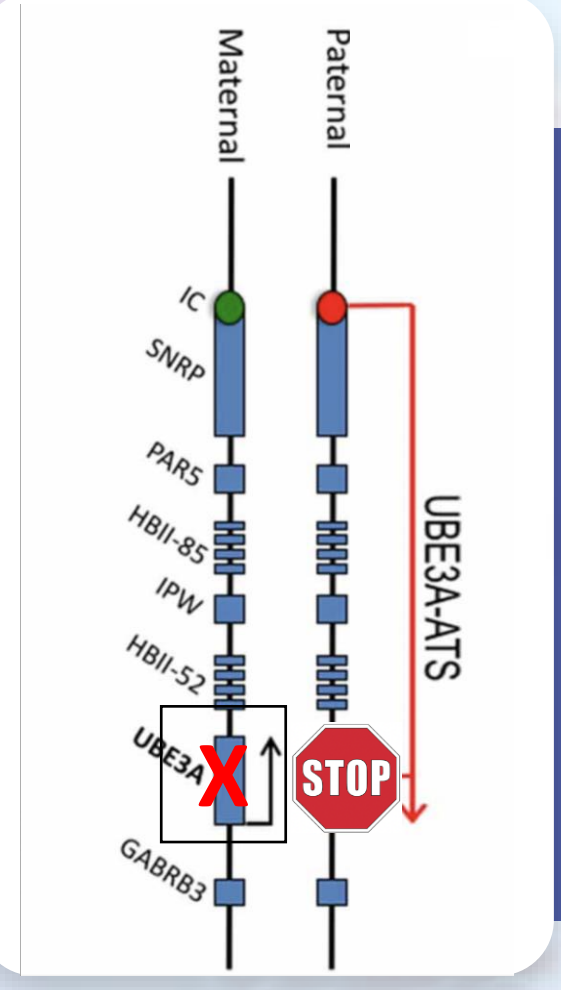


D-day

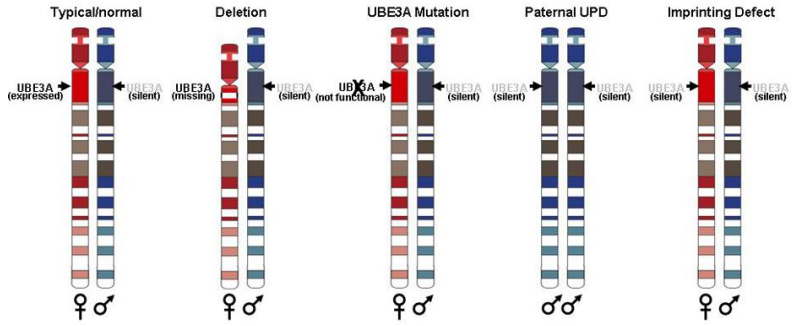
- How do you spell “Angelman syndrome?”
- ALL THE NOT’s!!!!
- What WILL she be able to do?
- What is the prognosis for survival?
- How do I give her the best life and advocate for all she is capable of?
- How do I ensure she is accepted and lives the most independent and fulfilled life?

- **I MUST <u>ADVOCATE</u> FOR QUINCY**
- **I MUST <u>LEARN</u> and <u>EXECUTE</u> IF I CAN CHANGE HER TRAJECTORY**

Angelman syndrome = disruption of expression of *UBE3A* maternal allele → decreased UBE3A protein ligase in CNS



N. Khatri et al. *Front. Mol. Neurosci.* 2019



- Deletion: ~70-80%
- Point mutation: ~10%
- Uniparental disomy (UPD): ~3%
- ICD: ~3%
- Clinical Diagnosis: <10%

1. Dagli A, Buiting K, Williams C. Molecular and Clinical Aspects of Angelman Syndrome. Mol Syndromol 2011; 2:100-112.
2. Dagli A, Mueller D, Williams C. Angelman Syndrome. GeneReviews, 2017. Editor, Adam. Seattle, WA. [https://www.ncbi.nlm.nih.gov/books/NBK1144/]
3. Williams C, Driscoll D, Dagli A. Clinical and genetic aspects of Angelman syndrome. Genet Med. 2010; 12(7): 385-395.

Clinical manifestations of AS are severe, with lifelong impact on the patient and their caregivers

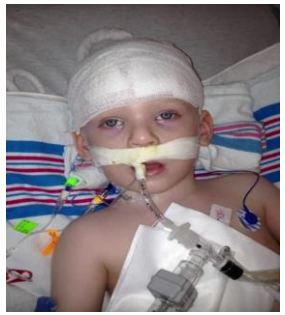
Symptoms of AS

- Universal lack of speech
- Life-threatening/debilitating seizures
- Severe developmental delays
- Ataxia/incoordination
- Apraxia/Dyspraxia
- Aggressive/disruptive behavior
- Sleep disturbances/severe insomnia
- Feeding issues/GI issues
- Unable to live independently
- **Significant clinical unmet need**

Impact on Family

- Inability to maintain employment
- Anxiety
- Depression
- Stress
- Loss of sleep
- Social isolation
- Impact on family relationships
- Difficulty caring for other children/home
- Fatigue



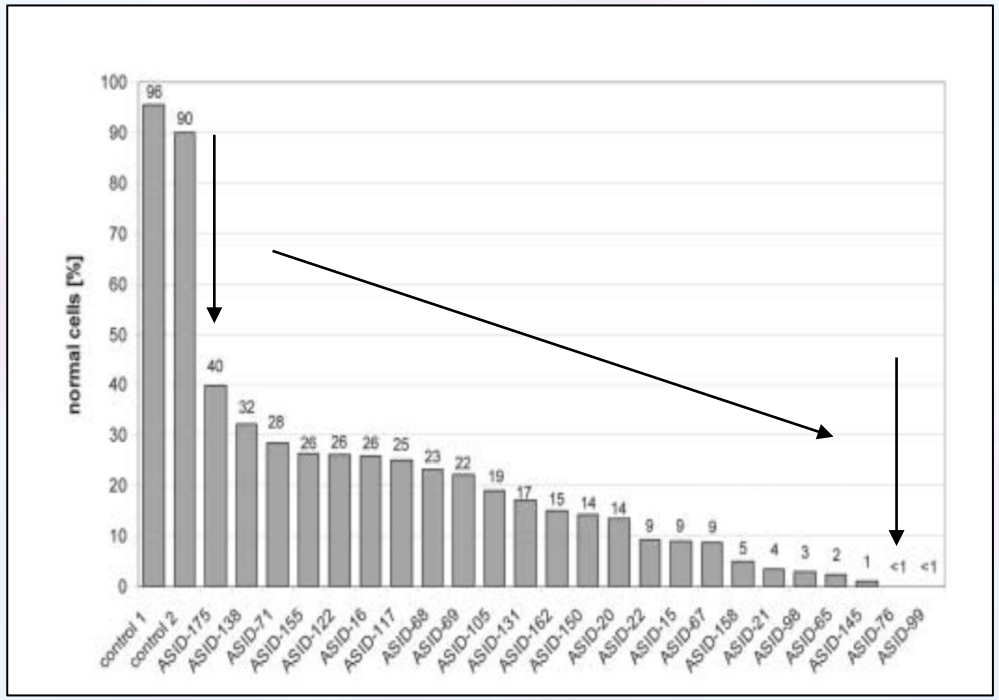




Strong hypothesis to support human translation

Human Molecular Genetics, 2004, Vol. 13, No. 21
doi:10.1093/hmg/ddh296
Advance Access published on September 22, 2004

Somatic mosaicism in patients with Angelman syndrome and an imprinting defect

- 1-40% functional UBE3A expression
- 1-5% UBE3A → few-no seizures, ambulatory, some ataxia, some speech
- ~20% UBE3A → no seizures, ambulatory, minimal to no ataxia and speak in sentences



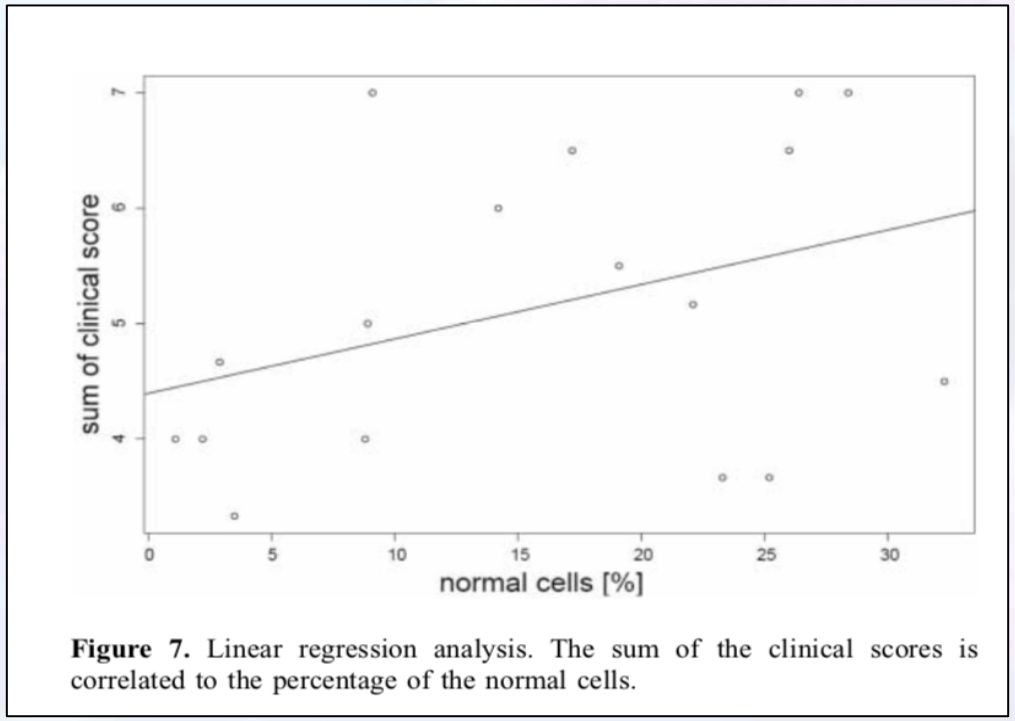


Figure 7. Linear regression analysis. The sum of the clinical scores is correlated to the percentage of the normal cells.

Why are we here?

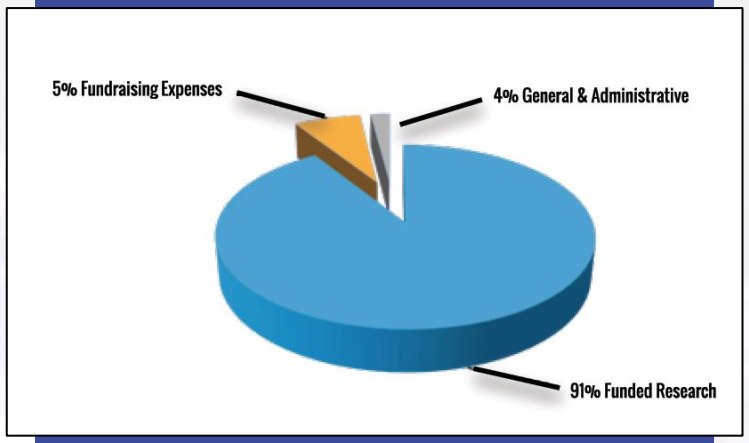
Vision

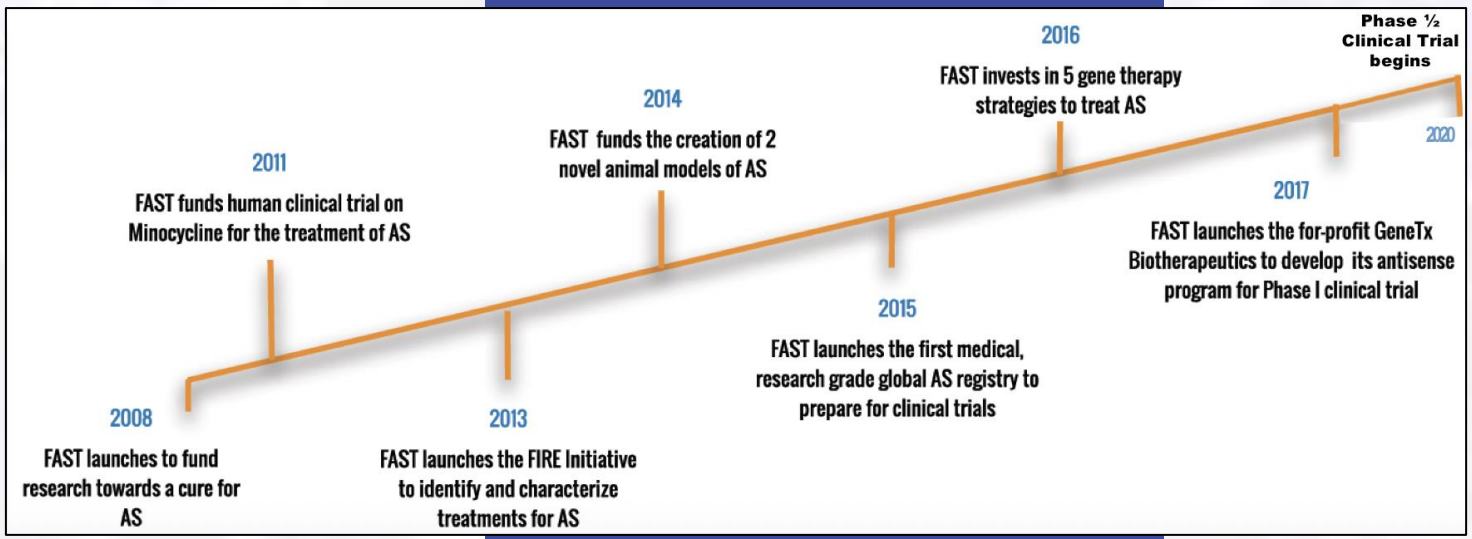
Our role & mission

FAST has an all-volunteer board of Angelman syndrome **(AS) parents and professionals** dedicated to bringing **transformative treatments to all individuals** in the world living with Angelman syndrome, regardless of **age or genotype**, for an **ultimate CURE**. This is done through the funding of an **aggressive research agenda** promoting **collaboration, understanding, readying and expediting** drug development. It is our hope that the programs we fund will **accelerate** a proof of concept from an animal model to a drug candidate for human clinical trials. FAST is served by two main boards: the board of directors and the scientific advisory board. Together, **we are working hard to bring practical treatments into current medical practice as quickly and safely as possible.**

Introduction to FAST

- $25+ million FAST-raised funds spent to support research toward treatments
  - $3+ million directed to create novel animal models of AS: currently being characterized
    - Large deletion rat, deletion and mutation pig, large deletion mouse +/- *Ube3a* underway
  - 20+ laboratories funded by FAST to understand etiology of AS and identify therapeutic options
- 9 gene therapy/disease modification-based strategies funded to support drug development life-cycle for AS





1. Born H, et al. EEG activity and seizure threshold in a novel Ube3a maternal deficiency rat model of AS. Abstract, Gordon Research Conference.
2. Berg E, et al. Developmental social communication in the Ube3a Rat model of AS. Abstract, SFN

FAST's roadmap for success

1

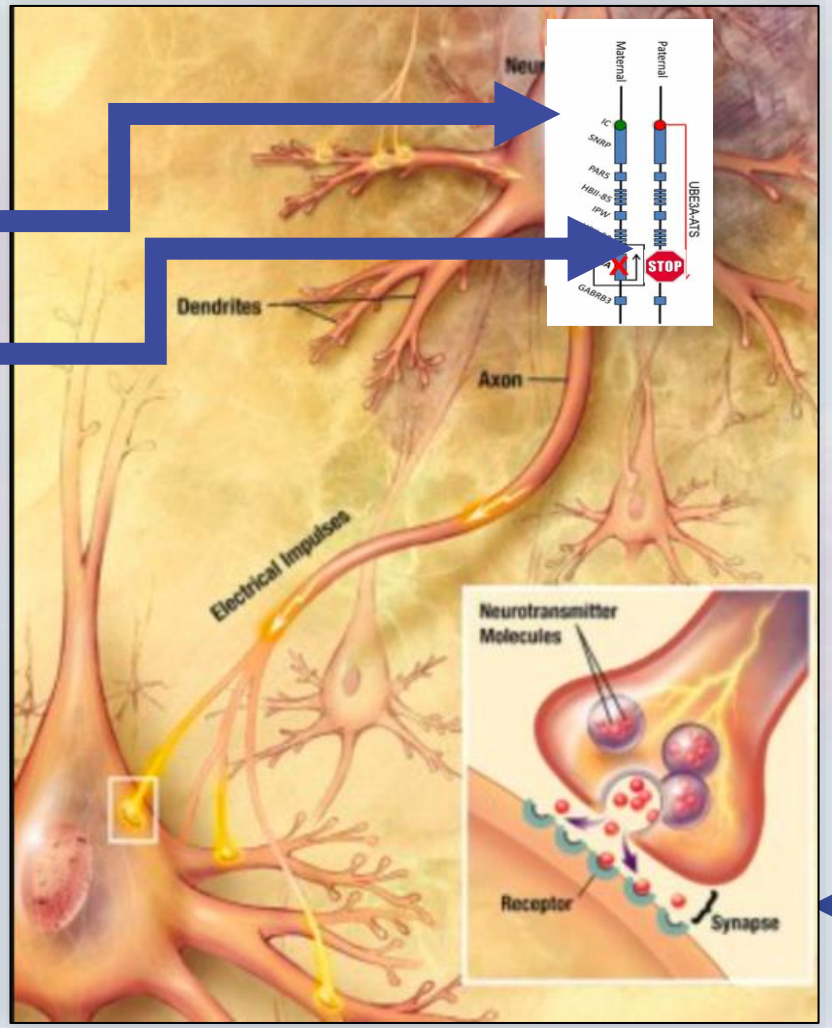
Investigate therapeutic strategies

- Gene/protein replacement therapy
- Paternal gene activation

3

PREPARE!

- Create/characterize animal models
- Biomarkers and outcome measures (ABOM)
- Clinical trial design
- Genotype specific testing
- INSYNC-AS



2

Identify symptomatic treatments

- Down stream therapeutics
- Symptomatic relief

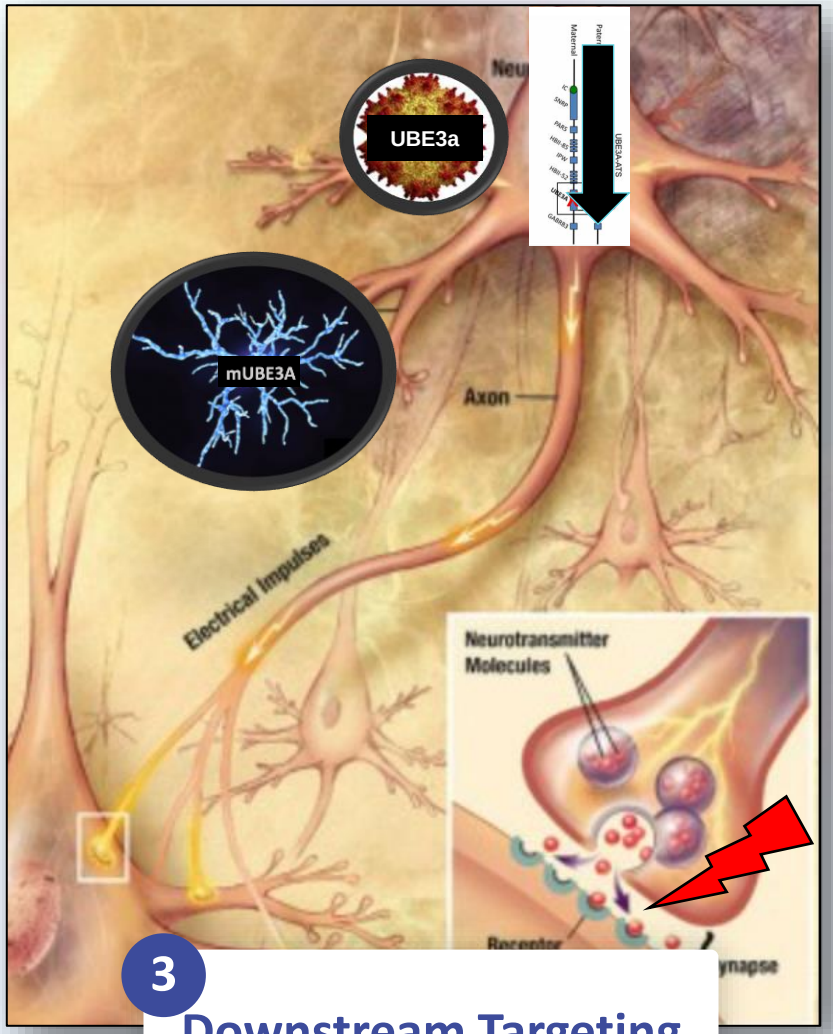
Disease modification strategies

1 Gene/Protein Replacement Therapy

- **AAV**
  - Gene replacement
  - Secretory Protein replacement
- **Lentivirus** with HSC
- Enzyme replacement therapy **(ERT)**

Penn · PTC Therapeutics · stridebio · Amicus Therapeutics · SAREPTA THERAPEUTICS · UCDAVIS · TAYSHA GENE THERAPIES

*Other programs are currently under development that may not be represented/disclosed



2 Paternal Gene Activation = "STOP THE STOP"

ASO/SNAs	IONIS · Biogen · genetx · ultragenyx · Roche · exicure
ATFs	UCDAVIS
CRISPR	UNC · Penn · UCDAVIS
shRNA/ miRNA	TAYSHA GENE THERAPIES · Ovid · Penn

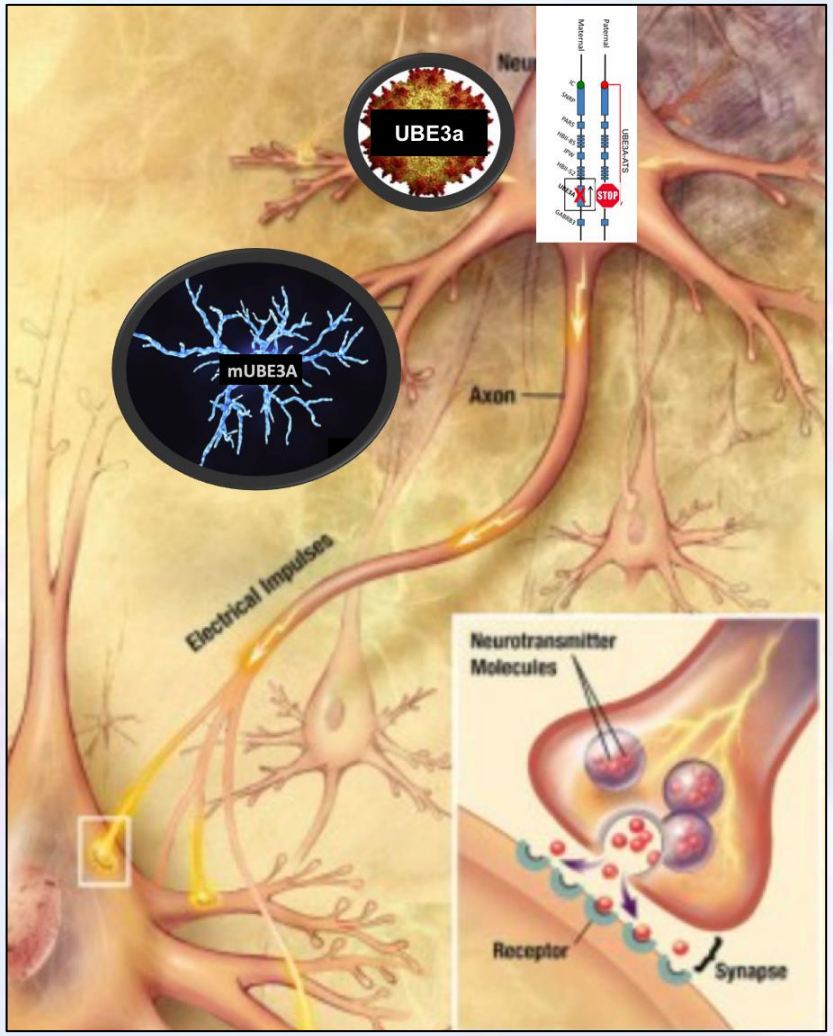
3 Downstream Targeting

Small Molecules/ Ligands

neuren pharmaceuticals · healx

Others*

Proof-of-concept

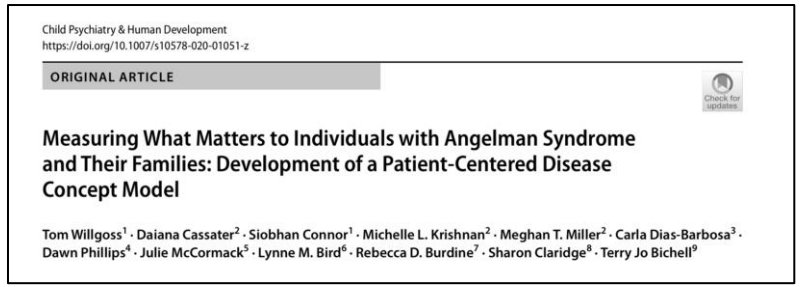


What matters to patients and caregivers?

fast
cureangelman.org

Efforts to support clinical trial readiness

- Disease burden and unmet clinical need publication with disease concept model
  - Explored patient-focused outcomes of critical importance to families
  - Disease Concept Model (Willgoss et al. 2020)
- NIH funded natural history (2006-2014) in US; FDA funded 2018-2022
  - 302 patients (2006); ~150 patients (2018)
  - Additional data from FAST UK, LATAM, Italy, Spain, France underway
- Global Angelman syndrome Registry
  - ~2K patients enrolled
- Angelman syndrome Biomarker and Outcome Measure Consortium (ABOM)
  - Focusing on relevant endpoints for all clinical domains
  - Biomarker development
- Model development & study support
  - Rat/Pig (full maternal deletion)
  - Large deletion mouse with/without *Ube3a*
  - iPSC/organoids available precompetitive
  - Landing pad (UPD/ICD; large deletion; mosaic)
  - AS core infrastructure for preclinical testing (first 12 months attracted 5 pharma companies for drug testing)
- INSYNC-AS: **IN**ternational Angelman **SYN**drome Research **C**ouncil


Child Psychiatry & Human Development
https://doi.org/10.1007/s10578-020-01051-z

ORIGINAL ARTICLE

Measuring What Matters to Individuals with Angelman Syndrome and Their Families: Development of a Patient-Centered Disease Concept Model

Tom Willgoss[1] · Daiana Cassater[2] · Siobhan Connor[1] · Michelle L. Krishnan[2] · Meghan T. Miller[2] · Carla Dias-Barbosa[3] · Dawn Phillips[4] · Julie McCormack[5] · Lynne M. Bird[6] · Rebecca D. Burdine[7] · Sharon Claridge[8] · Terry Jo Bichell[9]

