# Angelman Syndrome: Research landscape

Ben Philpot, Ph.D. , University of North Carolina
Stormy Chamberlain, Ph.D., University of Connecticut

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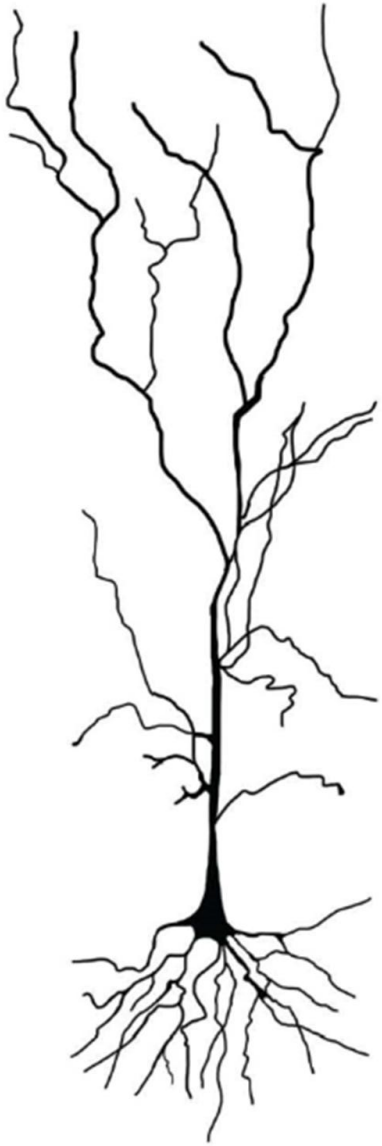
# OUTLINE

Research
- Biochemistry
- Mouse studies
- Other models

Therapeutic approaches
- Gene therapy
- *UBE3A* unsilencing approaches
- Other approaches

Clinical trials
- What's going on?
- Biomarkers



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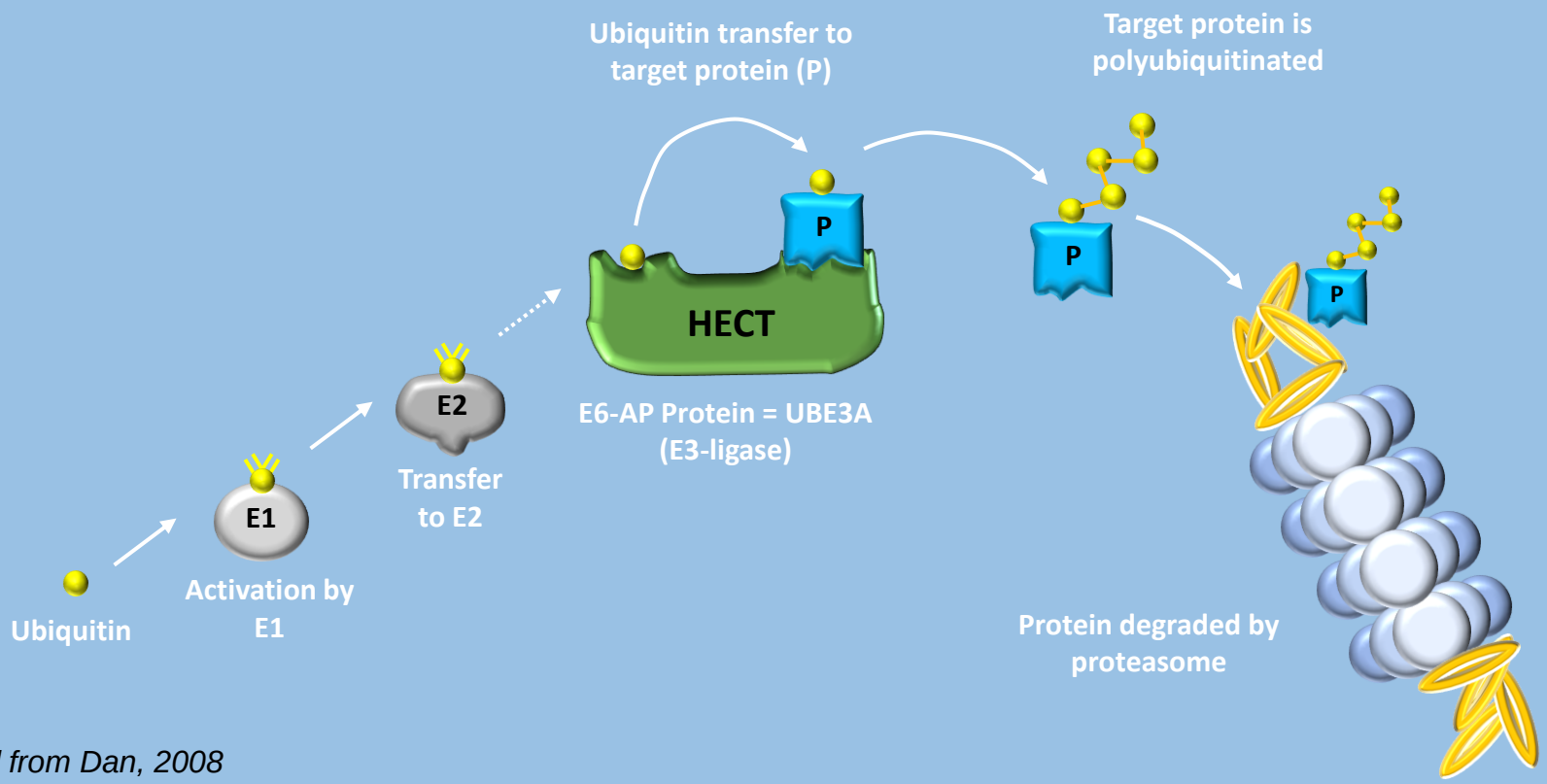
# RESEARCH: What does UBE3A do?