INSYNC-AS

ORCA
Observer-Reported Communication Ability Measure

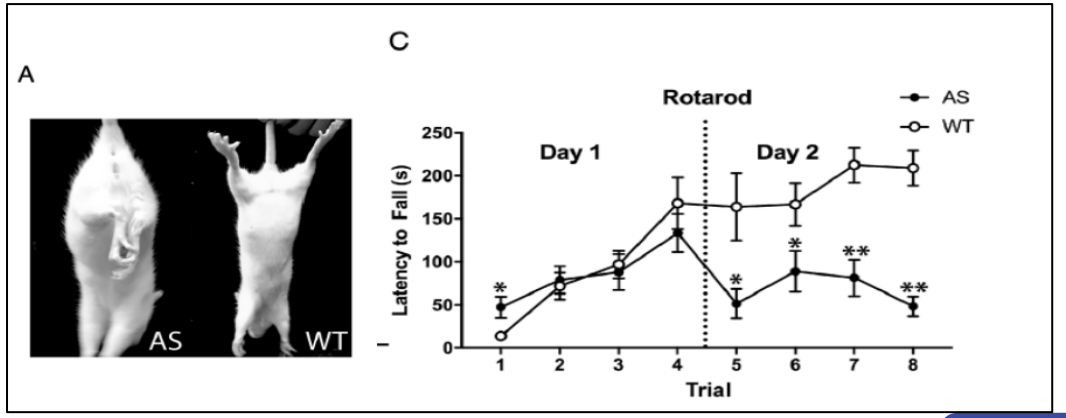
A-BOM
ANGELMAN SYNDROME
BIOMARKER & OUTCOME MEASURE CONSORTIUM

NIH National Institutes of Health

A Prospective Natural History Study of Angelman Syndrome: A Fresh Approach to a 10-year Longitudinal Study to Facilitate Development of Novel Therapeutic Products

Tan, Wen-Hann

Boston Children's Hospital, Boston, MA, United States



Angelman syndrome natural history studies since 2006

- 2006-2014:
  - 302 patients enrolled, mean **age 5.5 years**
- **Median 3.3 years follow-up (range 1-8 years)**
  - Neuropsych testing
  - EEGs
  - Seizure history
  - Medication history
  - Sleep history
  - Behavior
  - FQOL and PSI
  - Clinical severity scale
- 2018-present:
  - >150 patients enrolled
  - Exploring most utilized endpoints supported by ABOM

Variable	*N=302*	
Age at baseline, years (mean, SD)	5.5	5.9
Age at diagnosis, years (mean, SD)	2.0	3.0
Male (n, %)	145	48.0
Female (n, %)	157	52.0
Seizure history (n, %)		
Clinical seizures	199	67.9
Age at first seizure years (mean, SD)	1.7	1.37
Other medical history (n, %)		
Otitis media	149	51.0
Pneumonia	72	24.9
Gastrointestinal reflux		
Never formally diagnosed	59	20.1
Diagnosed	136	46.3
Vomiting with Feeds	61	20.7
Gagging	146	49.7
Tight heels cords/toe walking	109	39.5
Strabismus	147	50.3
Years of follow-up, (mean, min-max)	3.3	1-9

Global Angelman Syndrome Registry (GASR)

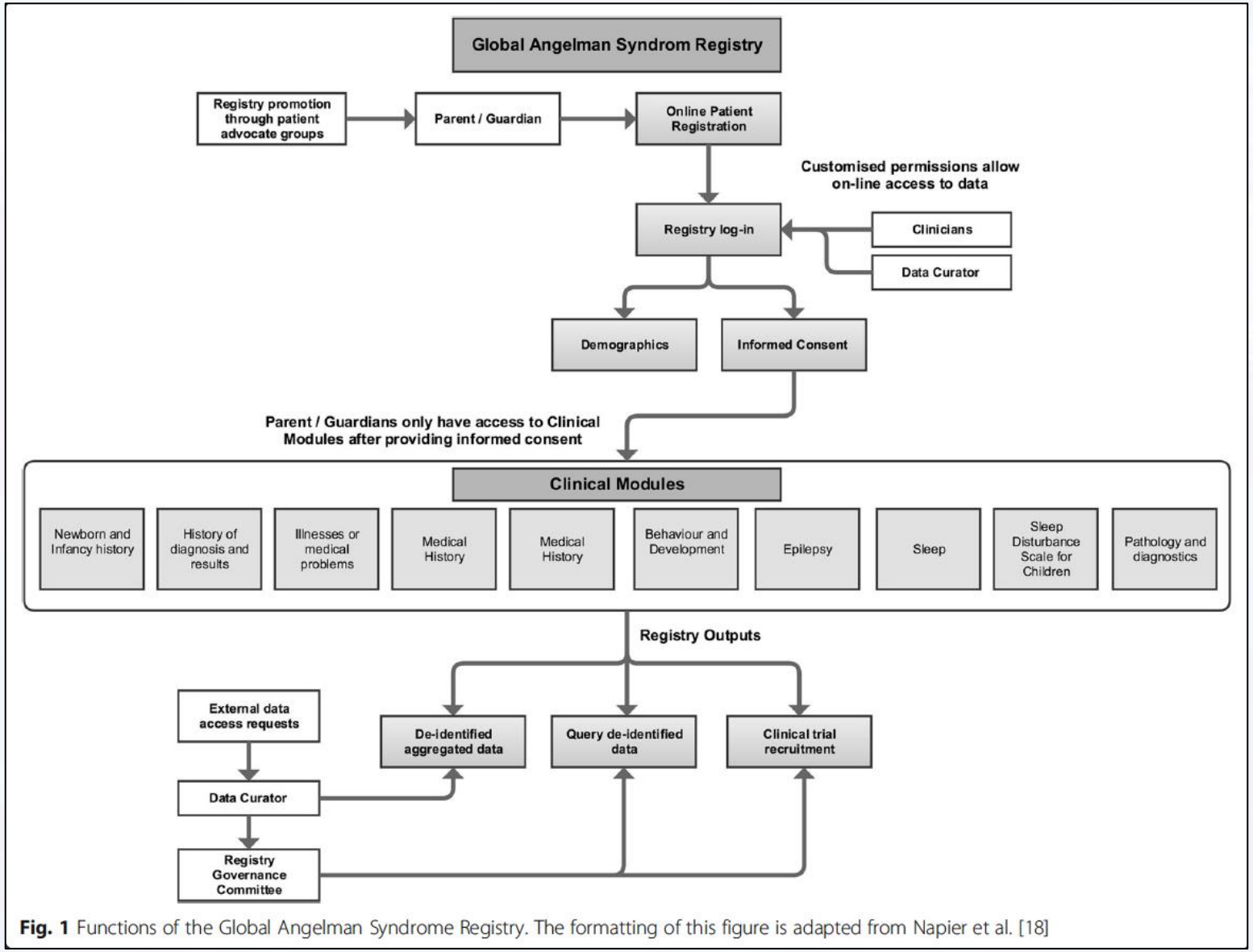


Fig. 1 Functions of the Global Angelman Syndrome Registry. The formatting of this figure is adapted from Napier et al. [18]

FAST/ABOM supported patient focused development efforts
Important outcomes to caregivers of patients with AS

AS Disease Concept Model

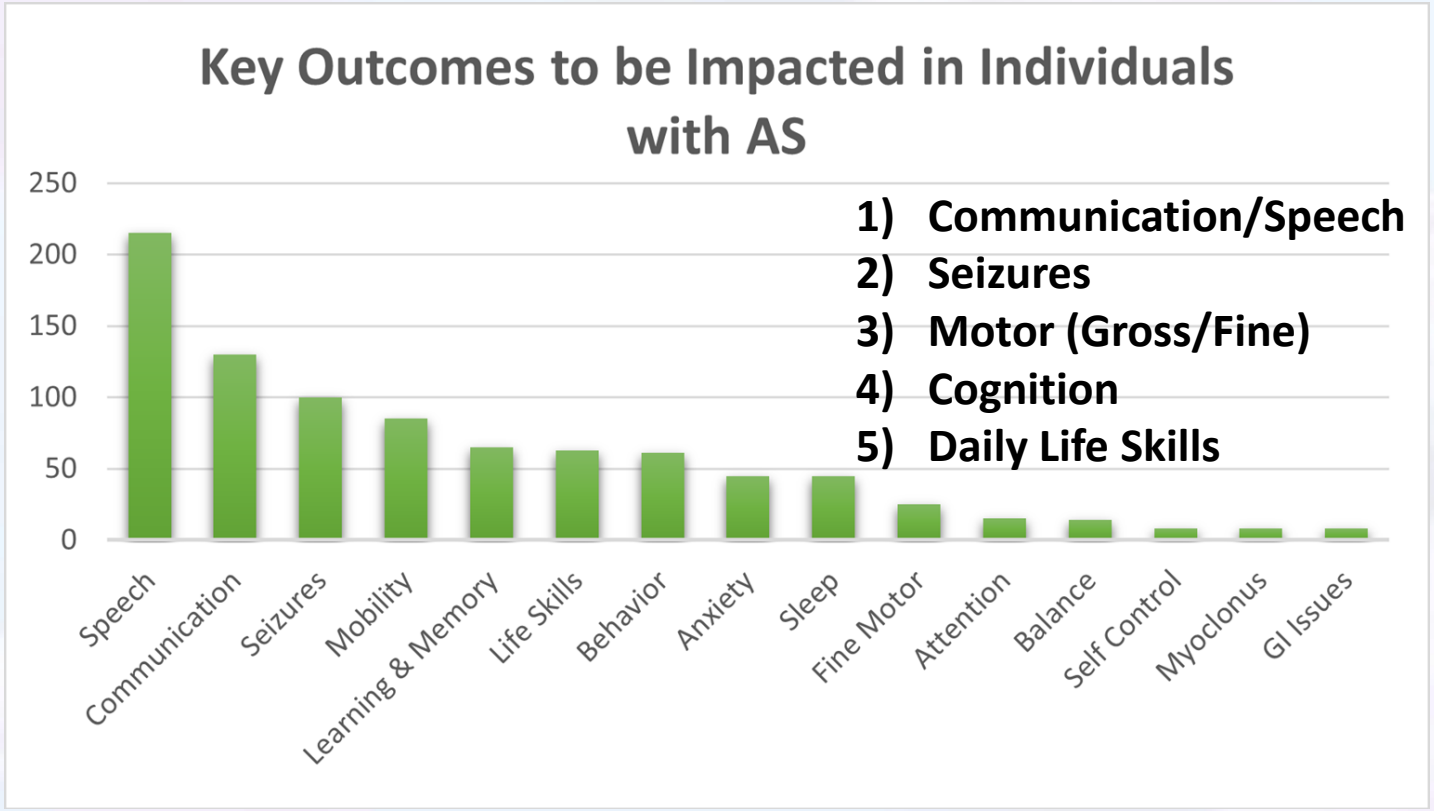
Table 4 Caregiver-rated most challenging AS symptoms, by age group

Most challenging symptoms	Number of caregivers reporting this AS symptom was challenging, per AS age group		
	≤5 years	6–12 years	15–17 years
Communication impairment or decreased speech	**3**	**5**	**4**
Seizures	**5**	2	1
Disruptive behavior	1	**3**	1
Learning challenges	1	1	1
Walking difficulties	**3**	2	1
Sleep issues	**4**	2	1
Ability to use the toilet	1	**3**	1

Bold, underlined numbers show where three or more caregivers reported this AS symptom as being challenging

AS Angelman syndrome

Willgoss, et al., 2020, *Child Psychiatry Hum Dev*



FAST Survey 2018: N=332 parent/caregiver respondents

Preparing stakeholders for trials
Patient focused listening session 2018

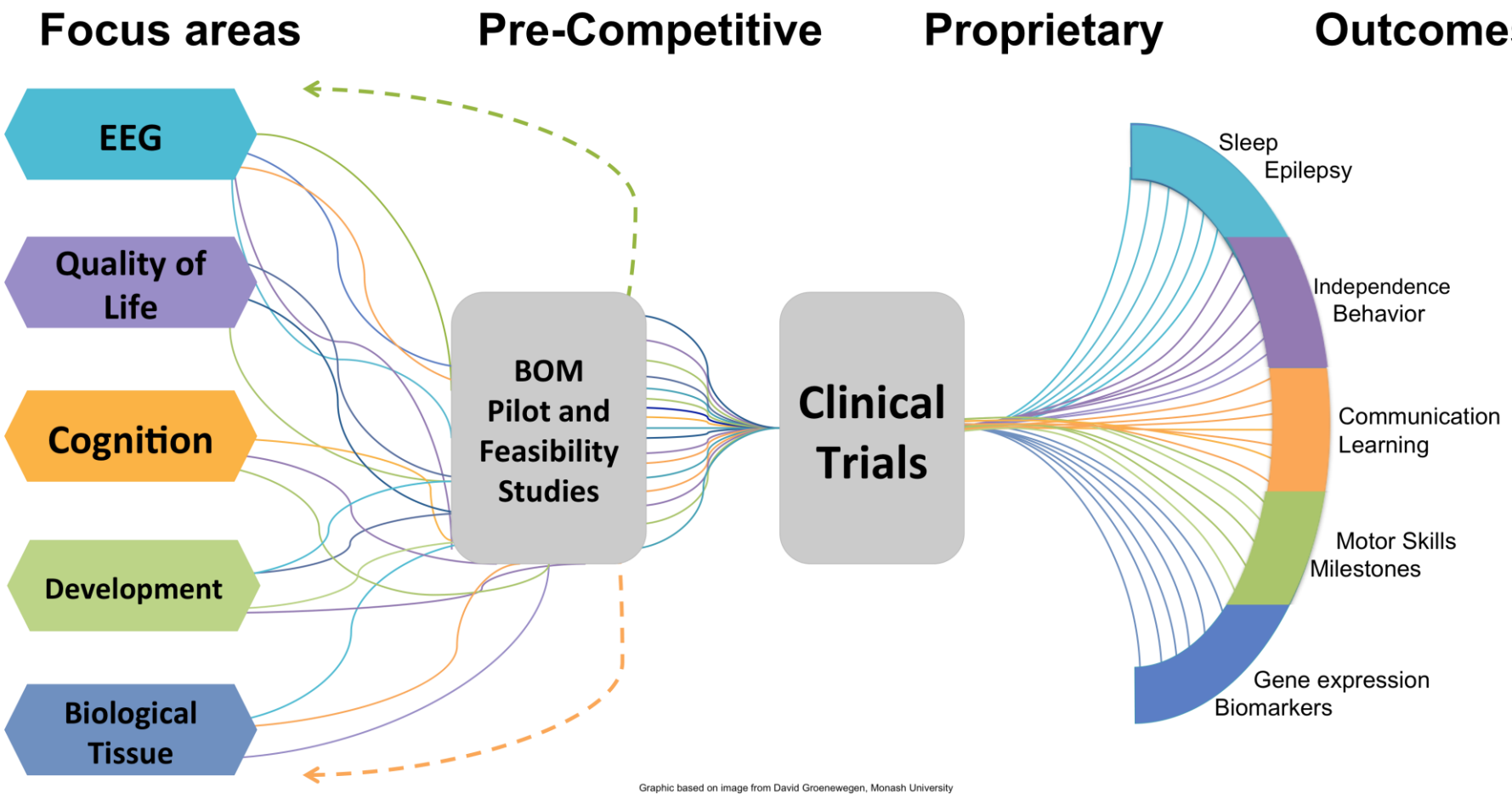
ORCA
Observer-Reported Communication Ability Measure

- FDA-requested patient-led initiative to share perspectives with the FDA
- June 2018: Meeting of FAST, CDER/CBER, Orphan Products, Rare Disease Staff, etc.
- Introduced FDA to patients and caregivers; education on AS, outcomes most important to caregivers, existing measures and limitations
- **Suggested FAST consider development of a simplistic communication assessment tool to capture basic, but likely important changes in communication for a child with AS**
  - Ability to clearly communicate basic personal needs (e.g. hunger) though whatever modality applicable to the child
- Clear message from parents that such changes would be clinically meaningful and dramatically impact their child's activities of daily living
- Supported design of the ORCA
  - Since FDA funded Duke University $2+million to develop ORCA for 14 other NDDs

A-BOM

ANGELMAN SYNDROME

BIOMARKER & OUTCOME MEASURE CONSORTIUM



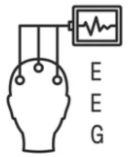
Graphic based on image from David Groenewegen, Monash University

Functional domains priorities

with

Biomarkers
e.g., Fluids, EEG

A-BOM
ANGELMAN SYNDROME
BIOMARKER & OUTCOME MEASURE CONSORTIUM

Focus Domain	Measures to consider	Measures specifically assessed for AS
 **Communication**	• ORCA • BSID-3, BSID-4 • VABS-2, VABS-3 • Communication Matrix • ASVA • CGI-AS	• ORCA • BSID-3, BSID-4 • VABS-2, VABS-3 • Communication Matrix • CGI-AS
 **Fine Motor**	• BSID-3, BSID-4 • VABS-2, VABS-3 • ASVA • CGI-AS	• BSID-3, BSID-4 • VABS-2, VABS-3 • CGI-AS
 **Gross Motor**	• BSID-3, BSID-4 • VABS-2, VABS-3 • Actimyo • GMFM • ASVA • CGI-AS	• BSID-3, BSID-4 • VABS-2, VABS-3 • Actimyo • CGI-AS
Global	• CGI-S-AS, CGI-I-AS • Caregiver CGI-AS	• CGI-S-AS, CGI-I-AS
 **ADL**	• VABS-2, VABS-3 • ASVA	• VABS-2, VABS-3
QOL	• QOL Inventory • Caregiver Burden Inventory • Parent Adjustment Questionnaire • EQ-5D-Y • Quality of Life Disability Measure	
 **Cognition**	• BSID-3, BSID-4 • VABS-2, VABS-3 • EEG	• BSID-3, BSID-4 • VABS-2, VABS-3 • EEG
 **Sleep**	• Sleep Diary • Wearables • EEG • Sleep Mats • CGI-AS	• EEG • Sleep Diary • CGI-AS
 **Seizure**	• Seizure Diary • EEG • CGI-AS	• Seizure Diary • EEG • CGI-AS
Behavior	• VABS-2, VABS-3 • ABC-C • BIAPAS	• ABC-C
 **Biomarkers**	• EEG • AERP • APP (plasma) • CSF: UBE3A others	• EEG

Collaborate

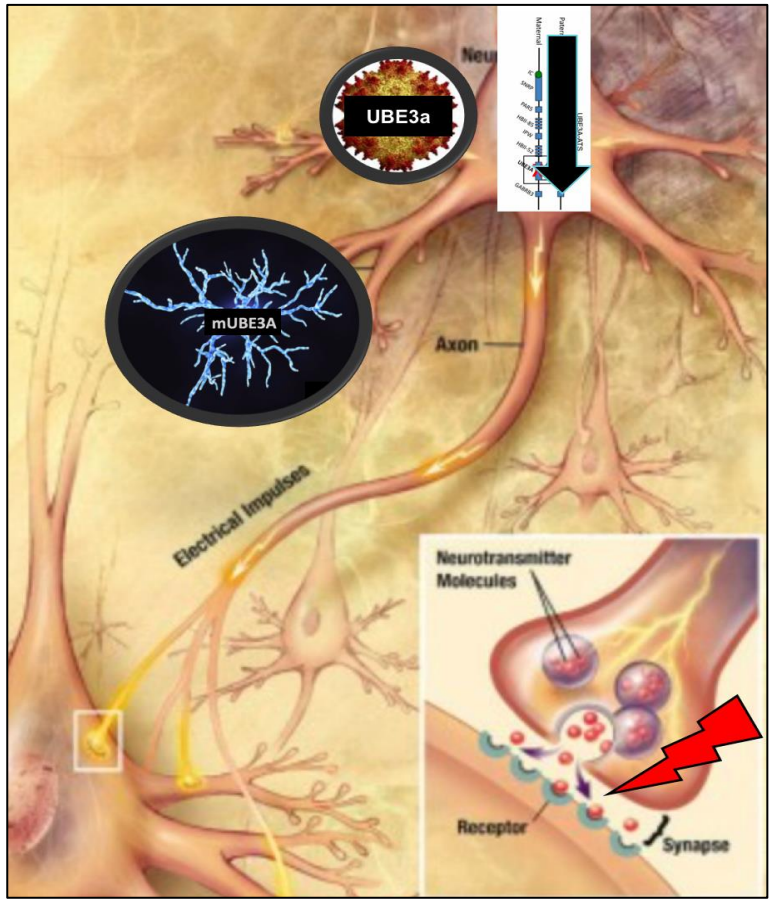
Ready

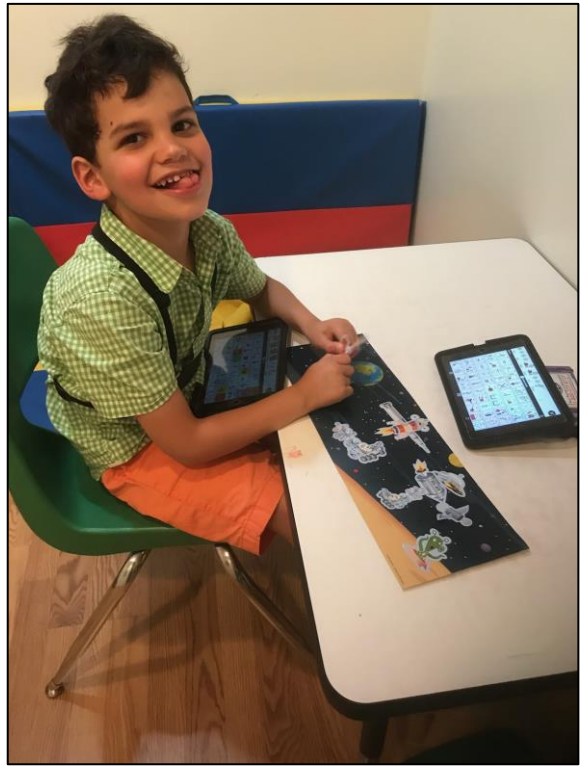
C.U.R.E^{AS}

Understand

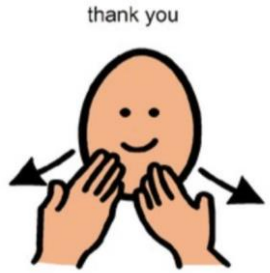
Expedite

- Numerous potential therapeutic platforms invested in AS
- AS is unique with some promising clinical results to date
- Where are our gaps to ensure we see a meaningful transformative treatments for all those living with AS regardless of genotype or ages?






Impossible


thank you

Novel Gene Replacement for Angelman Syndrome

Ben Philpot, PhD

Associate Director of the UNC Neuroscience Center

A novel gene transfer therapy for Angelman syndrome

Ben Philpot, Ph.D.

Carolina Institute for Developmental Disabilities, Neuroscience Center,

Department of Cell Biology and Physiology @ the **University of North Carolina**, Chapel Hill

UNC SCHOOL OF MEDICINE Cell Biology and Physiology

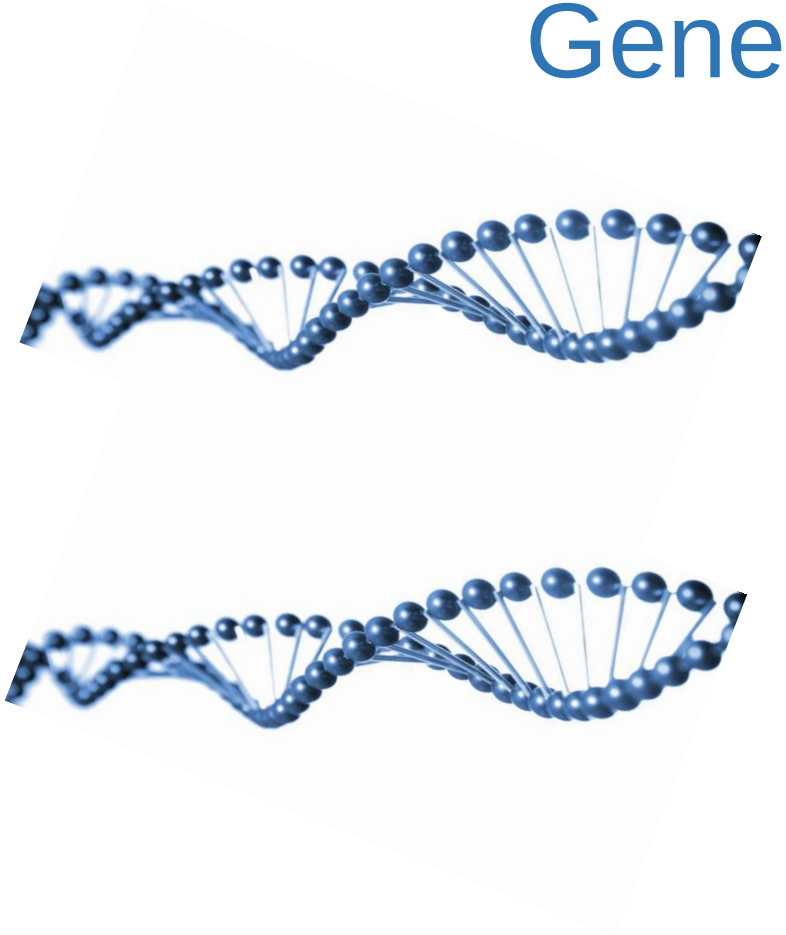
Disclosures

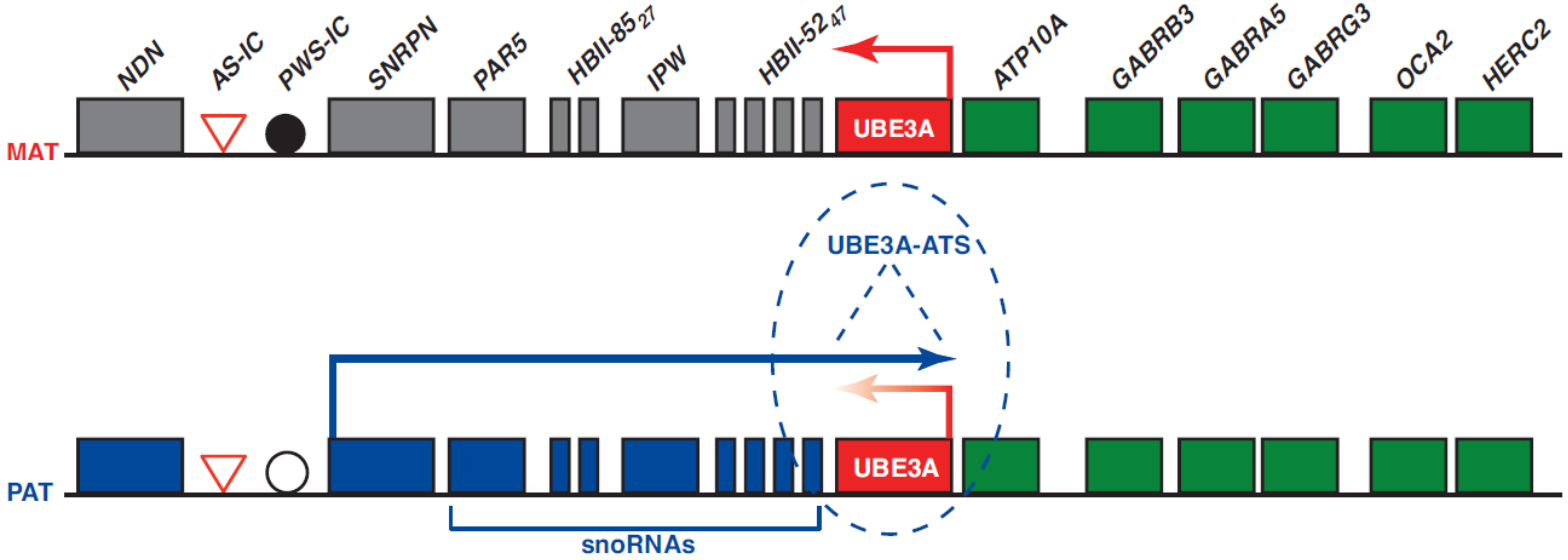
- Dr. Philpot has licensed his gene therapy to Taysha Gene Therapies
- Dr. Philpot has a Sponsored Research Agreement with Taysha Gene Therapies

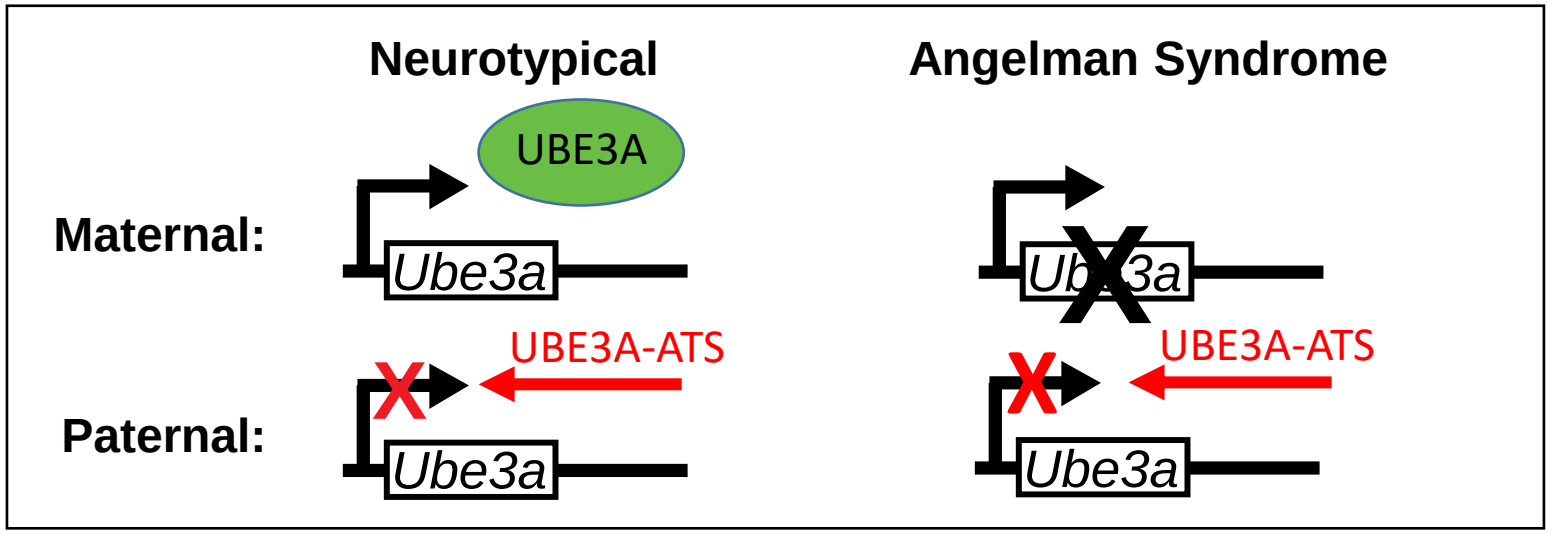
Angelman syndrome is caused by mutations or deletions of *UBE3A*

- Prevalence of 1 in 15,000
- >70% caused by deletions of the 15q11-q13 region, which includes *UBE3A*
- ~10% caused by mutations restricted to UBE3A

Genetic imprinting of *UBE3A*

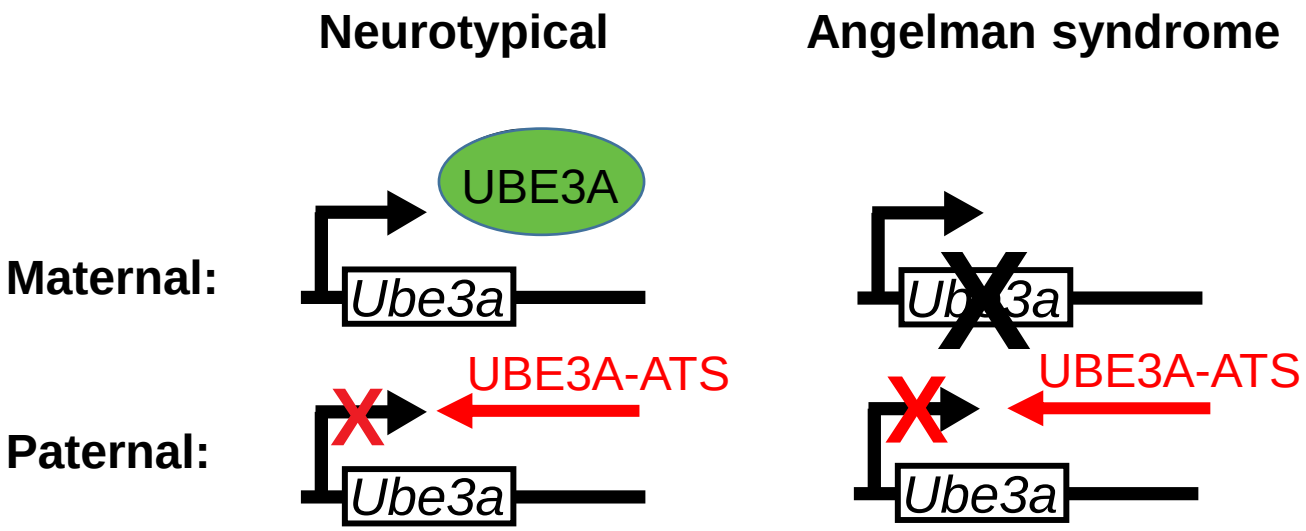






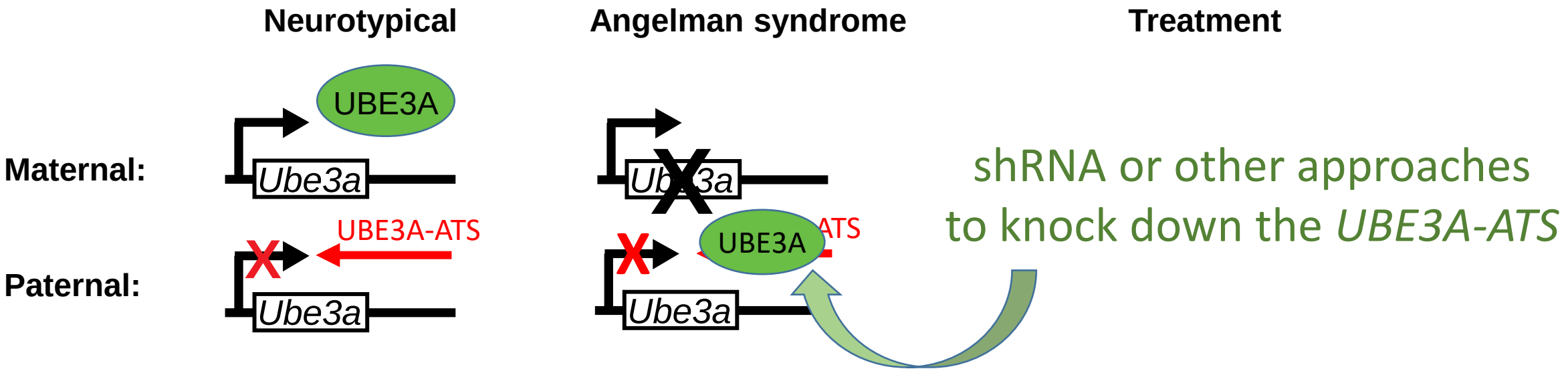
Treatment strategies for Angelman syndrome

- Gene reactivation strategies
- Gene addition strategies



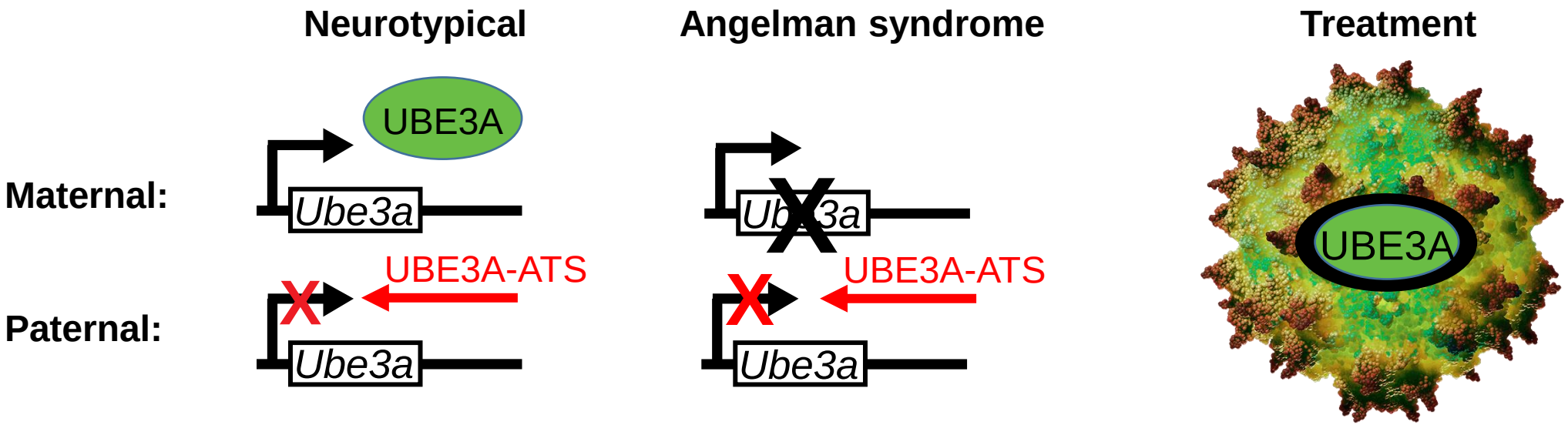
Treatment strategies for Angelman syndrome

- **Gene reactivation strategies**
- Gene addition strategies



Treatment strategies for Angelman syndrome

- Gene reactivation strategies
- **Gene addition strategies**



Preclinical data for AS recently published

JCI insight

RESEARCH ARTICLE

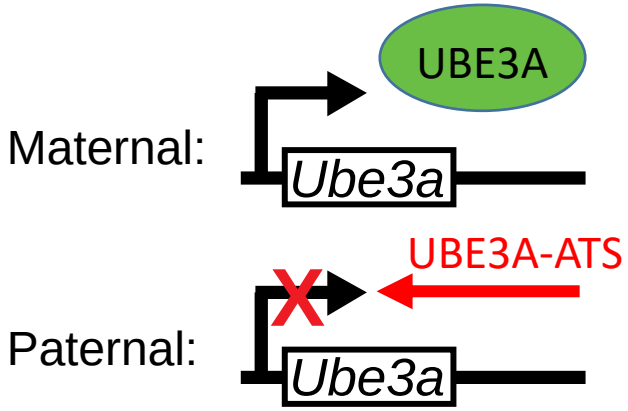
Dual-isoform hUBE3A gene transfer improves behavioral and seizure outcomes in Angelman syndrome model mice

Matthew C. Judson,[1,2,3] Charles Shyng,[3,4] Jeremy M. Simon,[1,3,5] Courtney R. Davis,[1,2] A. Mattijs Punt,[6,7] Mirabel T. Salmon,[8] Noah W. Miller,[1,2] Kimberly D. Ritola,[1,9,10] Ype Elgersma,[6,7,11] David G. Amaral,[12,13] Steven J. Gray,[4,14,15] and Benjamin D. Philpot[1,2,3]

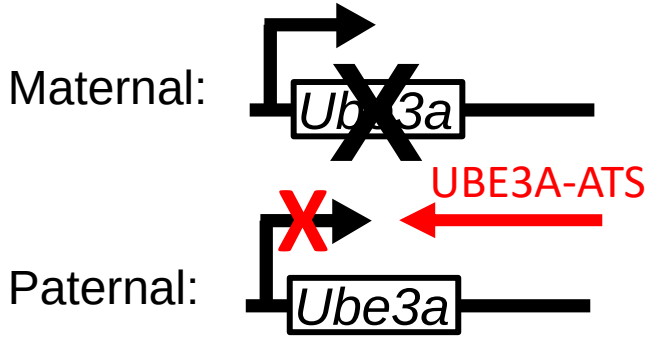
Loss of the maternal *UBE3A* allele causes Angelman syndrome (AS), a debilitating neurodevelopmental disorder. Here, we devised an AS treatment strategy based on reinstating dual-isoform expression of human UBE3A (hUBE3A) in the developing brain. Kozak sequence engineering of our codon-optimized vector (hUBE3Aopt) enabled translation of both short and long hUBE3A protein isoforms at a near-endogenous 3:1 (short/long) ratio, a feature that could help to support optimal therapeutic outcomes. To model widespread brain delivery and early postnatal onset of hUBE3A expression, we packaged the hUBE3Aopt vector into PHP.B capsids and performed intracerebroventricular injections in neonates. This treatment significantly improved motor learning and innate behaviors in AS mice, and it rendered them resilient to epileptogenesis and associated hippocampal neuropathologies induced by seizure kindling. hUBE3A overexpression occurred frequently in the hippocampus but was uncommon in the neocortex and other major brain structures; furthermore, it did not correlate with behavioral performance. Our results demonstrate the feasibility, tolerability, and therapeutic potential for dual-isoform hUBE3A gene transfer in the treatment of AS.

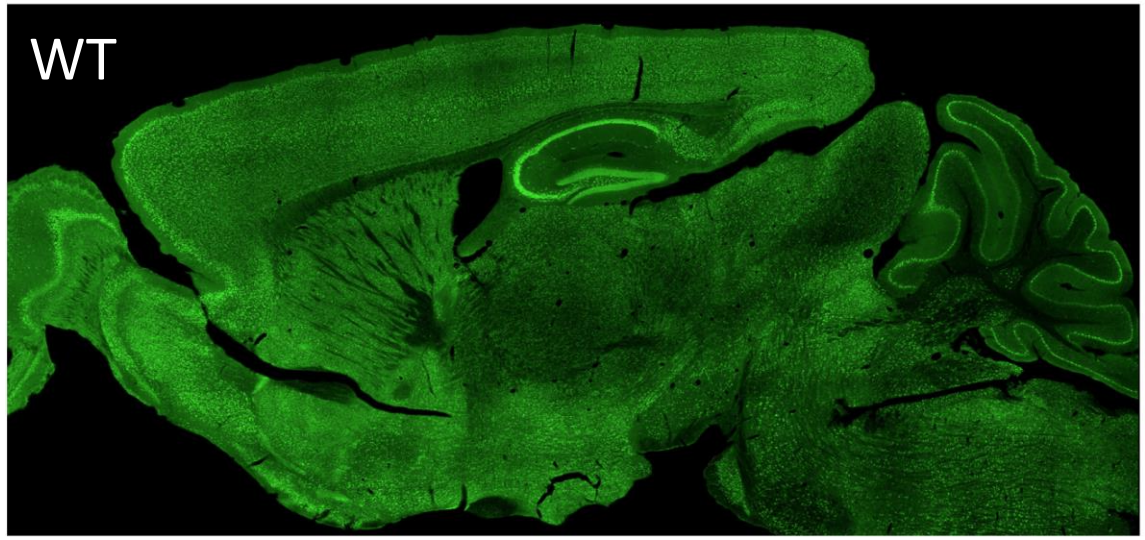
AS target biology:
Broad expression of UBE3A in brain

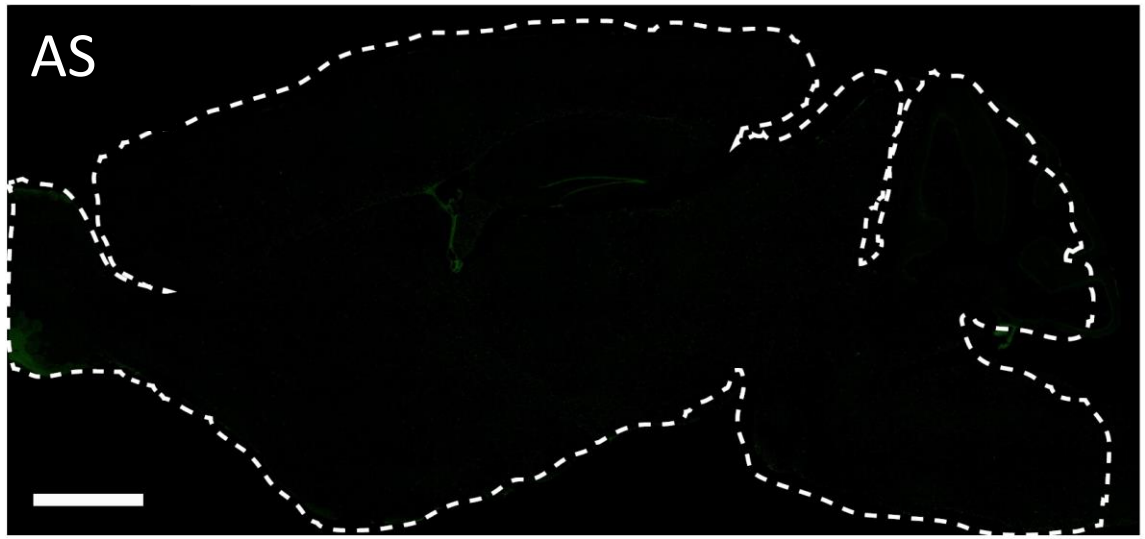
Neurotypical



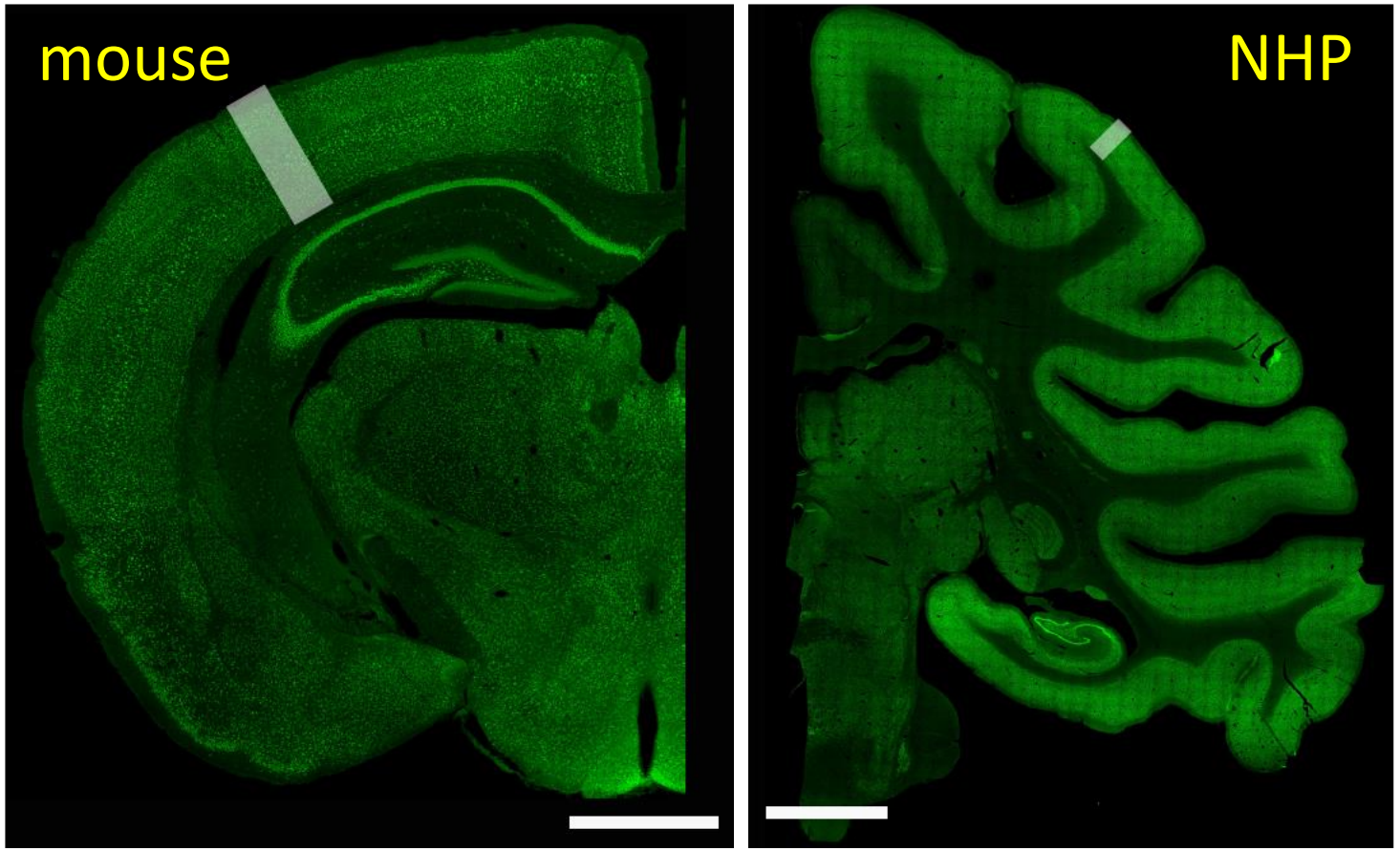
Angelman syndrome





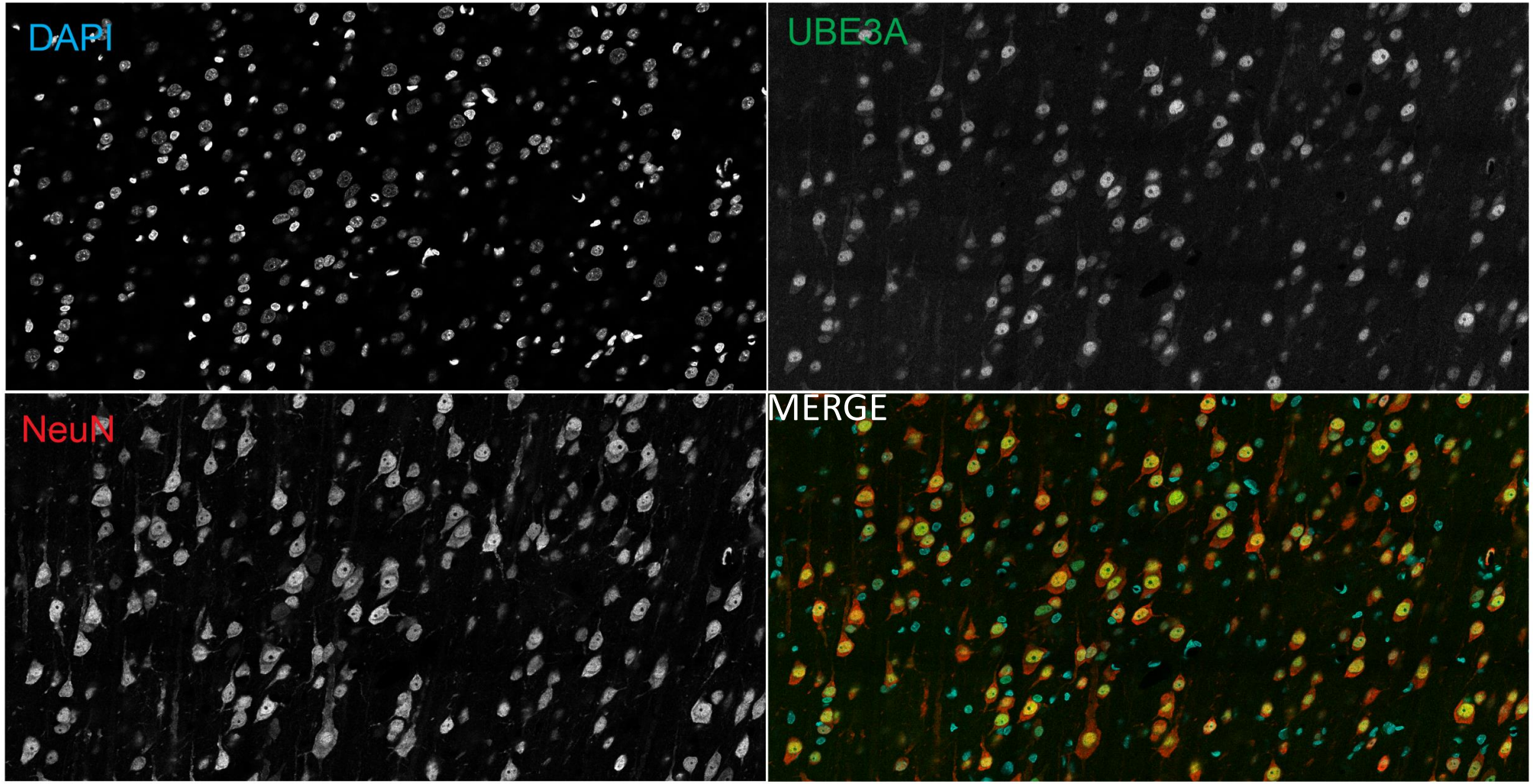


AS target biology:
Broad expression of UBE3A in brain



- Broad, virtually ubiquitous expression
- Fairly uniform distribution across brain regions

AS target biology:
High expression of UBE3A in neurons

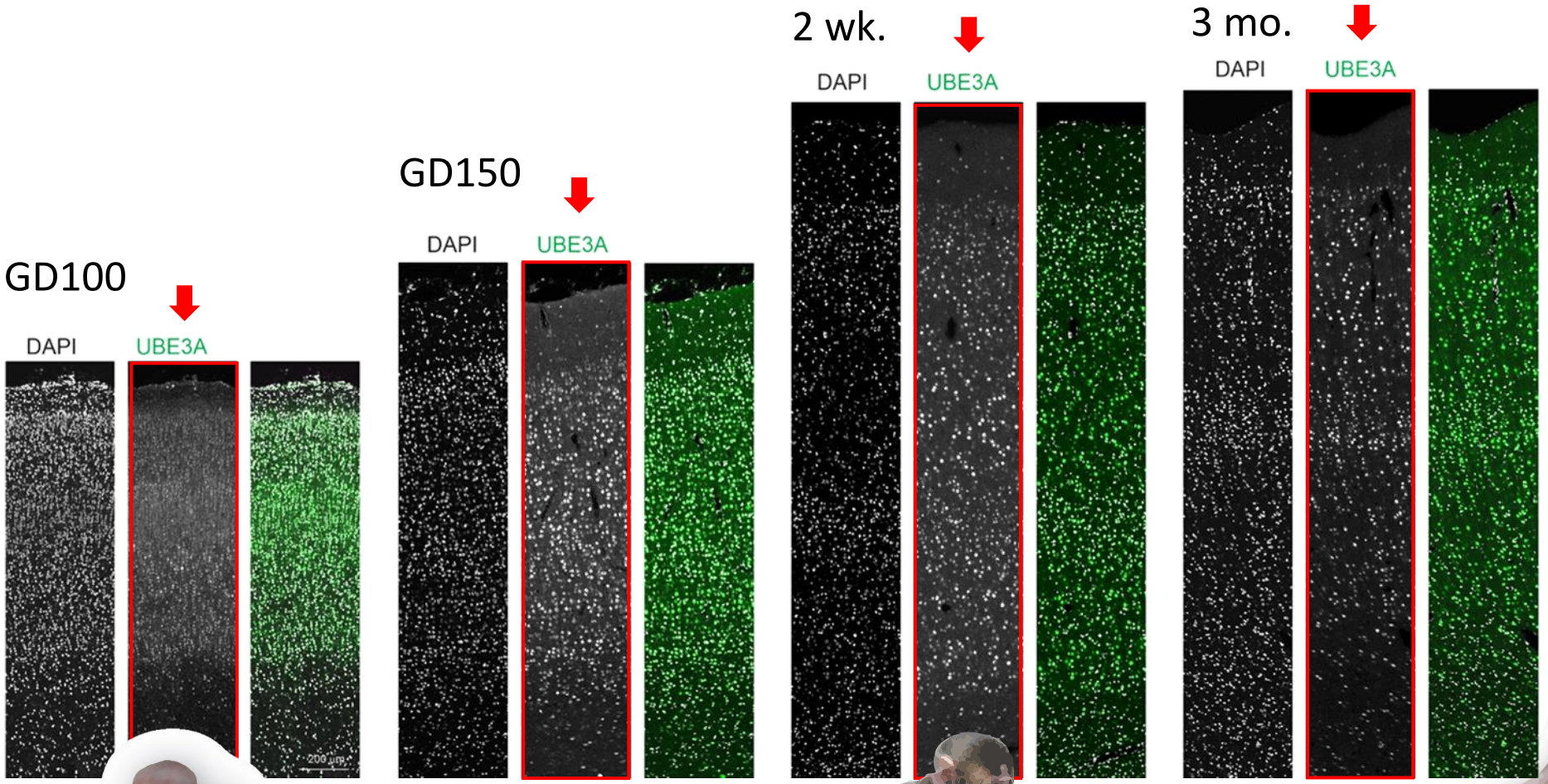


UBE3A is expressed in most, if not all, neurons

NHP, 2 wk.