*modified from Dan, 2008*

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# Which proteins are targeted by UBE3A?

UBE3A “labels” specific proteins for disposal

- Which proteins are tagged by UBE3A?
- Which ones are relevant and amenable for pharmacological targeting?
- Do other proteins help UBE3A in this effort?

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# ASF funded research leading to identification of substrates

## EphB-Mediated Degradation of the RhoA GEF Ephexin5 Relieves a Developmental Brake on Excitatory Synapse Formation

Seth S. Margolis,[1,3] John Salogiannis,[1,3] David M. Lipton,[1] Caleigh Mandel-Brehm,[1] Zachary P. Wills,[1] Alan R. Mardinly,[1] Linda Hu,[1] Paul L. Greer,[1] Jay B. Bikoff,[1] Hsin-Yi Henry Ho,[1] Michael J. Soskis,[1] Mustafa Sahin,[2] and Michael E. Greenberg[1,*]

[1]Department of Neurobiology, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115, USA

[2]F.M. Kirby Neurobiology Center, Departments of Neurology, Children's Hospital Boston, Harvard Medical School, Boston, MA 02115, USA

[3]These authors contributed equally to this work

*Correspondence: michael_greenberg@hms.harvard.edu

DOI 10.1016/j.cell.2010.09.038

Mike Greenberg, Ben Distel, Peter Howley, others

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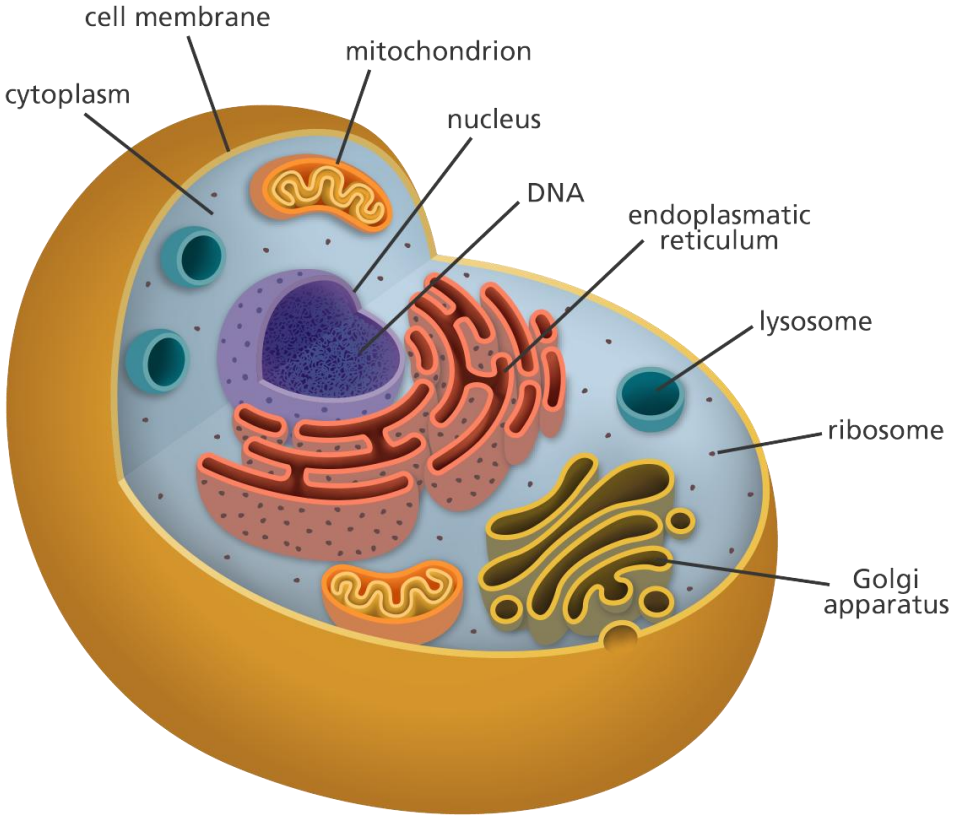
# Where in the cell is UBE3A?




There are 3 forms of UBE3A

- Where are the different forms located?
- Do they all have the same job?
- Which one is most important for Angelman syndrome?

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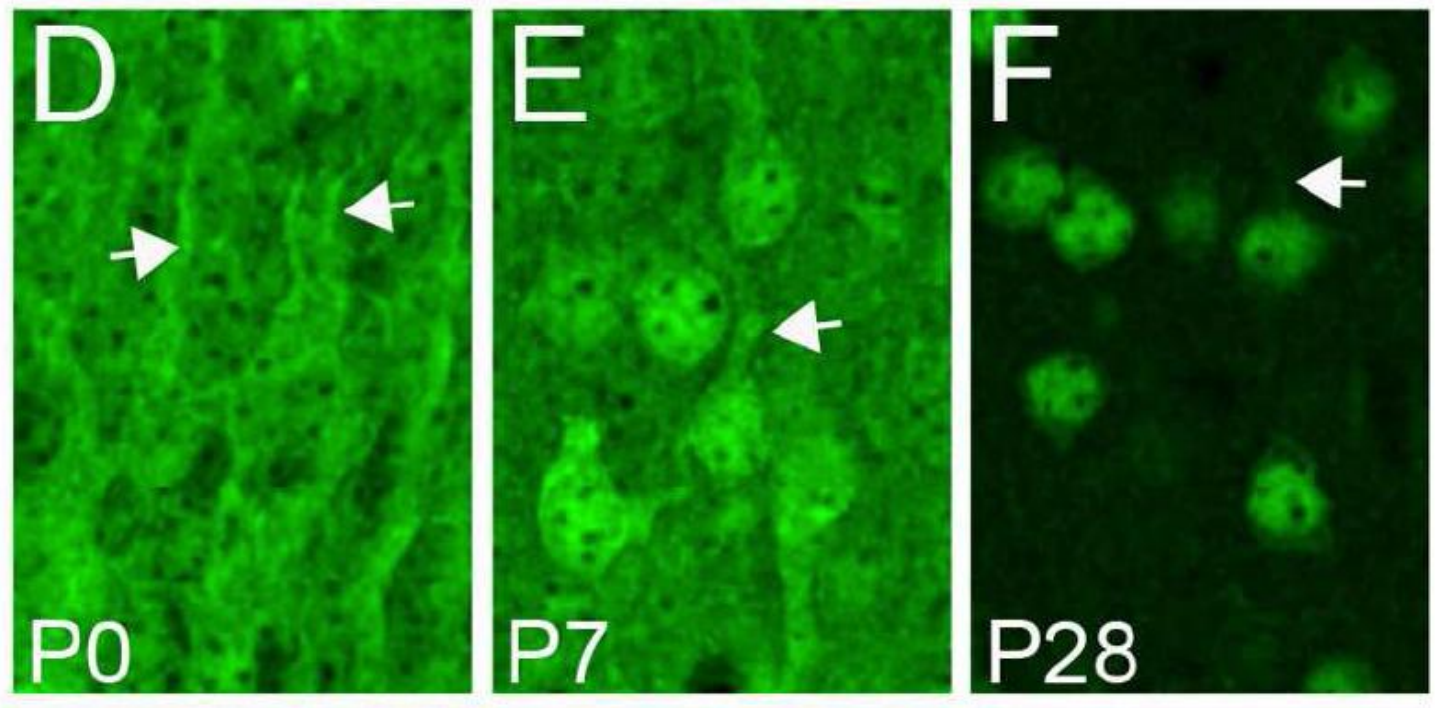
# ASF funded research