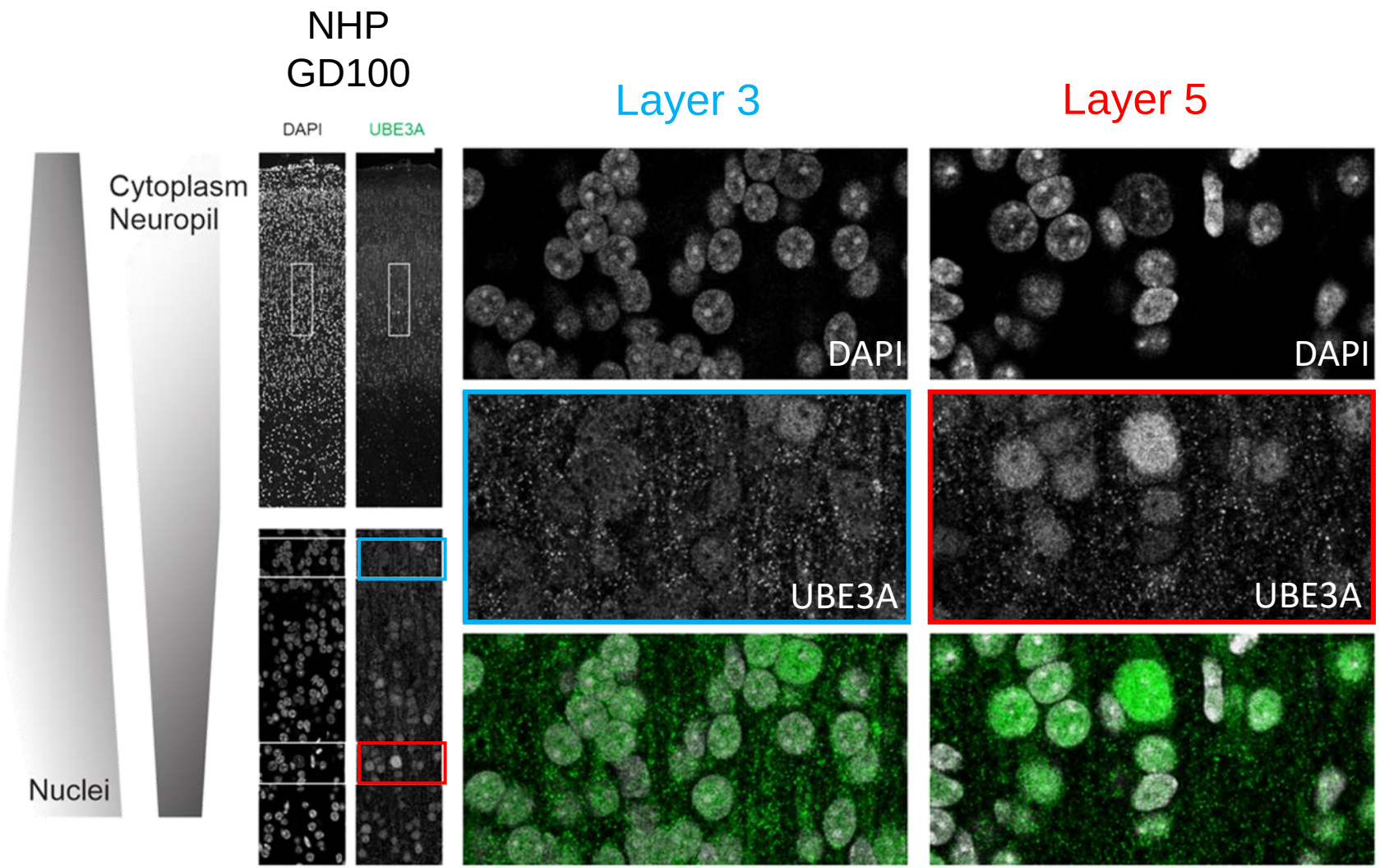
Alain Burette

AS target biology:
Developmental shift in UBE3A subcellular localization



Alain Burette

AS target biology:
Developmental shift in UBE3A subcellular localization



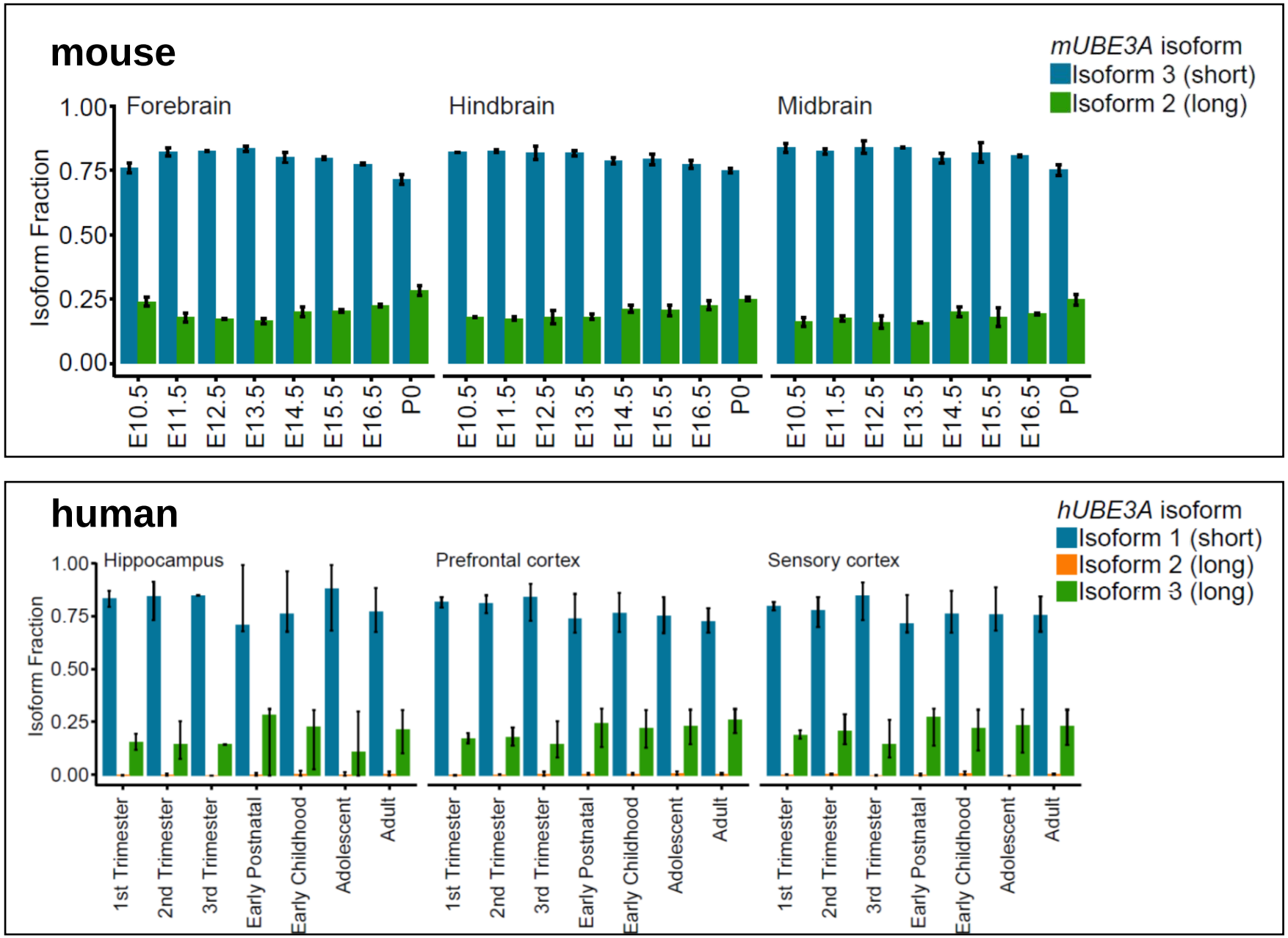
- UBE3A becomes increasingly nuclear as neurons mature
- This dynamic appears to be conserved from mouse to primates

Alain Burette

AS target biology: Three UBE3A isoforms exist

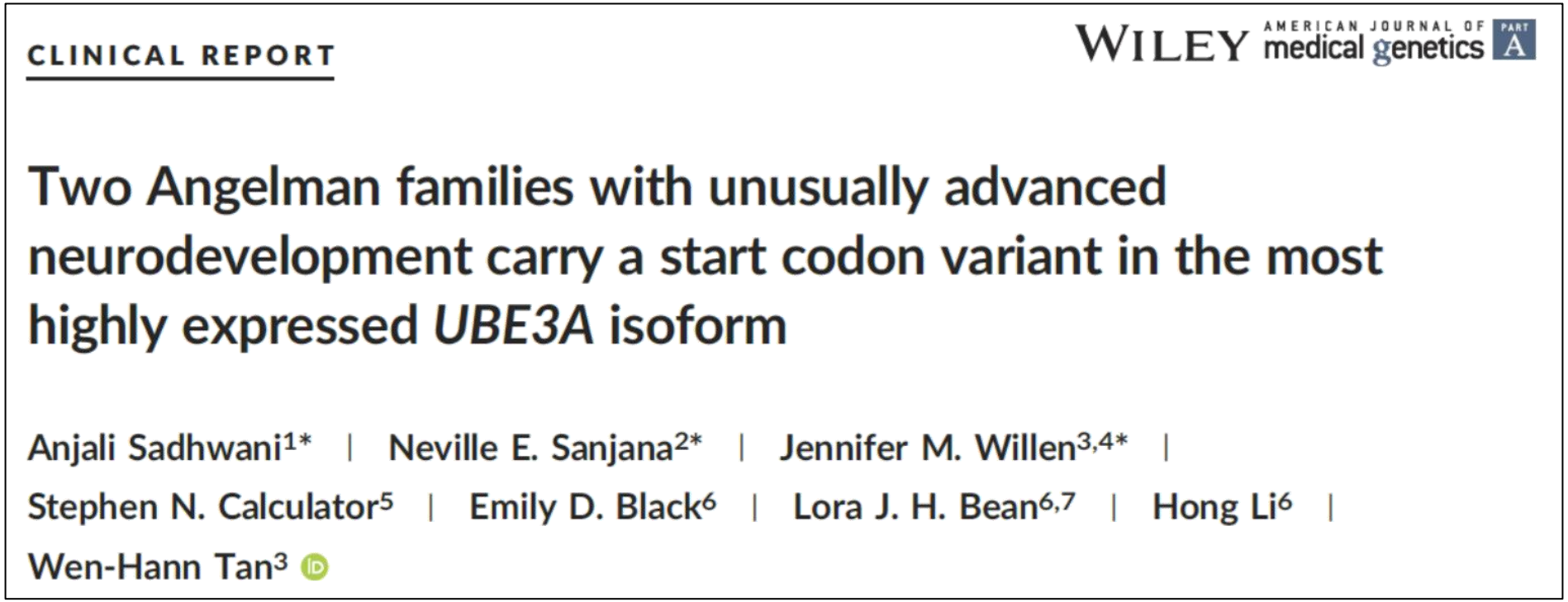
- Perfect conservation of short UBE3A during mammalian evolution
- Long UBE3A is also highly conserved
- Different N-termini can potentially mediate distinct cellular functions
  - **Subcellular localization**
    - Zampeta et al., 2020; Sirois et al., 2020
  - **Access to unique protein partners**
    - Martinez-Noel et al., 2012

Evolutionarily conserved expression of short and long UBE3A isoforms



- Human: ~4:1 short/long expression ratio, irrespective of brain region or developmental stage
- This ratio is highly conserved in mouse, suggesting its evolutionary importance
- Of the long hUBE3A isoforms, expression of human isoform 3 is predominant

Evidence for importance of both short and long UBE3A isoforms



CLINICAL REPORT

WILEY AMERICAN JOURNAL OF medical genetics PART A

Two Angelman families with unusually advanced neurodevelopment carry a start codon variant in the most highly expressed *UBE3A* isoform

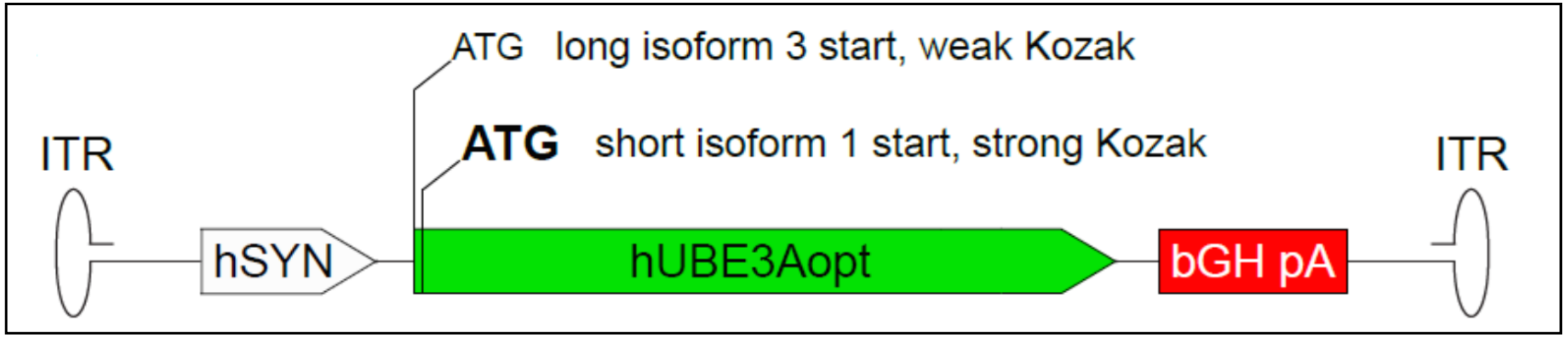
Anjali Sadhwani[1*] | Neville E. Sanjana[2*] | Jennifer M. Willen[3,4*] | Stephen N. Calculator[5] | Emily D. Black[6] | Lora J. H. Bean[6,7] | Hong Li[6] | Wen-Hann Tan[3]

- AS patients with residual expression of long hUBE3A present with a less severe form of the disorder — another clue that these isoforms may play important developmental roles

Goal: Develop an AAV vector for on-target UBE3A reinstatement in Angelman syndrome

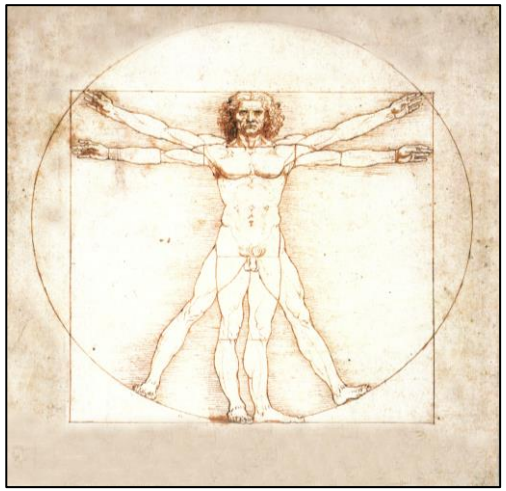
- Broad distribution in **neurons**
- **Both short and long isoforms** expressed
- Express isoforms at **endogenous ratio** of short:long
- Recapitulate **endogenous subcellular localization**
- Ability to **trace** virally-expressed *UBE3A* transgene to assist preclinical studies

hUBE3Aopt vector for dual-isoform UBE3A expression

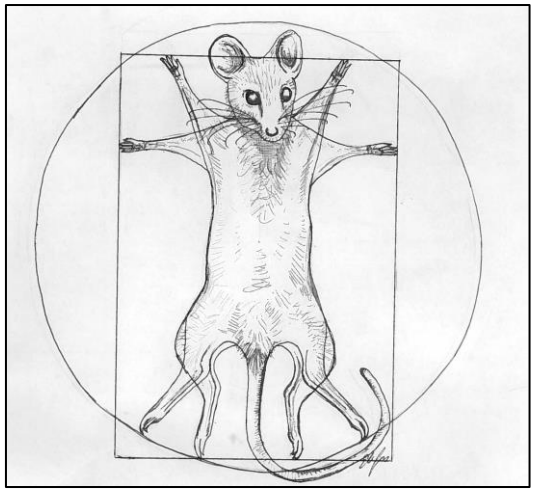


- Human synapsin promoter
  - Target re-expression of UBE3A to neurons
  - Reduce peripheral toxicity
- Codon optimization
  - Facilitate tracing in recipient tissues
- Package in AAV9/PHP.B capsids
  - Robust, widespread delivery to the brain
- ICV delivery
  - Early onset of expression
  - Maximum opportunity for therapeutic benefit
  - Robust test of toxicity

Angelman syndrome model mice provide a preclinical platform to assess viral vector design



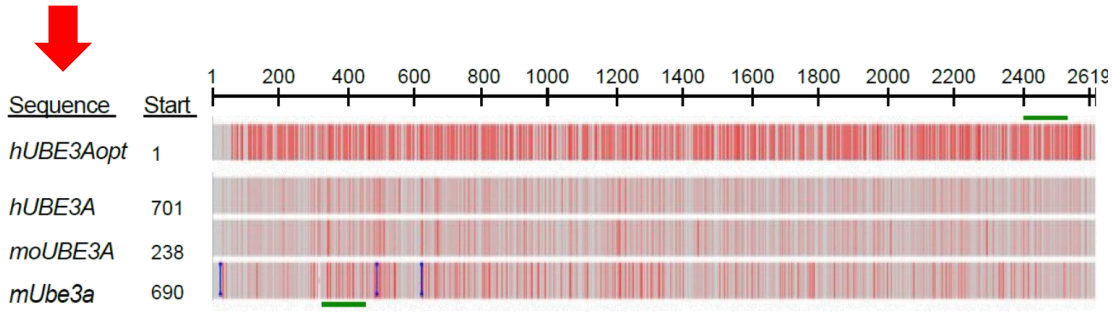
- Caused by mutation of maternal *UBE3A*
- Severe cognitive impairments; paucity of speech
- Ataxia
- Epilepsy (~90% penetrance)
- Enhanced EEG delta-wave activity
- Highly penetrant microcephaly (80-90% of cases)



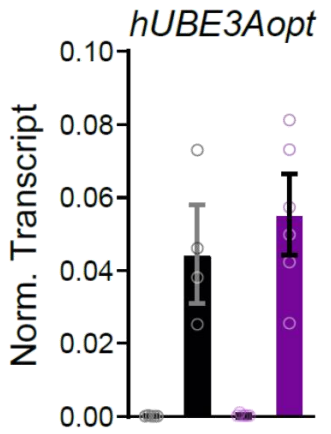
- Targeted disruption of maternal *Ube3a*
- Learning and memory impairments
- Ataxia
- Increased seizure susceptibility
- Enhanced EEG delta-wave activity
- Reduced brain weight (microcephaly)

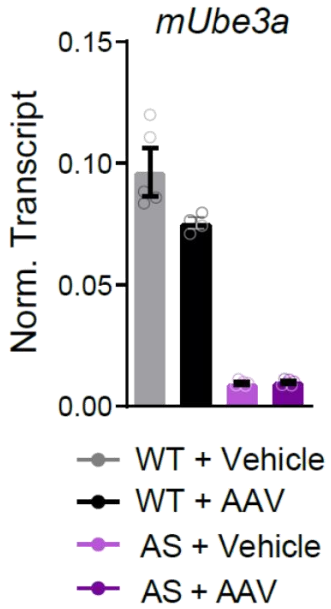
Codon optimization: Efficient hUBE3Aopt payload tracing

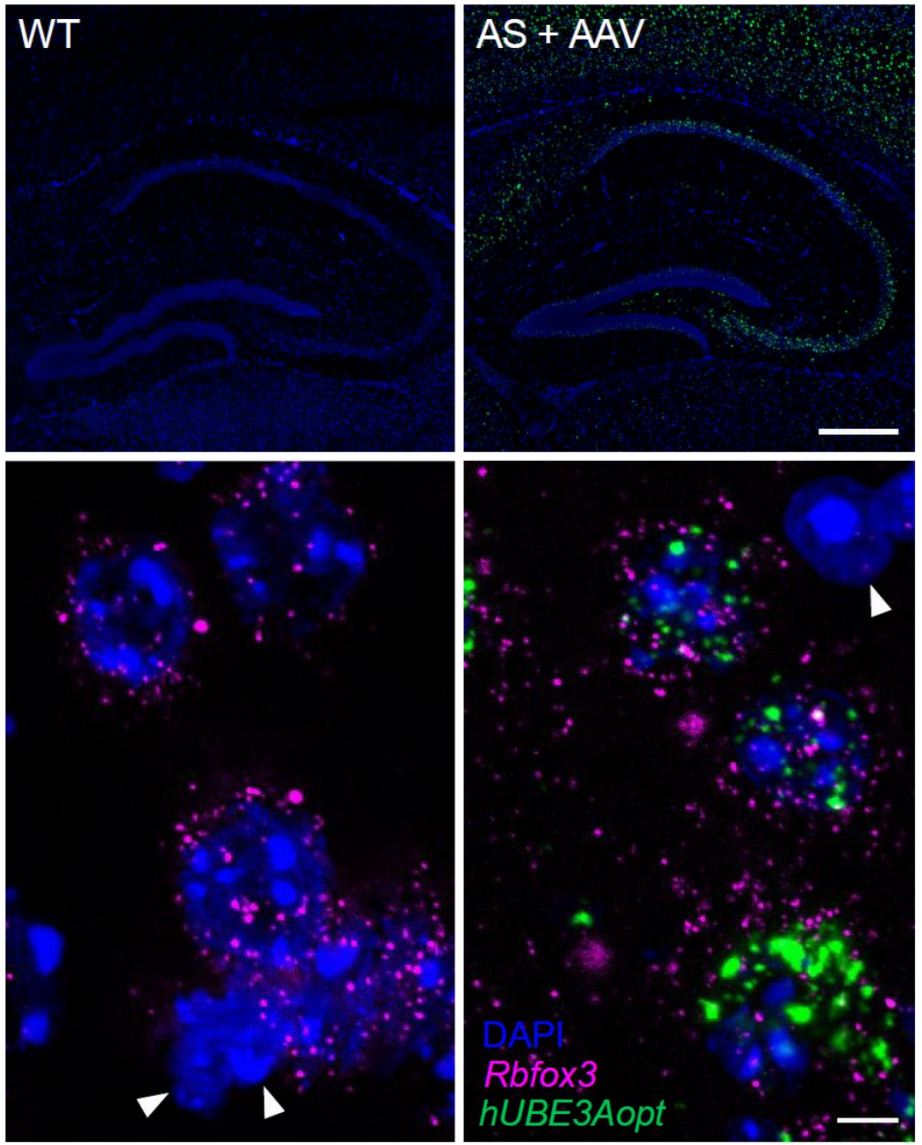
MSA: red signals divergent sequence in hUBE3Aopt



- Human (*hUBE3A*), NHP (*moUBE3A*), and mouse (*mUbe3a*) transcripts
- Darker shades of red indicate greater sequence divergence
- Green lines overlay *hUBE3Aopt* and *mUbe3a* amplicons in ddPCR assays

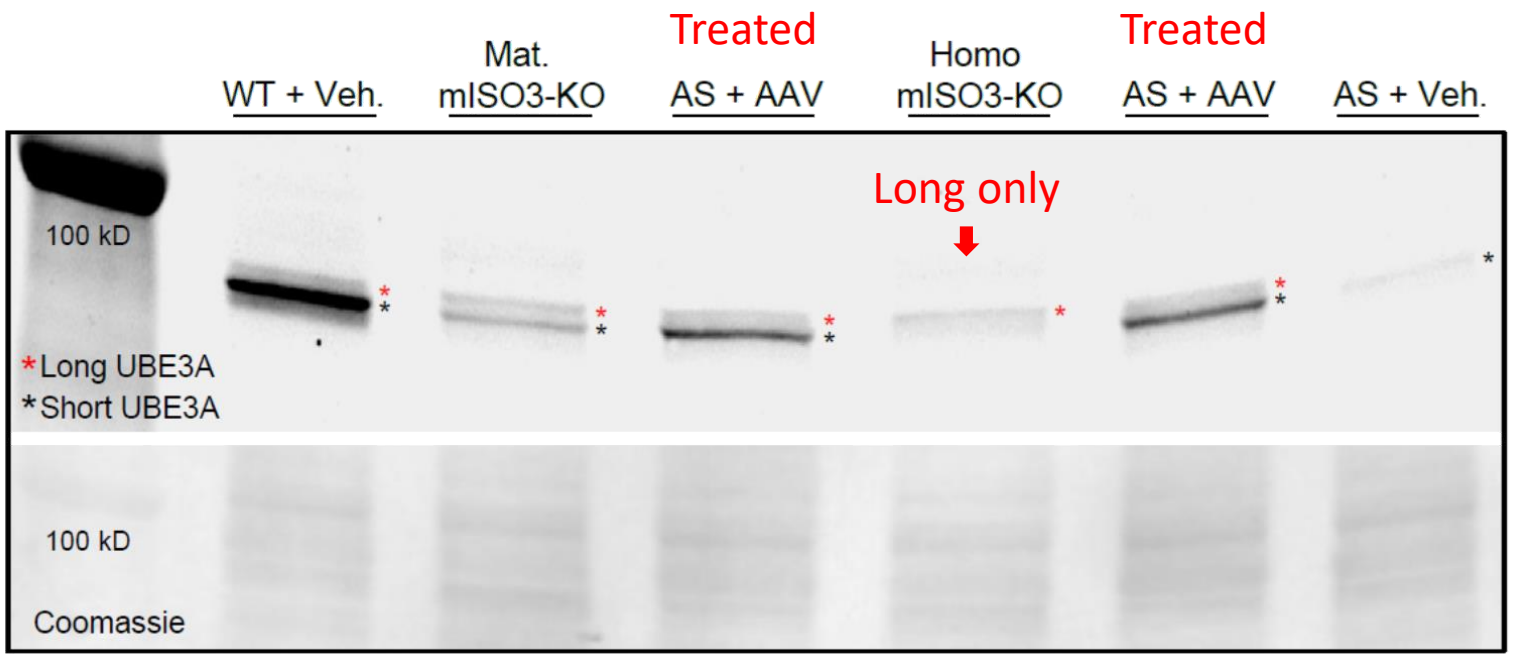




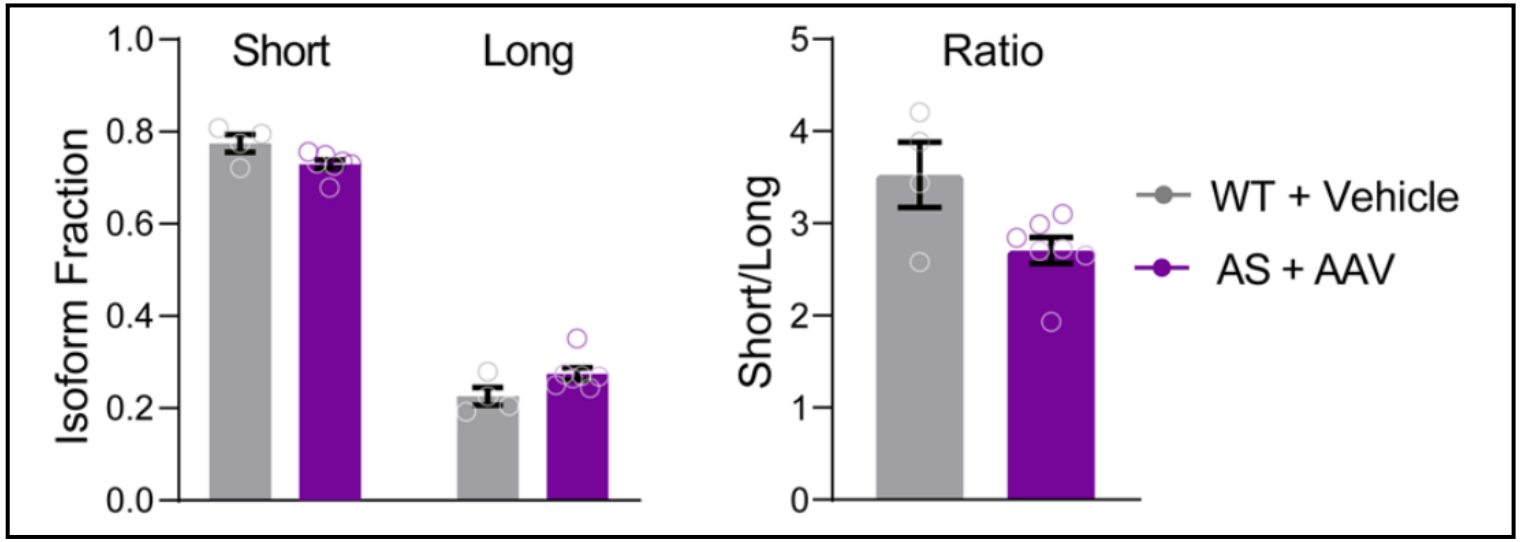


Arrowheads indicate nuclei of putative glia

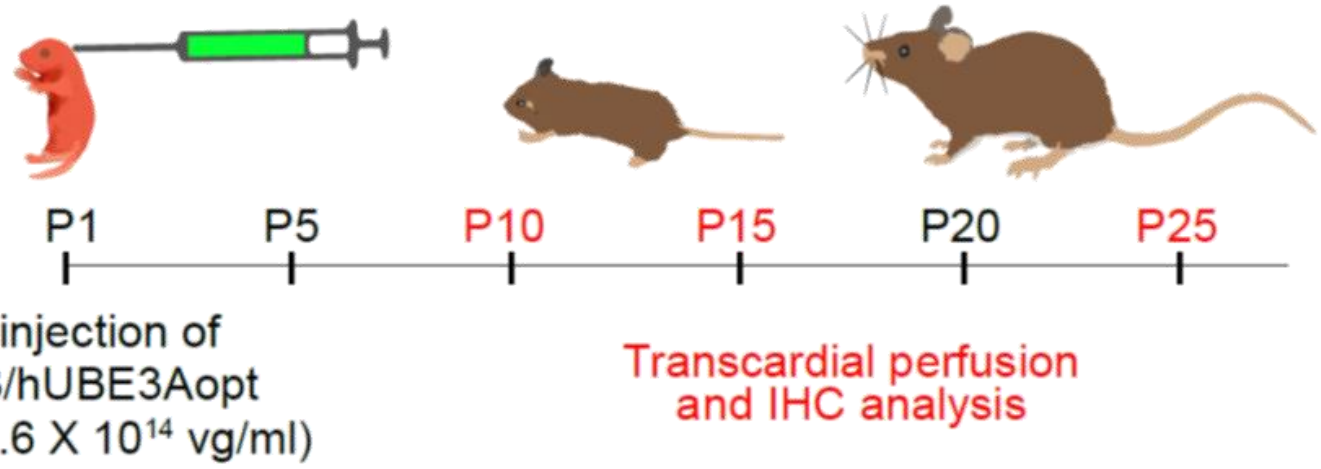
Recapitulation of endogenous short:long UBE3A isoform ratios

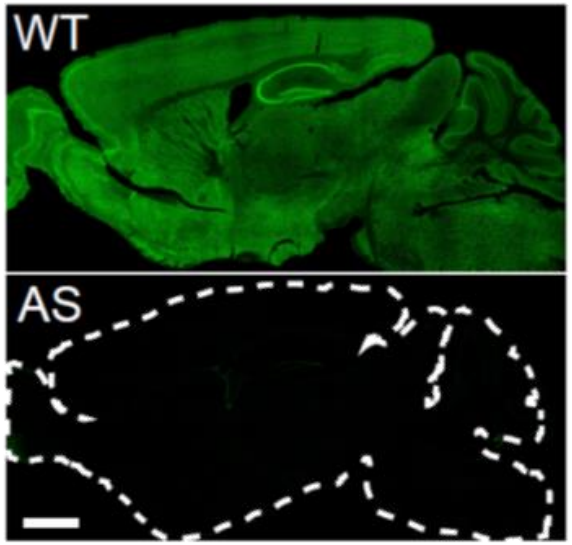


AS + AAV mice were administered 1 μL of 1.6×10^{14} vg/mL PHP.B/hUBE3Aopt as neonates. Homozygous mISO3-KO mice completely lack expression of short UBE3A, while mice with a maternally inherited deletion of isoform 3 (mat. ISO3-KO) lack neuronal expression of short UBE3A.

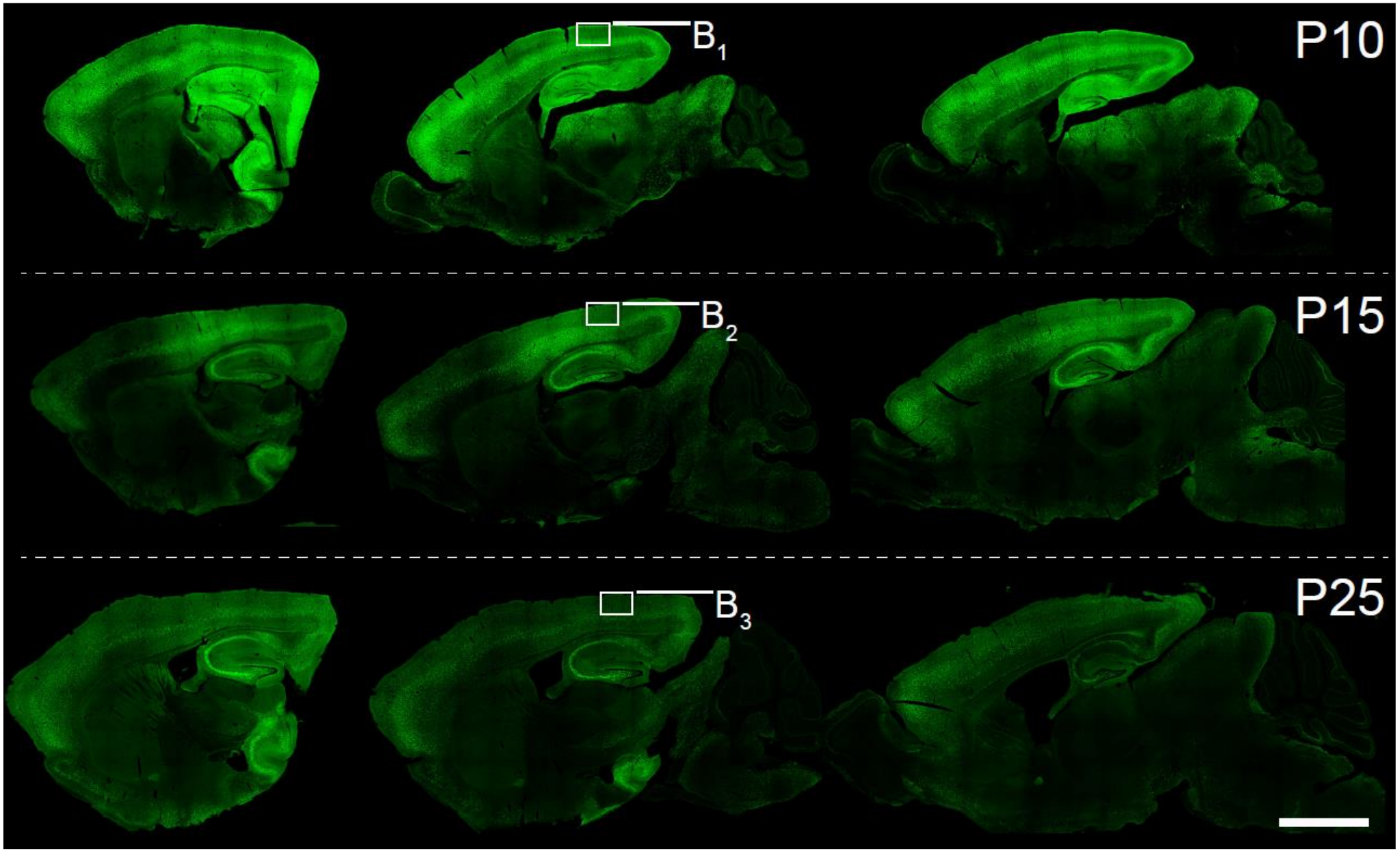


Tracing the biodistribution of UBE3A re-expression

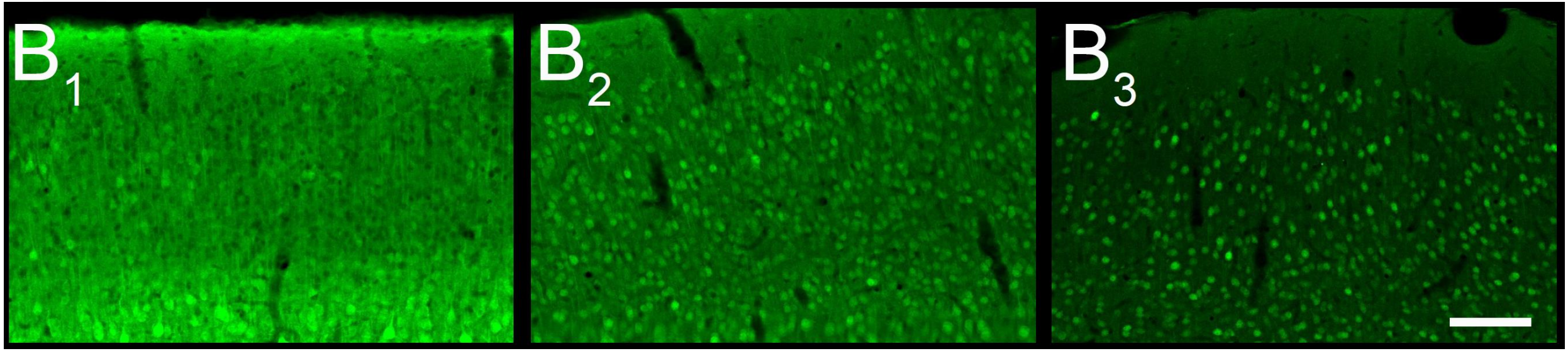




Fast onset and widespread viral transduction



Gene therapy recapitulates developmentally dynamic localization of UBE3A



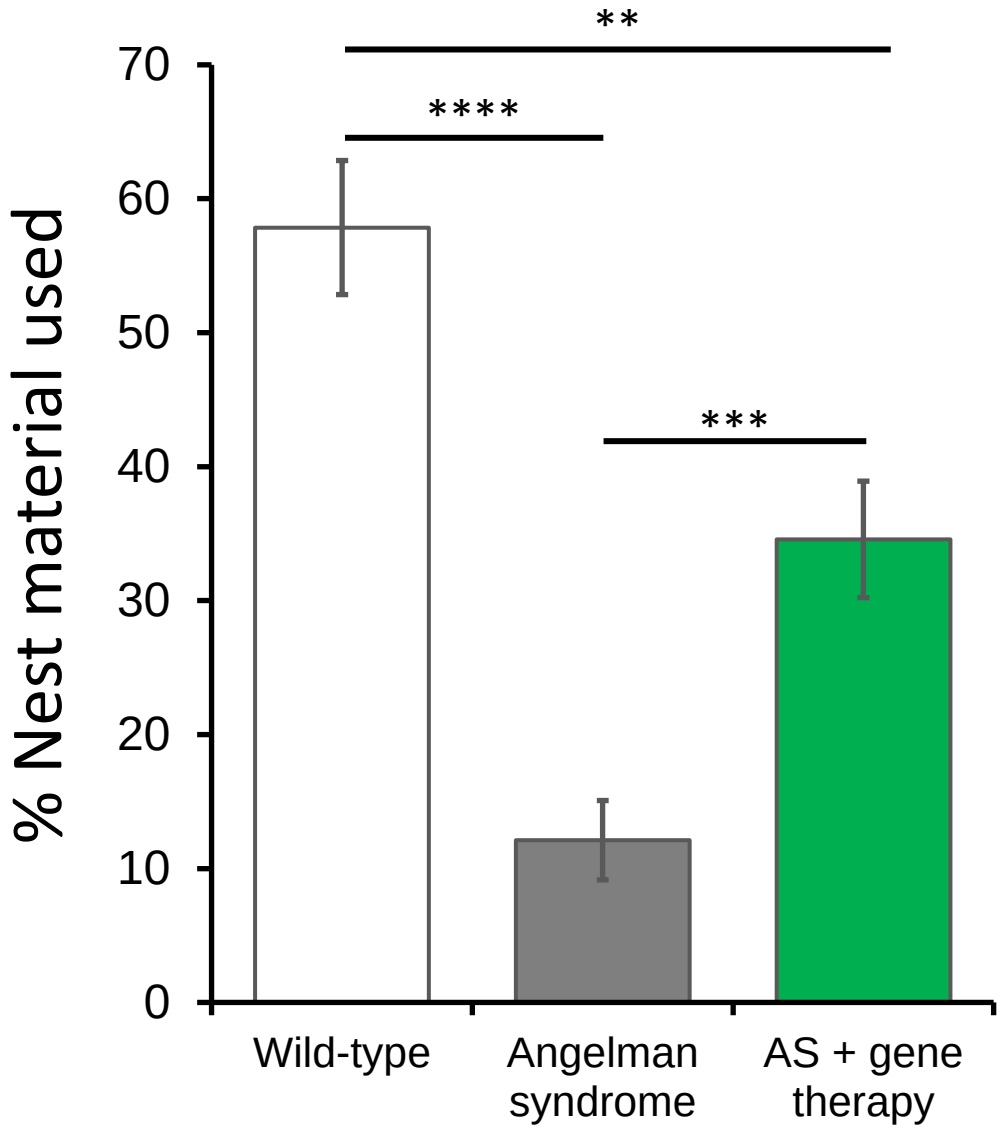
Experiments performed by Dr. Matt Judson

Preclinical efficacy in AS model mice

UBE3A gene transfer rescues species-appropriate behaviors: nest building

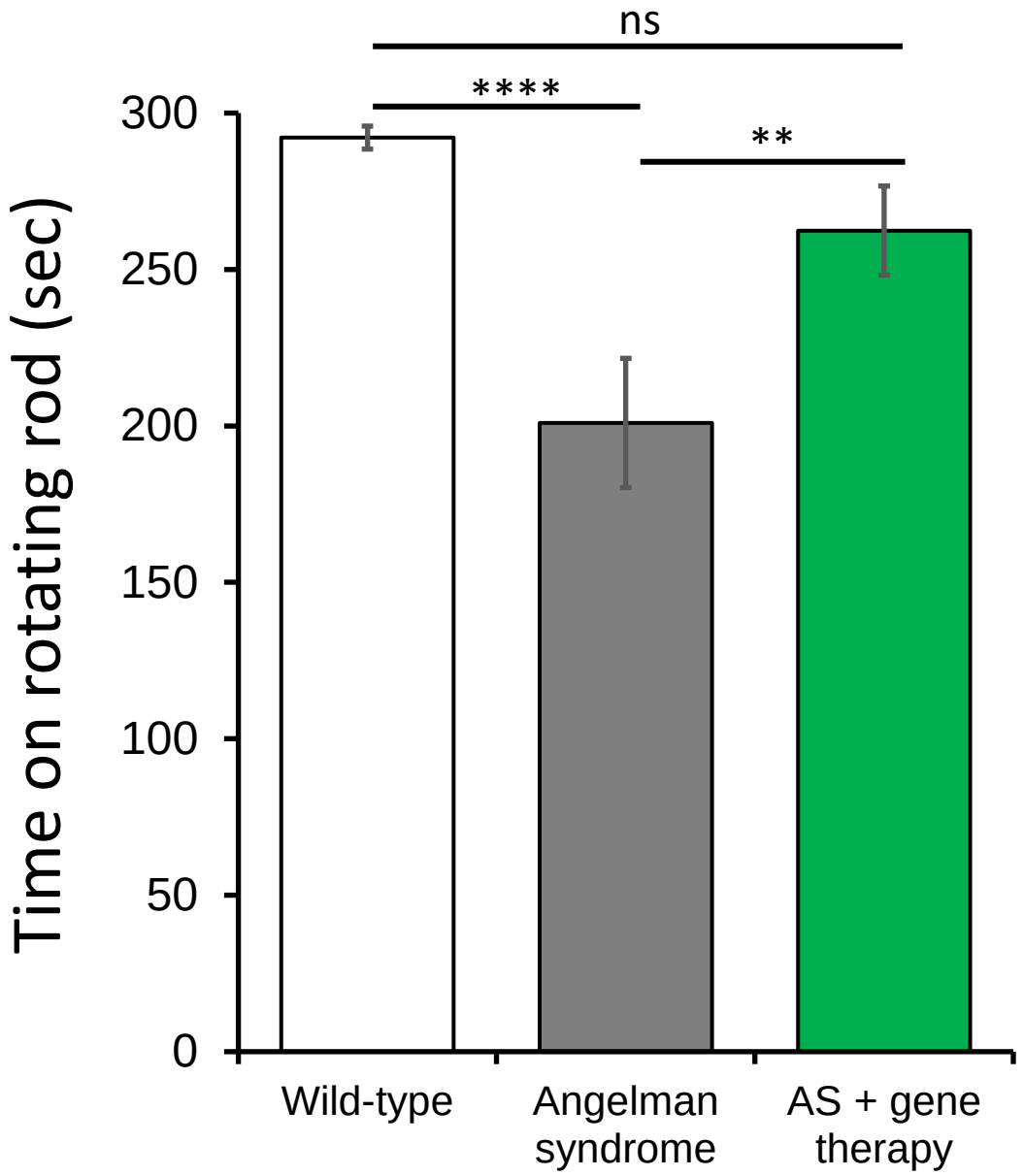
Little nest material used

Most nest material used



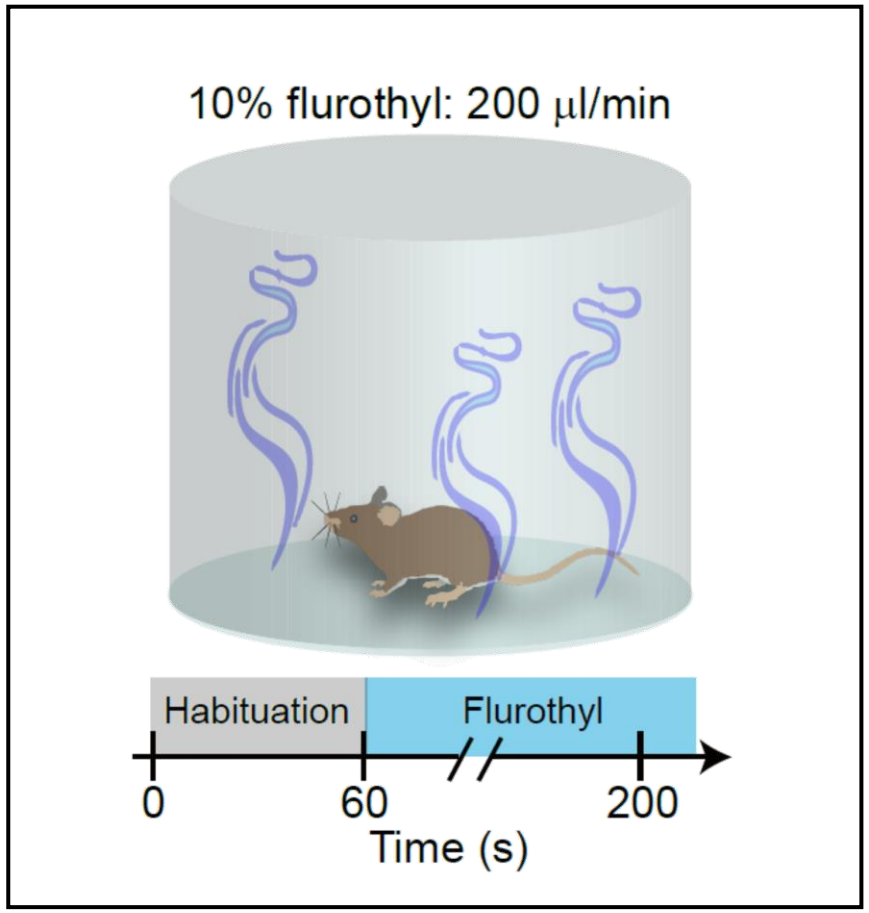
Experiments performed by Dr. Matt Judson

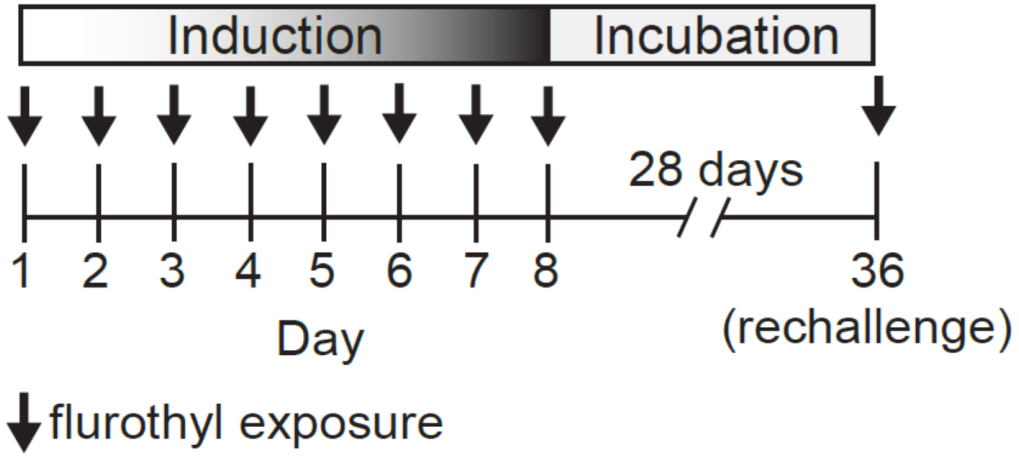
UBE3A gene transfer rescues motor performance



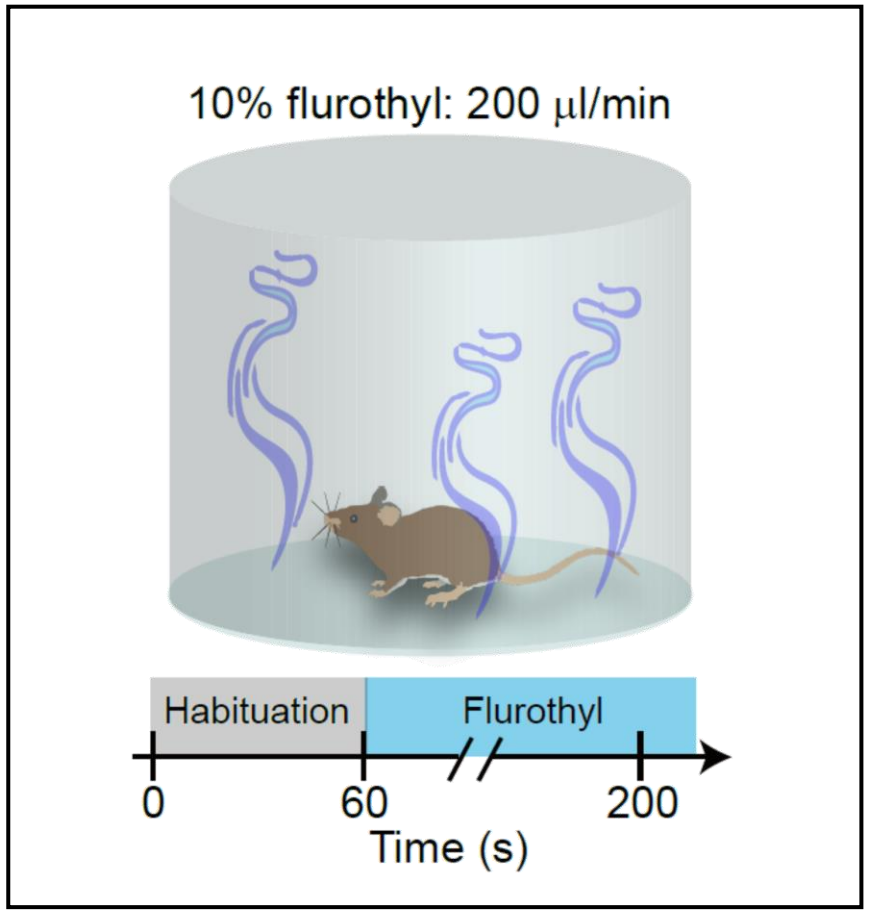
Experiments performed by Dr. Matt Judson