Ben Philpot, Ype Elgersma, Stormy Chamberlain

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# Mouse studies

1. Mice in which UBE3A can be turned on at different times and in different places

2. Mice in which UBE3A can be removed at different times/places

- What is the critical window to restore UBE3A?
- Which brain region or neuron type is most important to target?
- Which neuron problems cause each phenotype?

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# Mouse studies

The Journal of Clinical Investigation

RESEARCH ARTICLE

## *Ube3a* reinstatement identifies distinct developmental windows in a murine Angelman syndrome model

Sara Silva-Santos,[1,2,3] Geeske M. van Woerden,[1,2] Caroline F. Bruinsma,[1,2] Edwin Mientjes,[1,2] Mehrnoush Aghadavoud Jolfaei,[1,2] Ben Distel,[4] Steven A. Kushner,[2,5] and Ype Elgersma[1,2]

[1]Department of Neuroscience, Erasmus Medical Center, Rotterdam, Netherlands. [2]ENCORE Expertise Center for Neurodevelopmental Disorders, Erasmus Medical Center, Rotterdam, Netherlands. [3]Graduate Program in Areas of Basic and Applied Biology, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal. [4]Department of Medical Biochemistry, Academic Medical Center, Amsterdam, Netherlands. [5]Department of Psychiatry, Erasmus Medical Center, Rotterdam, Netherlands.

Ben Philpot, Ype Elgersma, Seth Margolis

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# Other models

- Human induced pluripotent stem cells (iPSCs)
  --iPSCs are turned into neurons
  --important for identifying human-specific drugs (i.e. ASOs)