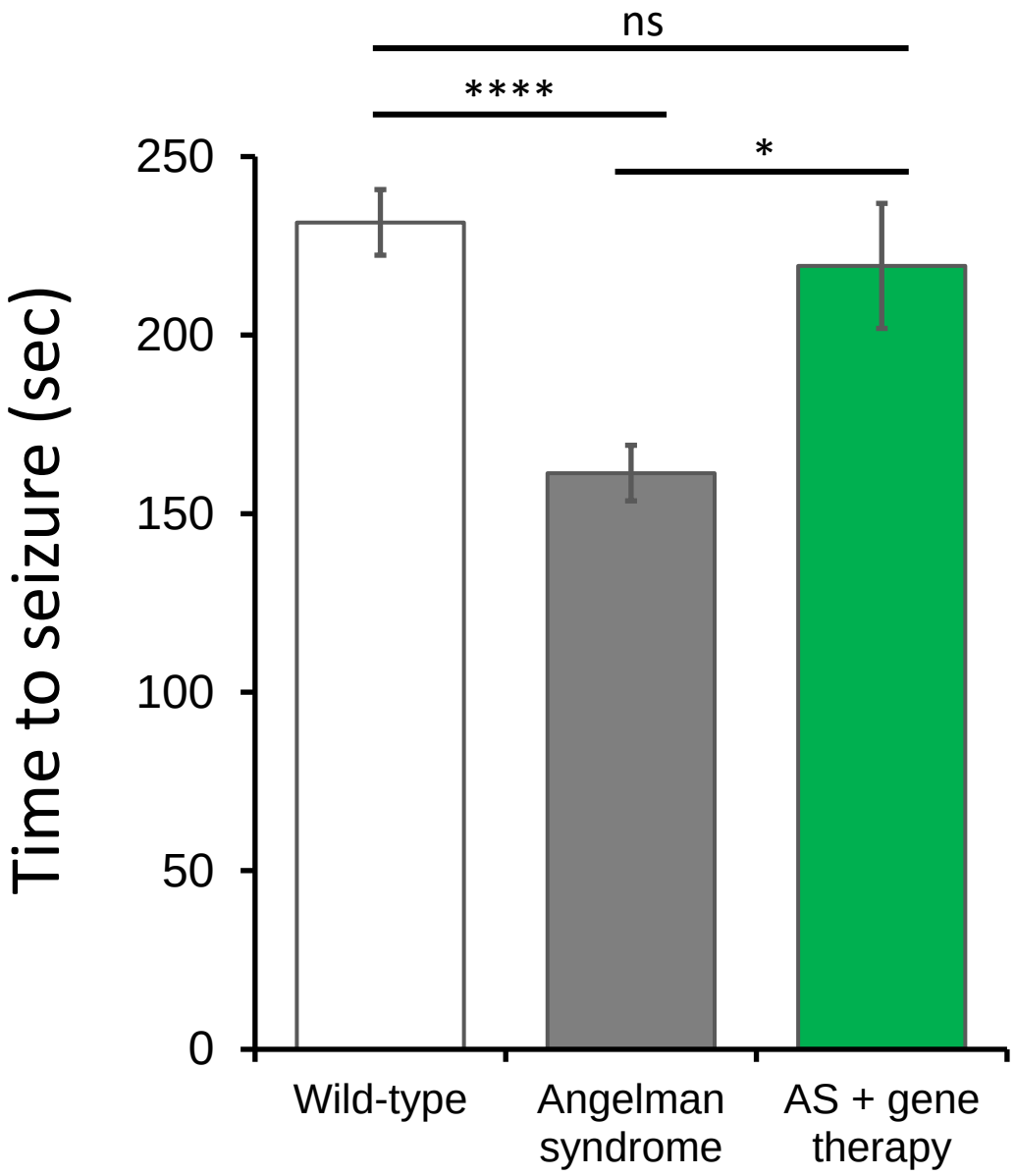
Rescue of seizure phenotypes: Kindling-induced epileptogenesis





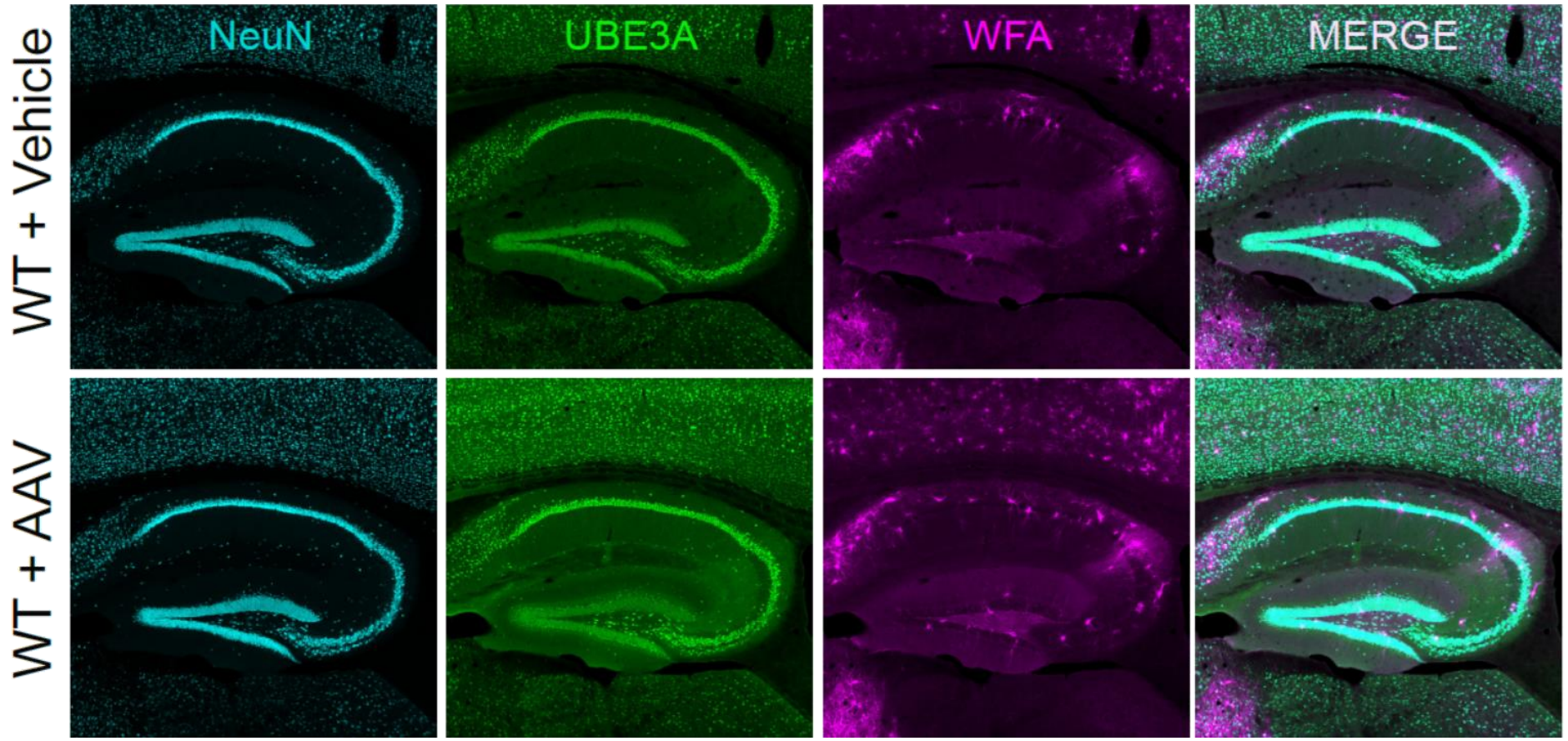
UBE3A gene transfer rescues seizure phenotypes



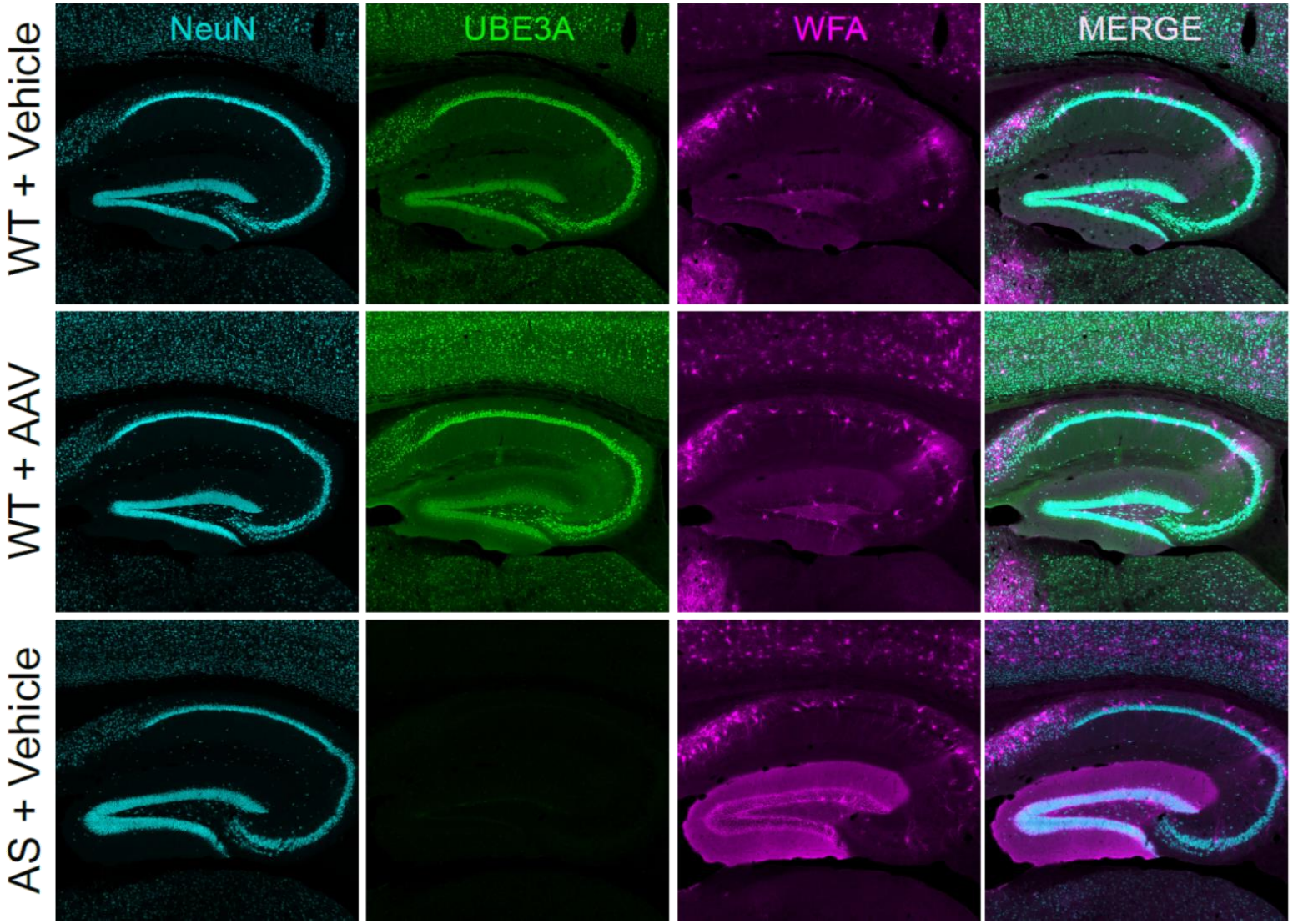


Experiments performed by Dr. Matt Judson

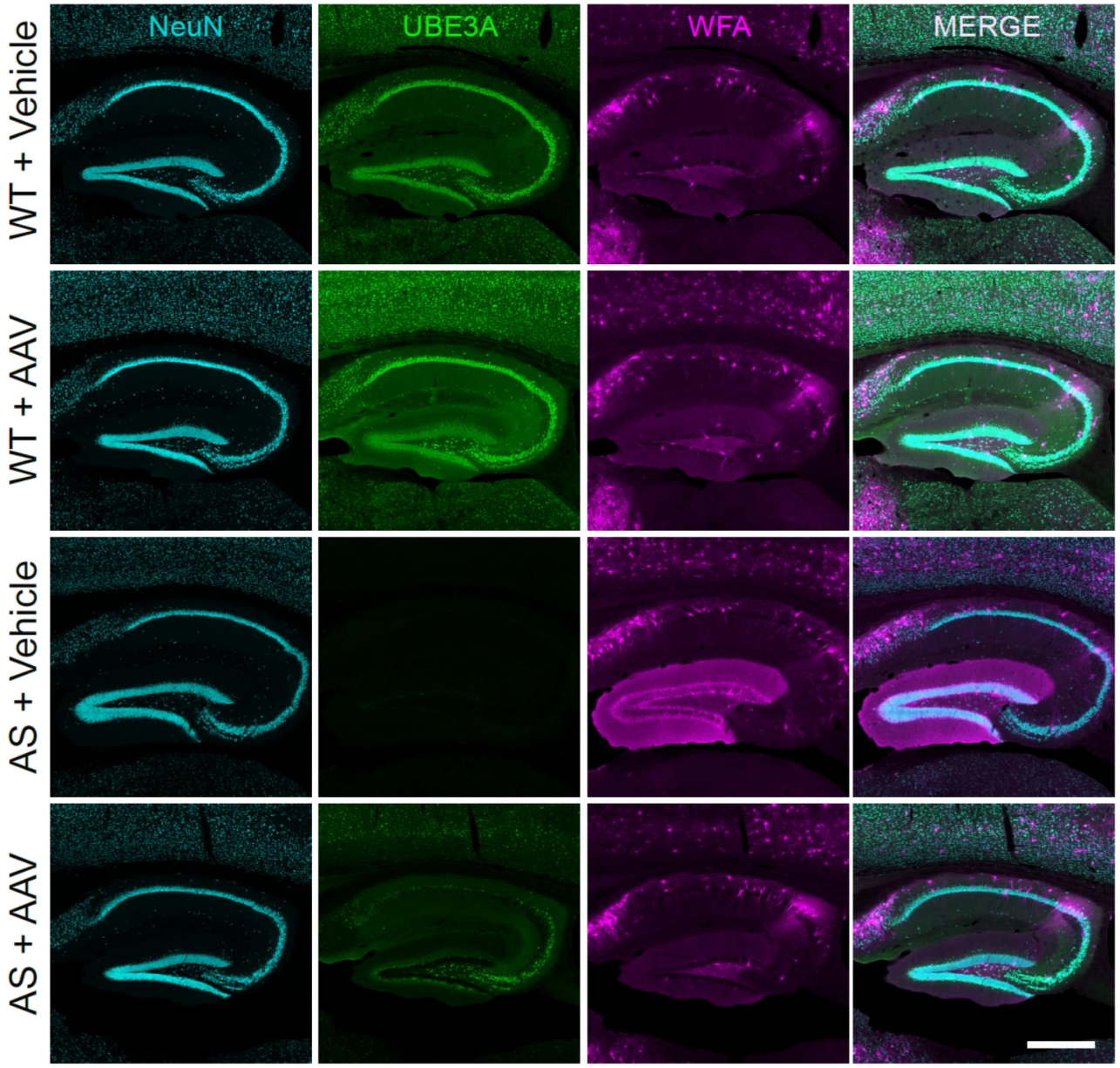
Normalization of kindling-induced histopathology: WFA



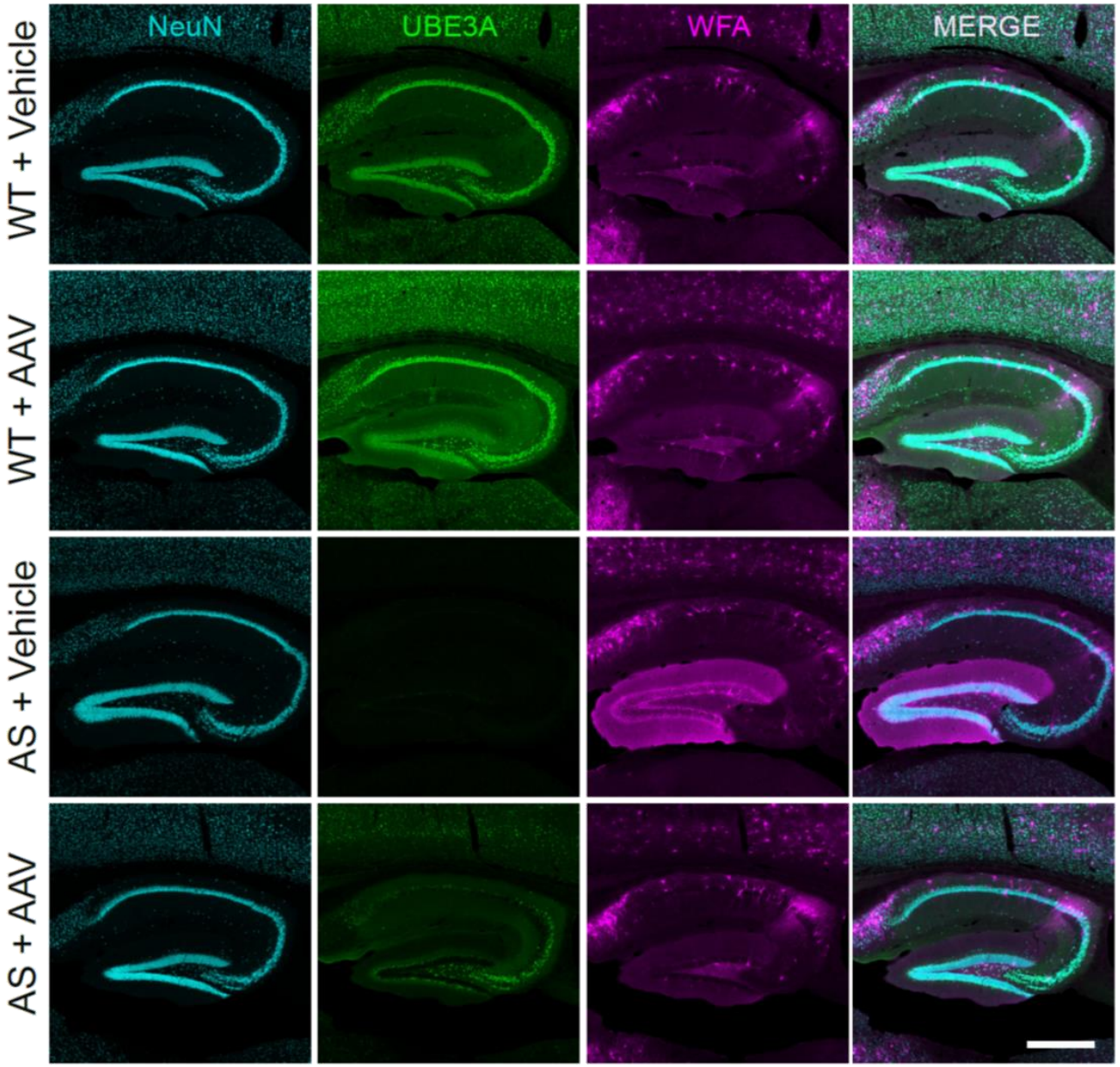
Normalization of kindling-induced histopathology: WFA

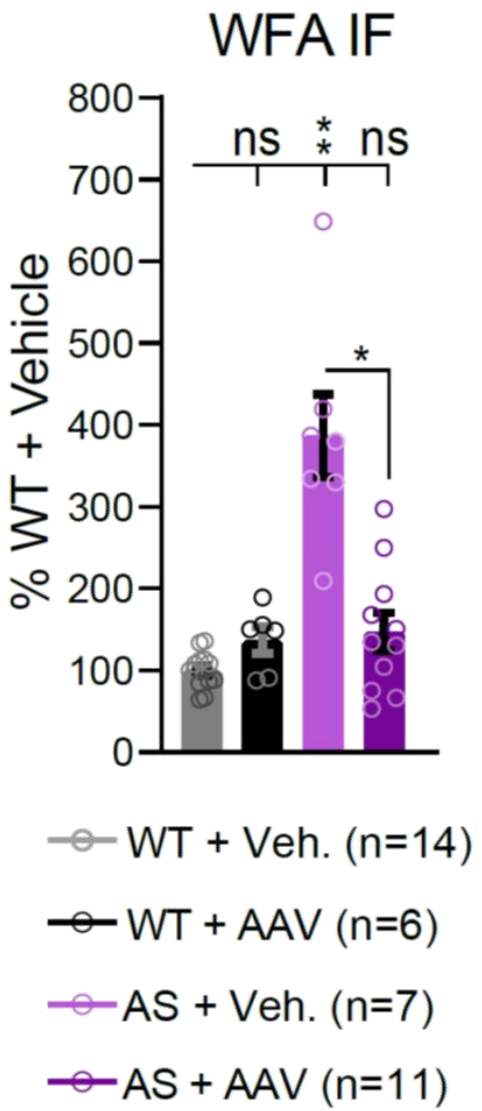


Normalization of kindling-induced histopathology: WFA



Normalization of kindling-induced histopathology: WFA



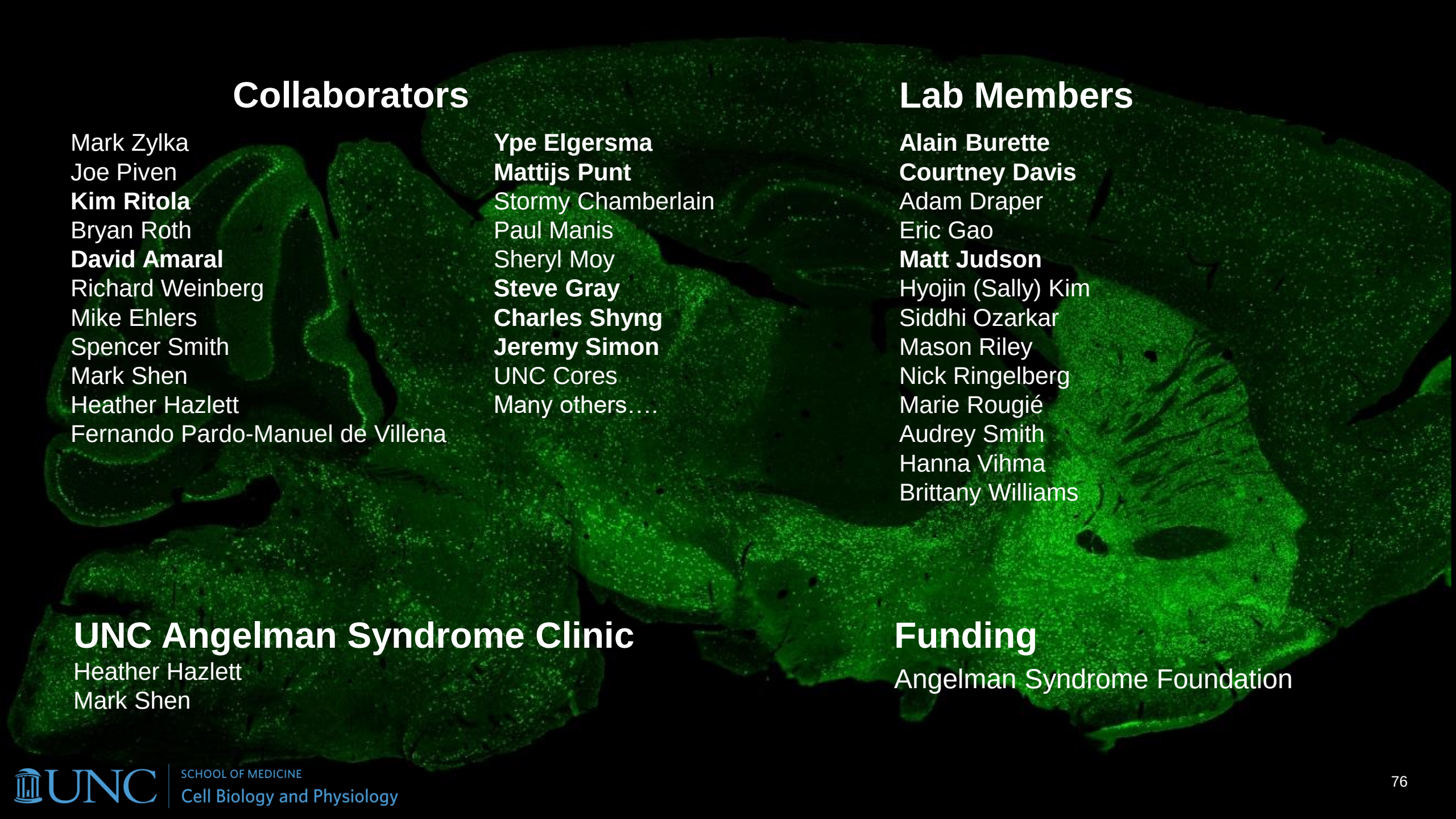


Conclusions:

- hUBE3Aopt recapitulates:
    - Endogenous UBE3A isoform expression
    - UBE3A subcellular expression
- hUBE3Aopt recovers anatomical and behavioral phenotypes
- Proof-of-concept that a UBE3A gene addition therapy could provide a treatment for Angelman syndrome

Caution:

- Additional preclinical optimization, safety, and efficacy studies are needed



Collaborators

Mark Zylka
Joe Piven
Kim Ritola
Bryan Roth
David Amaral
Richard Weinberg
Mike Ehlers
Spencer Smith
Mark Shen
Heather Hazlett
Fernando Pardo-Manuel de Villena

Ype Elgersma
Mattijs Punt
Stormy Chamberlain
Paul Manis
Sheryl Moy
Steve Gray
Charles Shyng
Jeremy Simon
UNC Cores
Many others….

Lab Members

Alain Burette
Courtney Davis
Adam Draper
Eric Gao
Matt Judson
Hyojin (Sally) Kim
Siddhi Ozarkar
Mason Riley
Nick Ringelberg
Marie Rougié
Audrey Smith
Hanna Vihma
Brittany Williams

UNC Angelman Syndrome Clinic

Heather Hazlett
Mark Shen

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Angelman Syndrome Foundation

Q & A

RNAi Gene Therapy for Angelman Syndrome

Ryan Butler, PhD

Assistant Professor, Department of Psychiatry and Pediatrics at UTSW

Disclosures

- I have a personal financial interest in Taysha through licensing and revenue sharing
- UTSW maintains a financial interest in Taysha due to Taysha's exclusive licensure of technology developed at UTSW
- Taysha has a sponsored research agreement for this research
- I am not being paid for this presentation

Contents

- Genetics of Angelman syndrome
- Strategy for AAV gene therapy
- Experimental plan and data

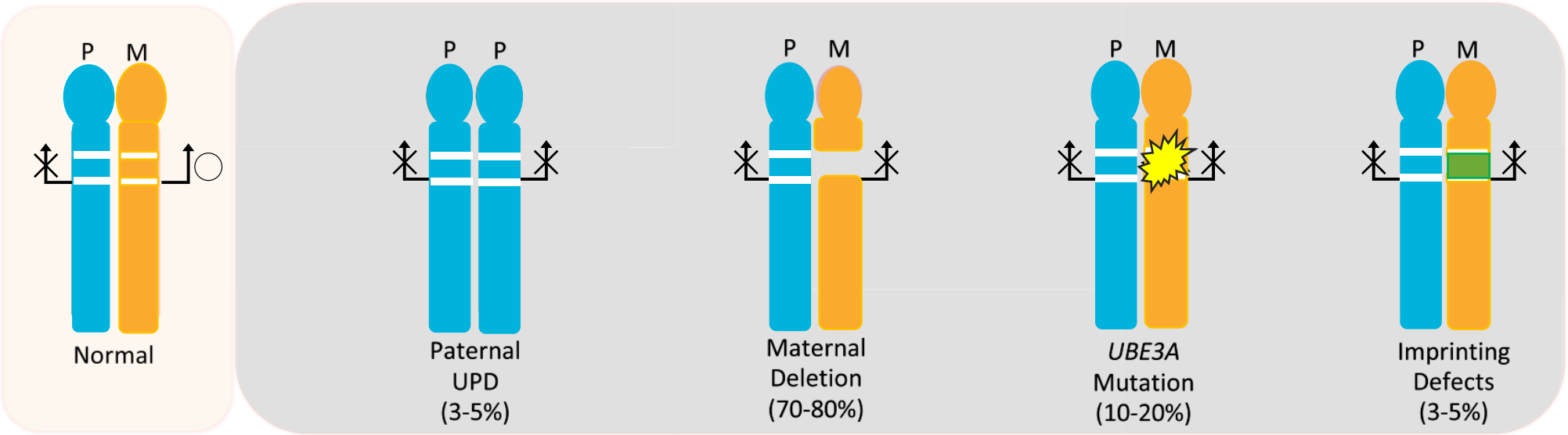
Current treatment for Angelman syndrome

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 help 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

Genetics of Angelman Syndrome

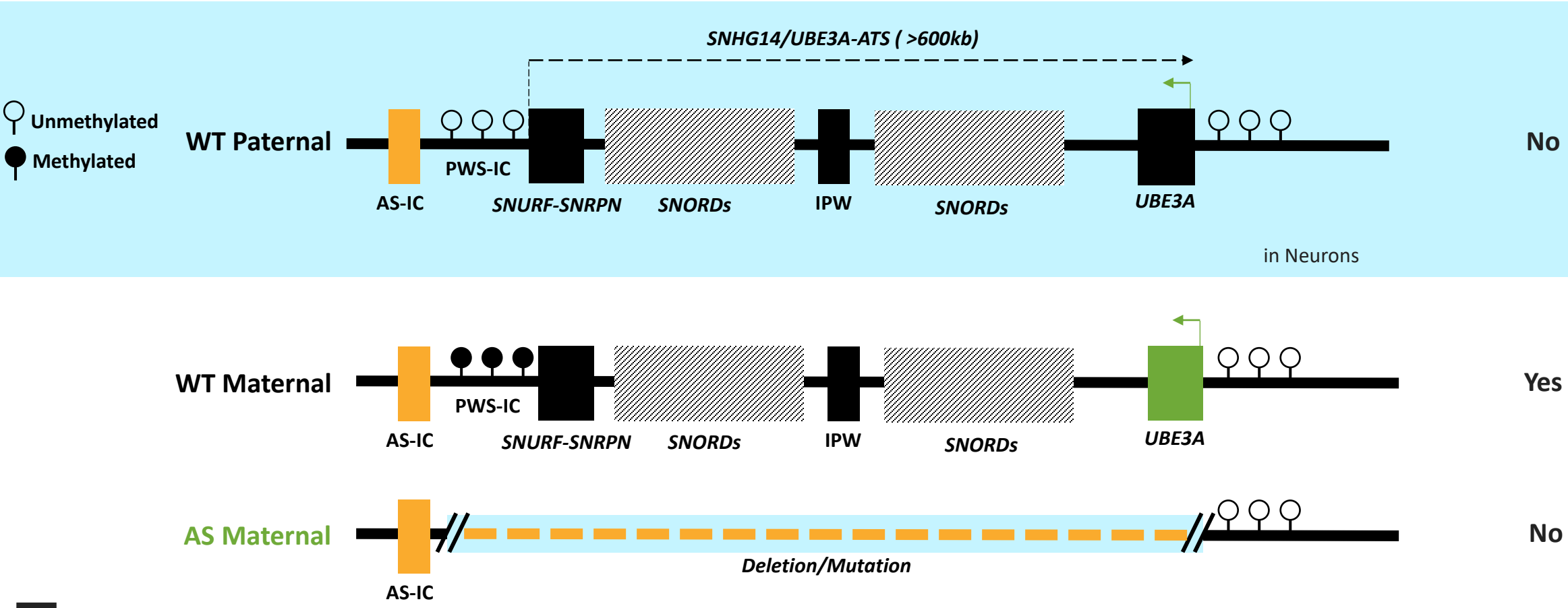


In neurons, the **maternally inherited UBE3A allele is the only active allele**, since the **paternally inherited UBE3A allele is silenced through cell type–specific imprinting**

Maranga et al/Frontier in FEBS/2020

UBE3A-ATS/Ube3a-ATS (Anti-sense)

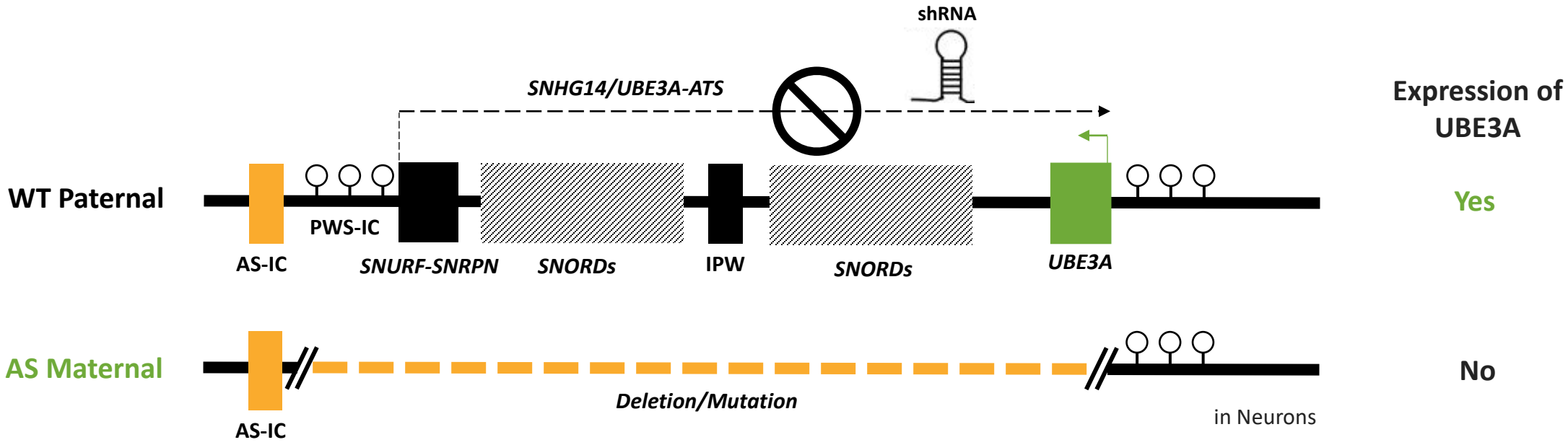
- Antisense DNA strand that is transcribed as part of a larger transcript called LNCAT (large non-coding antisense transcript) at the UBE3A locus



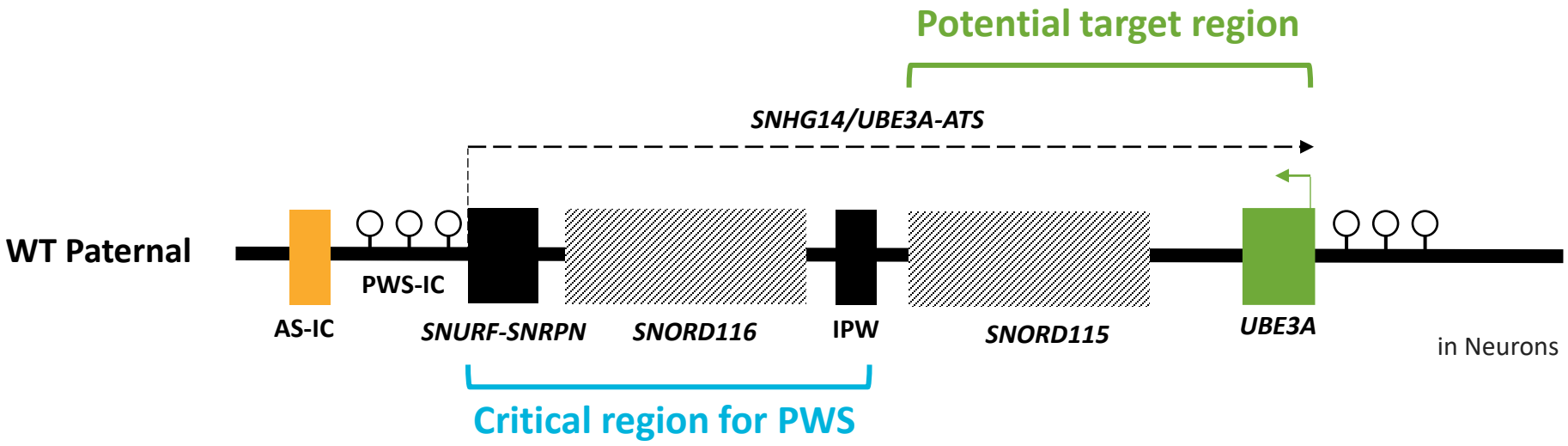
PSW/AS: Prader-Willi syndrome/Angelman syndrome, **IC:** Imprinting control center, **IPW:** Imprinted in Prader–Willi, **SNORDs:** C/D-box snoRNAs

Strategy for the treatment of Angelman syndrome

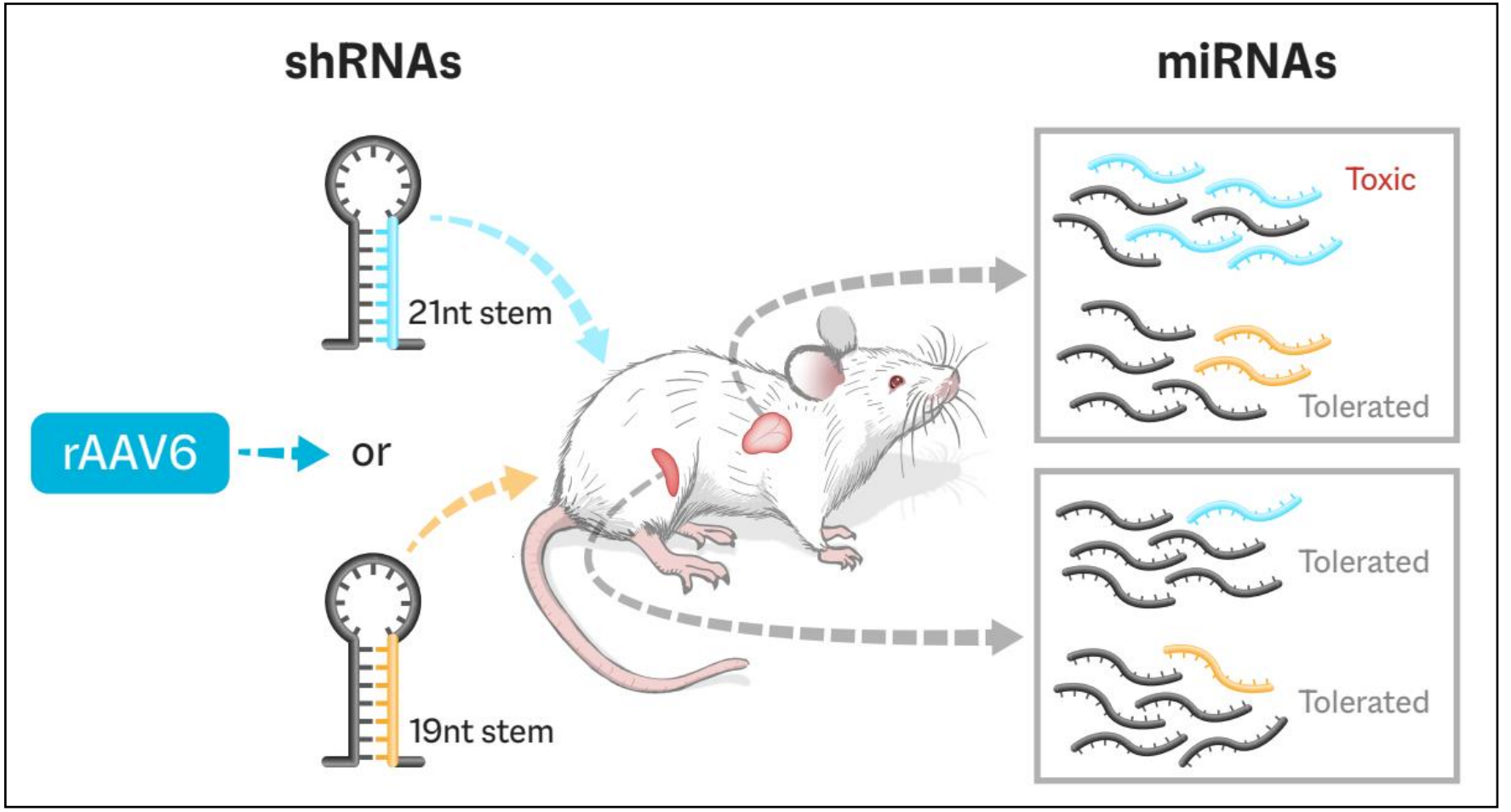
Reinstate the paternal allele by targeting *UBE3A*-ATS with short hairpin RNA (shRNA)



Target region on UBE3A-ATS

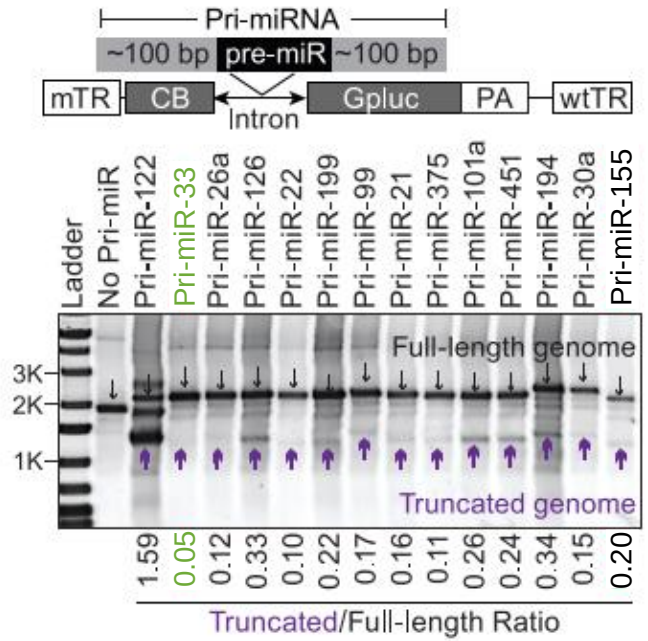


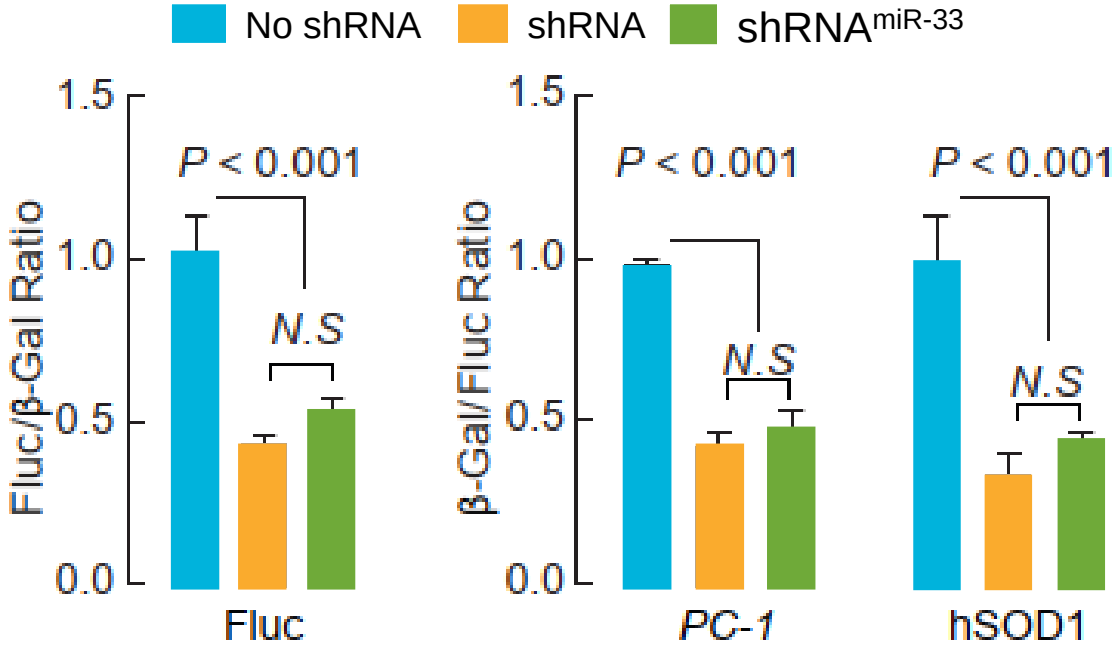
Endogenous microRNA competition as a mechanism of shRNA-induced cardiotoxicity

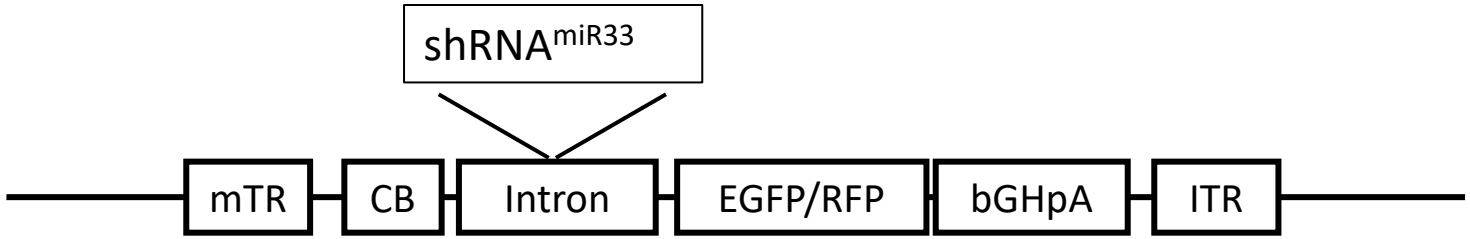


Course et al. 2020

Effective and accurate gene silencing by a recombinant AAV-compatible microRNA scaffold







Process of finding candidates to target *UBE3A-ATS*

STEP I: Screen human AS shRNA candidates
(BROAD Institute GPP Web Portal https://portals.broadinstitute.org/gpp/public/seq/search)

↓

STEP II: Check off-targets of STEP I candidates in human background
(siRNA Sequence Probability-of-Off-Targeting Reduction siSPOTR (uiowa.edu)

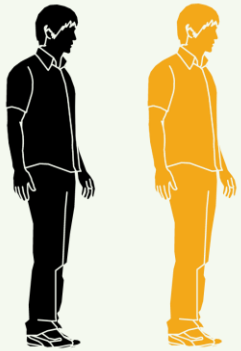
↓

STEP III: Check off-targets of STEP II candidates in monkey background
(using NCBI BLAST function/ Blast 21nt target sequence in Rhesus macaque mRNA_ NCBI Blast n and Look at the match with seed sequence region)

Although the guide strand is usually designed to specifically target one mRNA sequence through perfect complementarity, it will also recognize additional mRNA transcripts through **partial base pairing** and **repress gene expression via the miRNA-like pathway.** As miRNA-like repression only requires the base pairing of as few as **6 nt in position 2–7 (seed region) of guide strand**, it is nearly impossible to eliminate the miRNA-like off-targeting completely.
Xavier Bofill-De Ros/Methods/2016

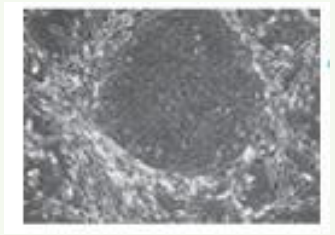
AS human and mouse experiment models

Human model



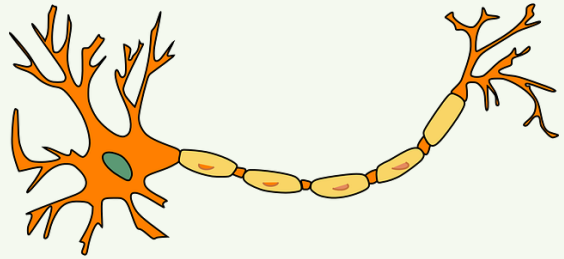
Primary Cells
from healthy donor
and AS donor

Reprogramming



Induced Pluripotent Stem Cell (iPSC)

Differentiation



Healthy/AS iPSC derived neurons

Mouse model

Ube3a $^{+/+}$

Ube3a $^{+/-}$ (m)

Maternal UBE3A deficiency
(AS phenotype)

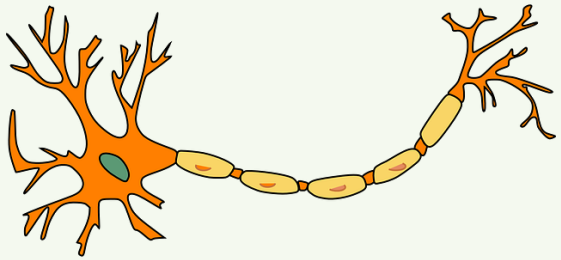
Ube3a $^{+/p\text{-}YFP}$

Paternal UBE3A-YFP
(siRNA/shRNA screening)

In vitro : Primary neurons
In vivo : Direct injection

AS human and mouse experiment models

Human model



Healthy/AS iPSC derived neurons

Test shRNA/siRNA/AAV-shRNA

- Check the expression of paternal *UBE3A*, *UBE3A*-ATS, defective signalings (mTORs, mitochondrial function, and *etc.*) and other non-targets (*SNORD genes and etc.*)

> Safety test in NHP model

Mouse model

Ube3a $^{+/+}$

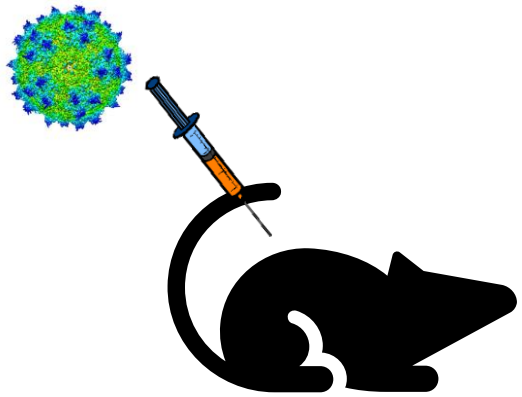
Ube3a $^{+/-\ (m)}$

Maternal UBE3A deficiency
(AS phenotype)

Test AAV-shRNA in vivo (IT injection)

- Check the expression of paternal *Ube3a*, *Ube3a*-ATS, defective signalings (mTORs, mitochondrial function, and *etc.*) and other non-targets (*Snord genes and etc.*)
- Brain mass
- Behavior tests (motor, memory, learning tests)

AS mouse experiment models



Intrathecal injection (IT injection), Day 7-10

Behavior test (3 months)

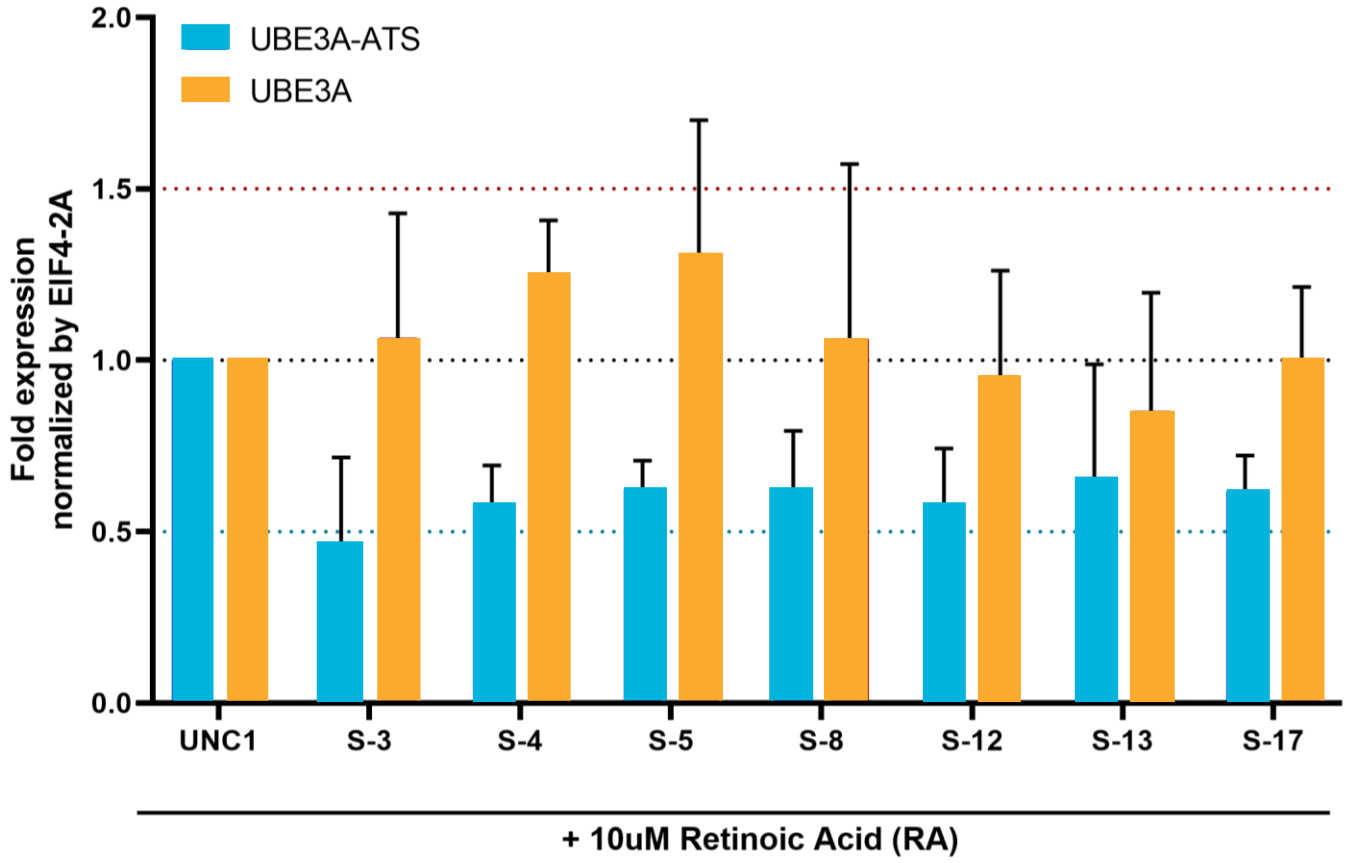
Check UBE3A/UBE3A-ATS expression and other related signalings
(Western blot, RT-Q-PCR, IHC etc.)