- Rat
  --Ube3a has been knocked out in a rat

- Pig
  --Ube3a is being knocked out in a pig

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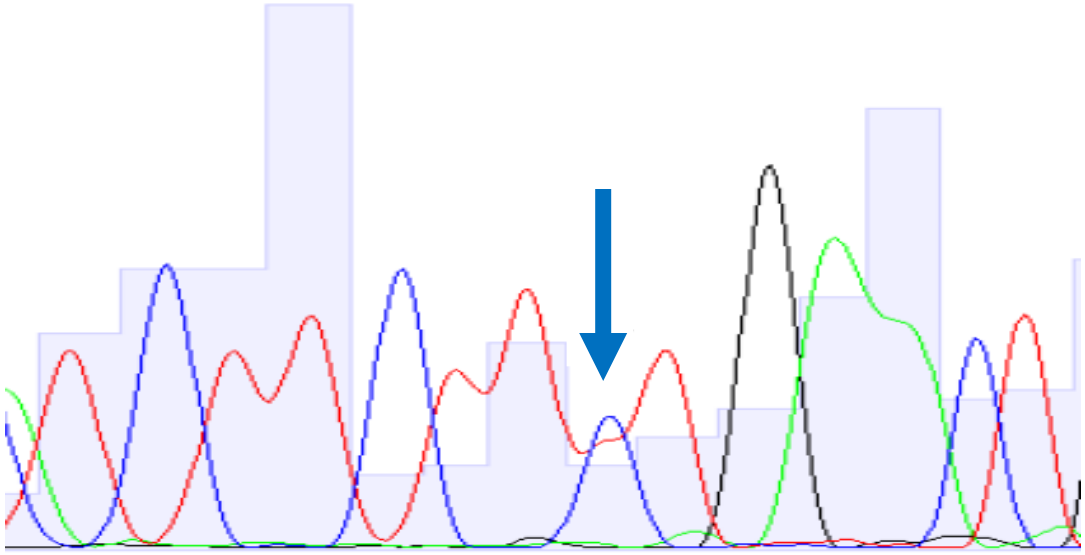
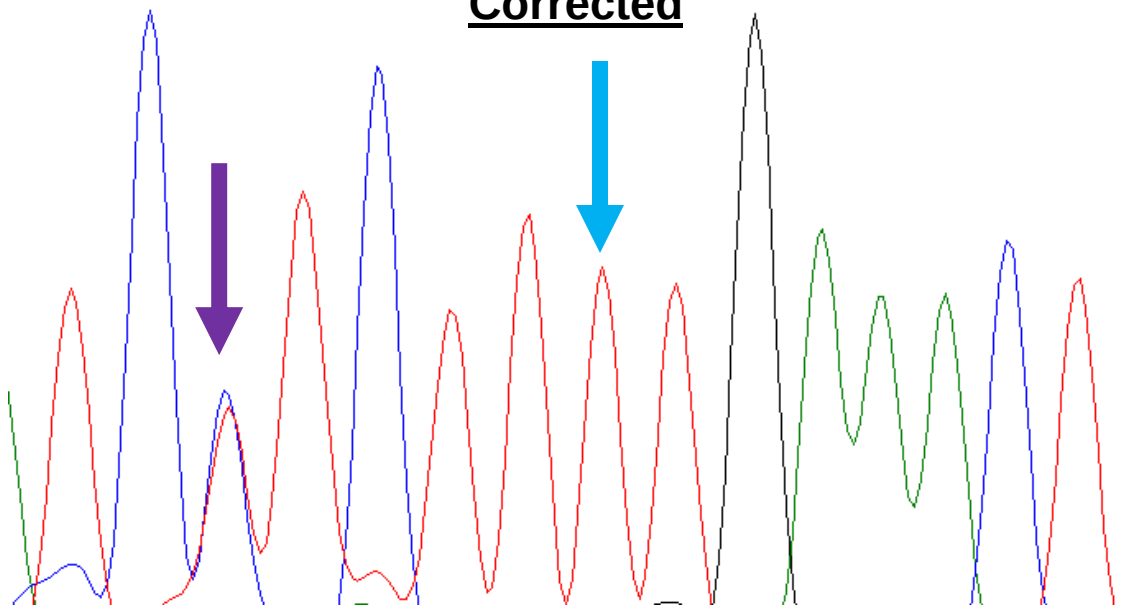
# Correction of AS-causing point mutation (CRISPR/Cas9)

**AS (uncorrected)**



AS-causing mutation

**Corrected**



Silent Mutation (TCT → TCC)

Corrected (WT) NT

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# Challenges facing research

- How do we balance the slow and steady research strategy versus high risk and high reward approaches?
- Which research studies should we be devoting most of our time towards?
- How well does the therapeutic window translate between mouse and human?
- How do we balance research toward a cure with basic research, which is essential for developing other therapies.