Neurological functions		 Phenotype	Test
Cognitive	Severe delay	Not present/ mild	Fear conditioning Water maze
Motor	Severe	Impaired	Rotarod Open field
Language/ Vocalization	Absent	Increased USVs	Ultrasonic vocalization
Behavioral	ASD and Anxiety	Impaired	Nest building, Marble burying Forced swim test Open field
Seizures	Severe	Present	Acute audiogenic or kindling with -flurothyl
EEG	Specific EEG: Increased delta activity Persistent theta activity Spikes and sharp waves	Increased delta power	Extracellular field recordings: EEG, ECoG, LFP
Sleep disturbances	Severe	Mildly impaired	Day/Night cycle EEG

Diana C. Rotaru et al. Neuroscience 2020

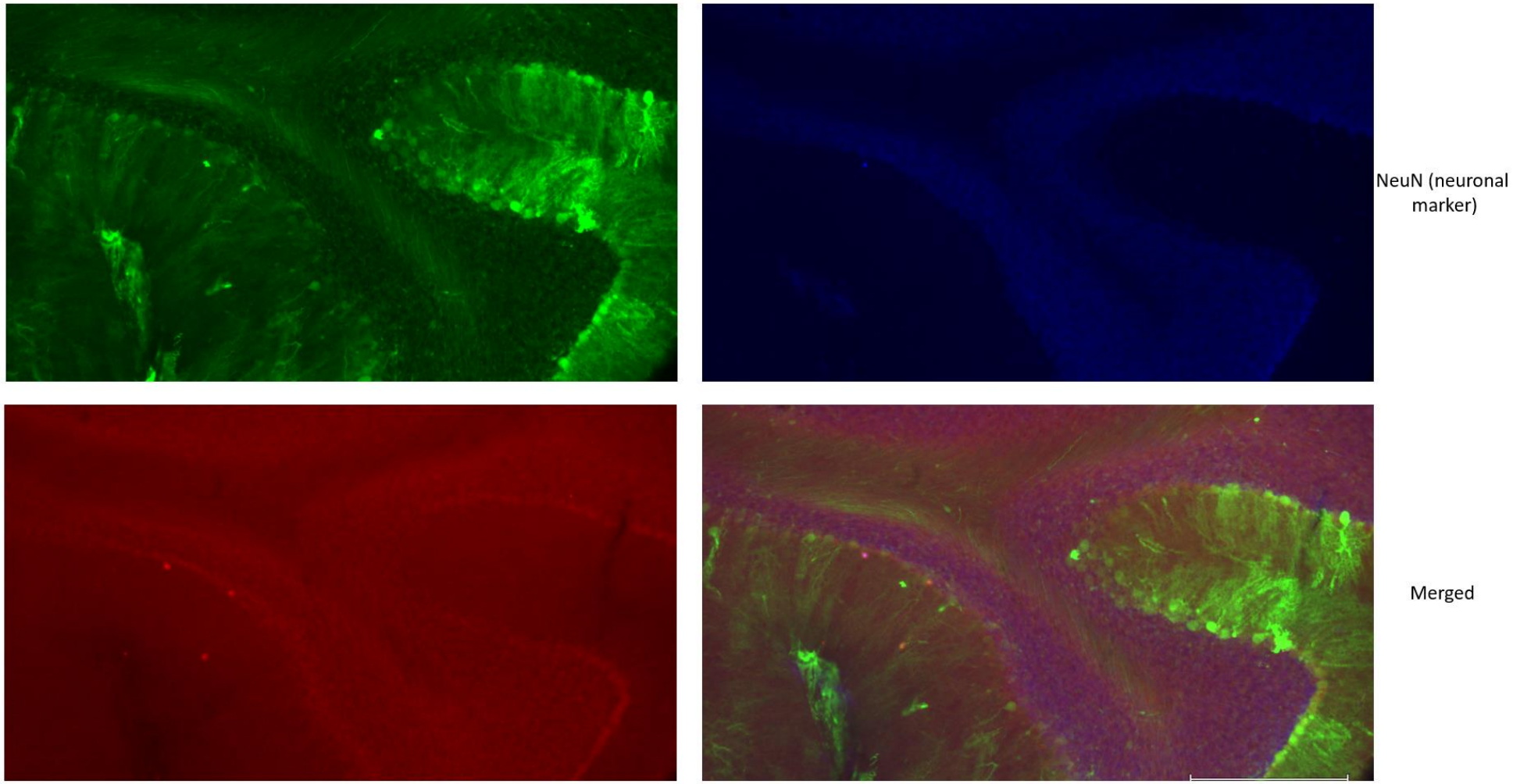
Screening of siRNAs candidates

- UBE3A-ATS and UBE3A expression in SH-SY5Y with RA



UBE3A expression following administration of shRNA candidate

Cerebellum



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Yale University

Dr. Yong-Hui Jiang

Q & A

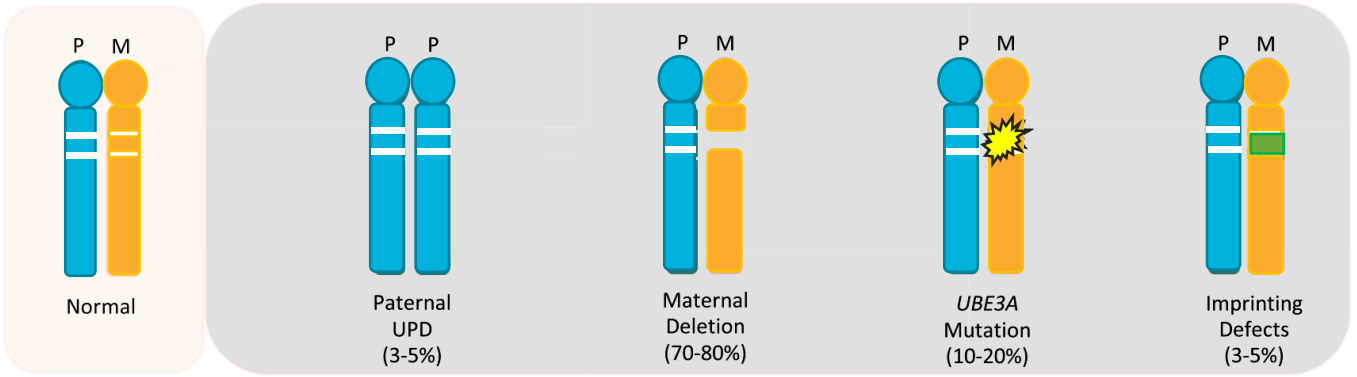
Clinical Development Strategy

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

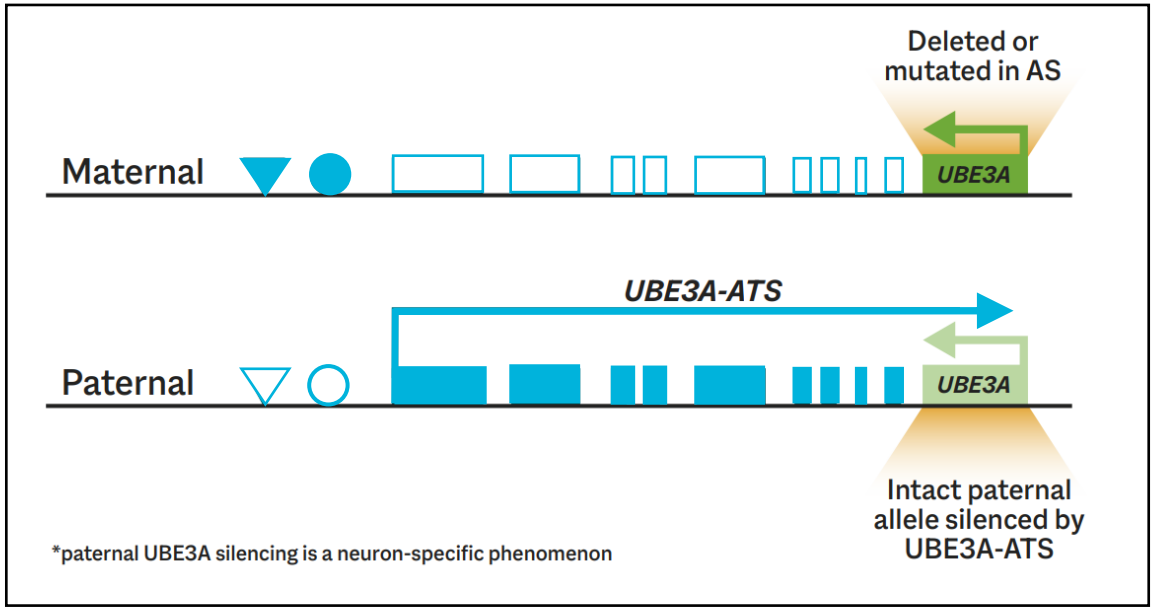
Chief Medical Officer and Head of R&D

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 UBE3A allele expression
- Currently developing both approaches



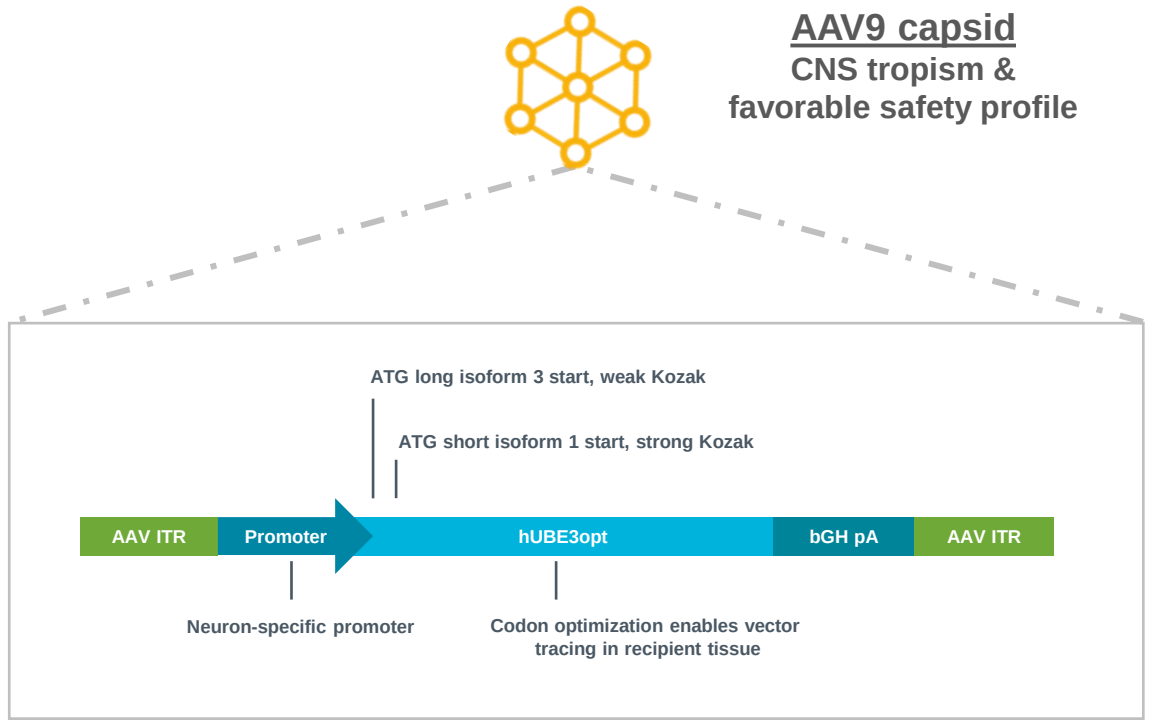
In neurons, the **maternally inherited UBE3A allele is the only active allele**, since the **paternally inherited UBE3A allele is silenced through cell type–specific imprinting**



UPD – Uniparental disomy

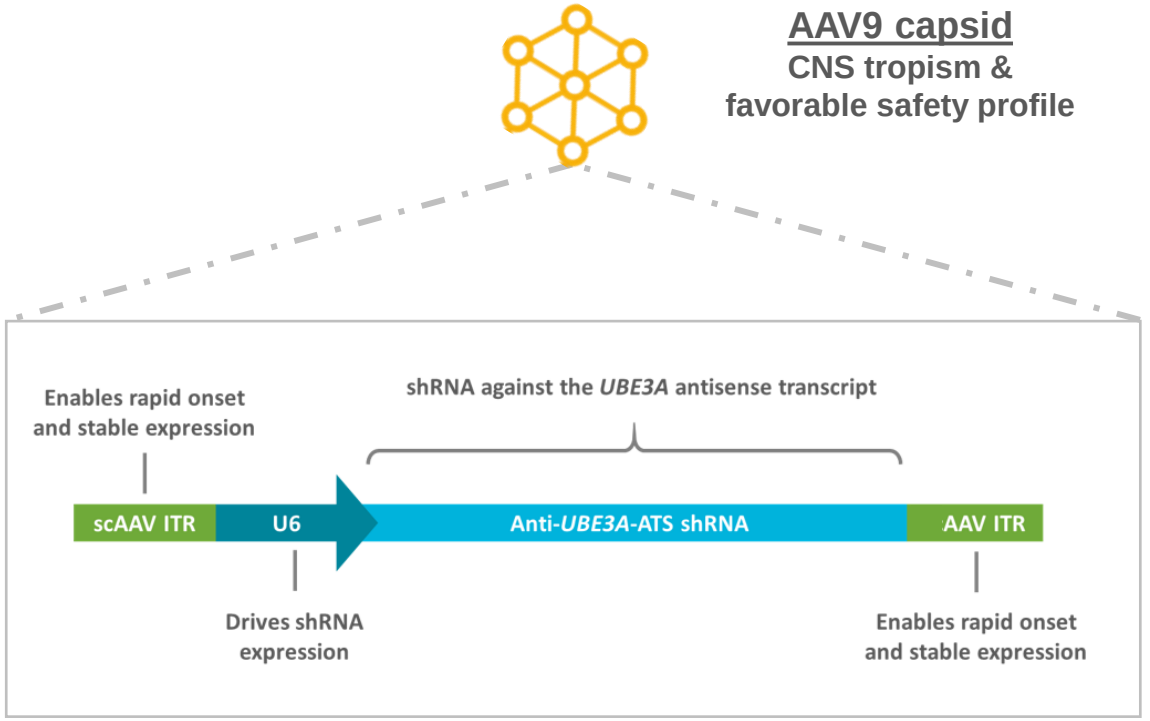
Gene replacement of *UBE3A* corrects the core genetic defect underlying Angelman syndrome

- Viral vector designed to replace *UBE3A* expression in neurons, the cell types that lack UBE3A protein in Angelman syndrome individuals
- Gene addition strategy allows for expression of the two major UBE3A isoforms
  - Recapitulates endogenous short to long UBE3A isoform expression ratio (3:1)
  - Recapitulates endogenous patterns of UBE3A subcellular localization
- Preclinical studies demonstrate therapeutic potential
  - Rescues motor performance and epilepsy phenotypes in Angelman syndrome model mice
  - Prevents anatomical defects linked to epileptogenesis
- Offers rapid onset of expression and long-lasting effects



Knockdown of *UBE3A-ATS* established, placing this strategy 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



We work closely with patients and families to inform our clinical development plan

CURIOSITY

Understand the patient experience, including most challenging symptoms and QOL impacts

Identify patient-centric endpoints and meaningful outcomes

Uncover educational gaps for families about gene therapy and clinical trials

COLLABORATION

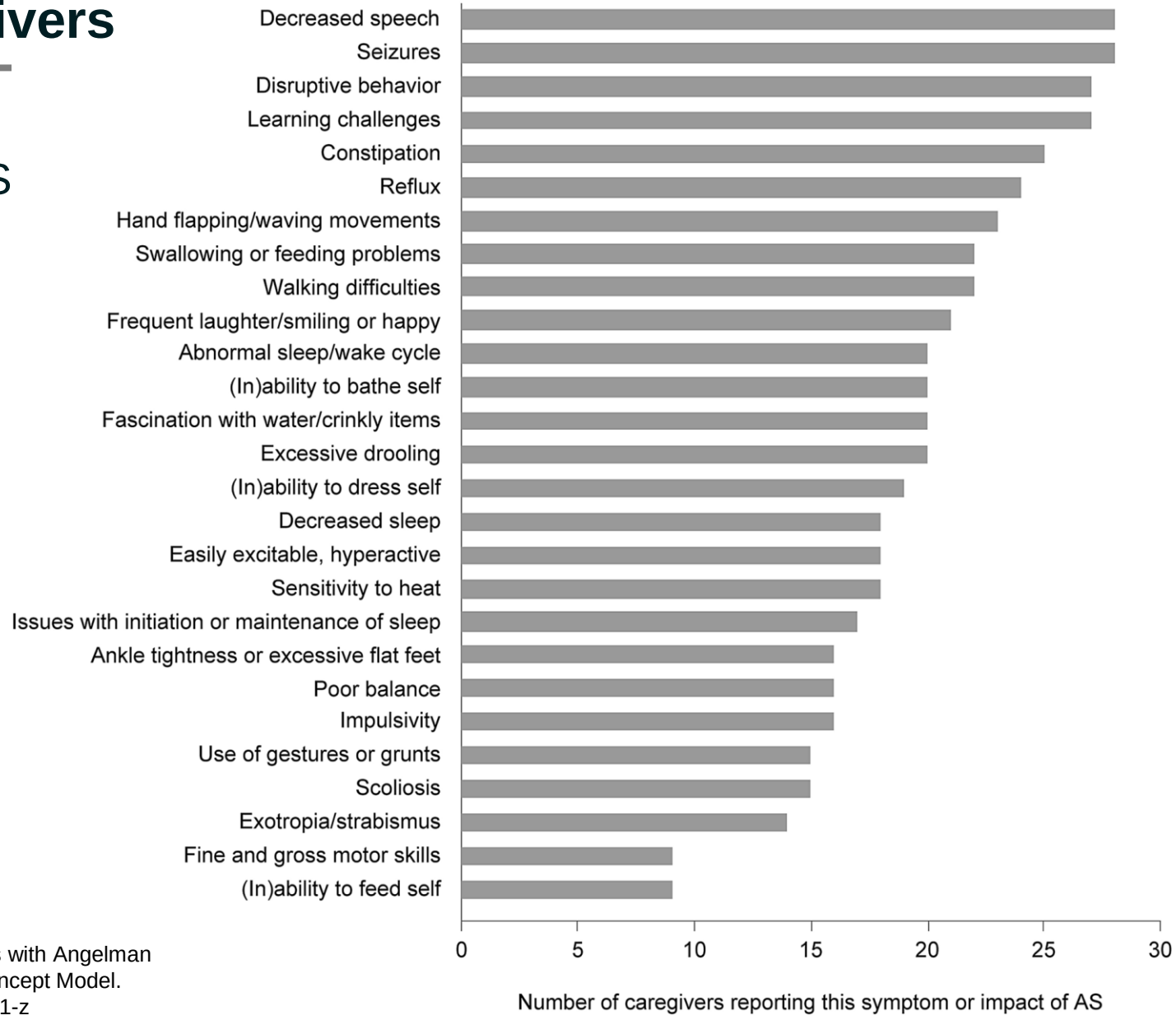
Develop clinical trial protocols based on patient and family insights

Partner with community to raise awareness and recruit clinical trials

Co-create the optimal clinical trial support to enhance experience and aid retention

AS symptoms reported by caregivers

Based on feedback from 30 caregivers, the most frequent concepts reported by AS caregivers were decreased speech, seizures, disruptive behavior, and learning difficulties



Willgoss T, Cassater D, Connor S, et al. Measuring What Matters to Individuals with Angelman Syndrome and Their Families: Development of a Patient-Centered Disease Concept Model. Child Psychiatry Hum Dev. 2021;52(4):654-668. doi:10.1007/s10578-020-01051-z

AS symptoms and key findings reported by 30 caregivers

Expressive communication impairment is a core component of AS. The majority of caregivers reported that the AS individual they cared for was non-verbal (83%), few AS individuals used 10–20 words (10%). Half the AS individuals used gestures and/or vocalizations to communicate (53%), and a minority of caregivers reporting an AS individual using sign language (27%)
Seizure frequency ranged from multiple times per day (40%), to a few times per month (13%), or a few times per year (23%). Seizures can impact the ability to leave the home, be a reason for frequent hospital visits, and be distressing for the individual and caregiver
Disruptive behavior can take different forms, for example, hair pulling, biting, grabbing, and pinching. This was reported across all age groups and all AS genotypes
Cognitive and/or learning impairment includes impaired judgement, limited concentration and difficulties focusing, although some caregivers also noted their children have a good memory for people and faces
Motor difficulties include both gross and fine motor: walking difficulties (73%), poor balance (53%) and fine motor skills or general motor skills issues (23%) and tremors or jerky movements
Sleep disturbances often included not sleeping well (80%) and could include snoring and teeth grinding (40%), bed-wetting (20%), and sleep terrors (17%). These sleep disturbances were also related to subsequent mood and disruptive behavior (13%). Sleep disturbances tended to improve with age
Self-care was reported as **impaired** by most caregivers including requiring assistance (63%) or inability to dress independently (10%). Assistance with meals was required by a third (30%), with some individuals requiring their food to be cut up (20%)

Willgoss T, Cassater D, Connor S, et al. Measuring What Matters to Individuals with Angelman Syndrome and Their Families: Development of a Patient-Centered Disease Concept Model. Child Psychiatry Hum Dev. 2021;52(4):654-668. doi:10.1007/s10578-020-01051-z

Patient / caregiver input into TSHA-106 clinical study design

We routinely engage with caregivers of loved ones with rare diseases to learn about their experiences, needs, and priorities as well as to inform clinical study design

Collection of caregiver perspectives on disease symptoms and therapeutic priorities via a focus group expected in 2022

Planned Phase 1/2 initial trial for TSHA-106 Gene replacement strategy

Goals and Targets of Trial

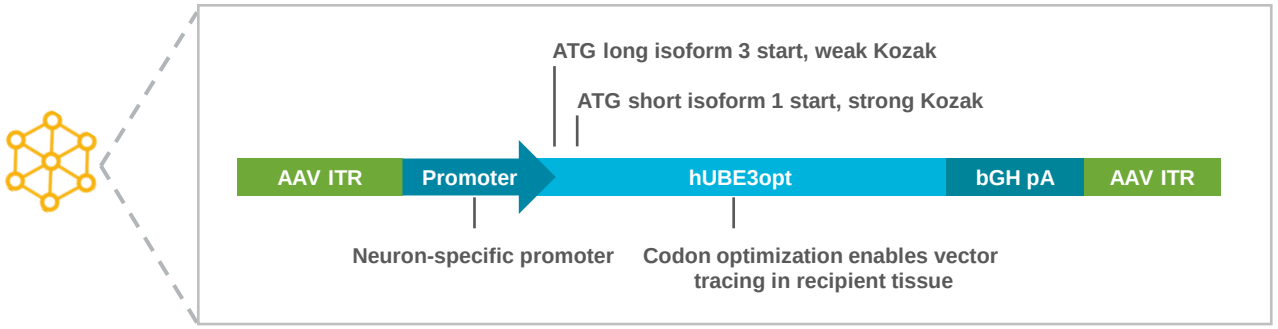
Goals

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

Target Recruitment

- Subjects with confirmed Angelman diagnosis

Product Details and Dose Cohorts



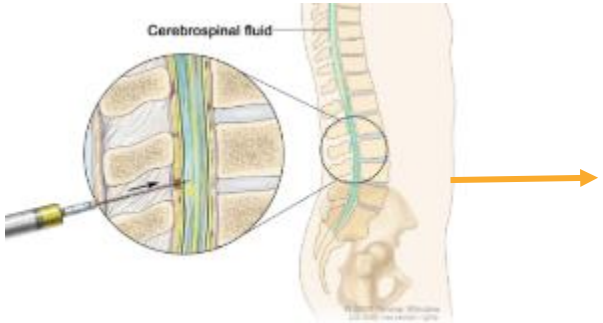
Dose Cohorts

- Starting dose
- Higher dose
- Dose expansion

Route and Method of Administration

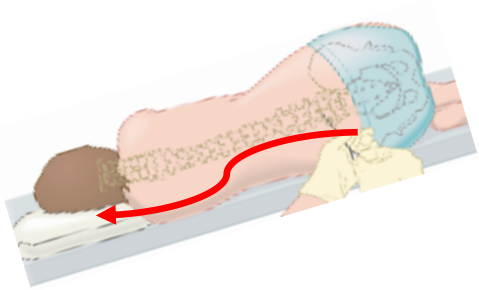
Administration

- 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 (15-30^{o})
- During infusion & 1 hour post infusion



Planned Phase 1/2 initial trial for TSHA-106 Vectorized RNA strategy

Goals and Targets of Trial

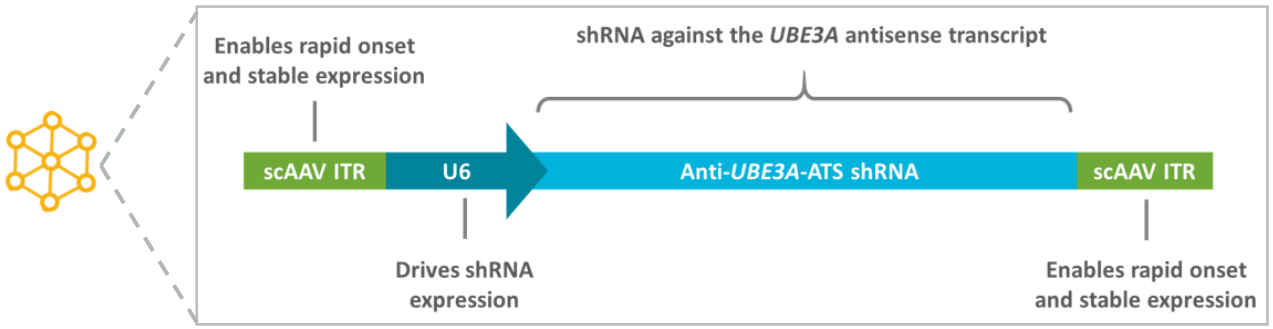
Goals

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

Target Recruitment

- Subjects with confirmed Angelman diagnosis

Product Details and Dose Cohorts



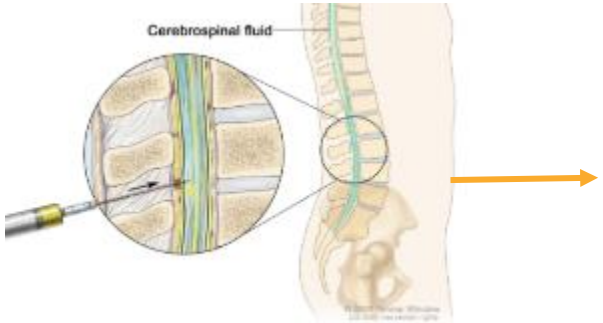
Dose Cohorts

- Starting dose
- Higher dose
- Dose expansion

Route and Method of Administration

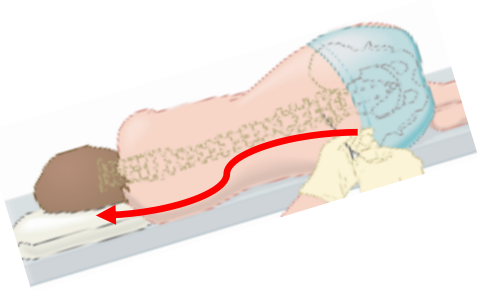
Administration

- 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 (15-30^{o})
- During infusion & 1 hour post infusion



Overview of potential efficacy endpoints

Disease-Specific/Global Assessments
- Clinical Global Impression of Severity – Angelman syndrome version (CGI-S-AS) to assess domains of sleep, behavior, expressive and receptive communication, gross and fine motor
- Developmental assessment by Bayley Scales of Infant/Toddler Development 4 (BSID-4)
- Vineland-III to assess adaptive behaviors
- Aberrant Behavior Checklist

Motor Assessments
- Ambulation measured by wearable device to assess motor function

Sleep Assessments
- Assessment of sleep by diary
- Child Sleep Habits Questionnaire (CSHQ)
- Polysomnography
- Wearables

Seizures Assessments
- Seizure type, frequency, and duration assessed by seizure diary
- Quantitative analysis of electroencephalogram (EEG) to assess delta waves and epileptiform discharges

Biomarkers
- EEG delta power
- CSF biomarkers (exploratory)

Imaging and Neurophysiology
- Brain MRI including volumetric changes (% gray matter volume, % ventricular volume, and total brain volume)

Communication Assessments
- Observer Reported Communication Assessment (ORCA)

Quality of Life/Other Assessment
- QoL scale *TBD*
- Healthcare resource utilization outcomes

Anticipated next steps for TSHA-106 program

Evaluate dose and age responses and finalize dose from pharmacology

Expression, biodistribution, and safety data from confirmatory NHP studies

Interventional trial protocol development underway

Scientific Advisory Board meeting to provide input into clinical study design in 2021

Patient focus group to provide input into clinical study design in 2022

Discussion with regulatory agencies for both approaches in 2022

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 safety / biomarker data in 2H 2021
Preliminary CLN7 data for first-generation construct by YE 2021

5 open IND/CTAs expected by the end of 2021 – GAN, GM2, CLN7, CLN1, and Rett syndrome

Major demolition and detailed design of internal cGMP facility completed

5 additional programs currently in IND-enabling studies
Numerous value generating catalysts over the next 18 months

Thank you to our partners!

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TAYSHA GENE THERAPIES

Thank you