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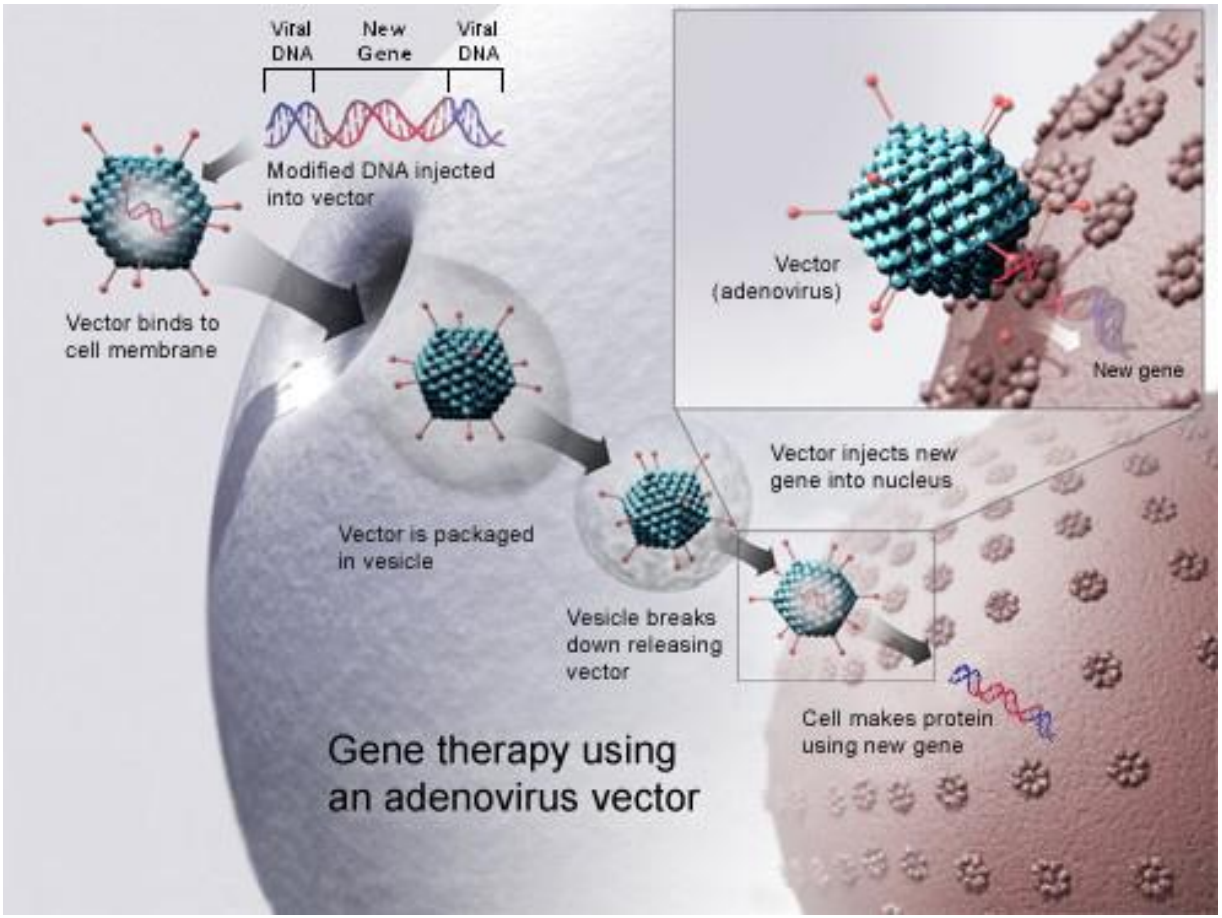
# Keeping Our Research Goal in Mind

- To improve the lives of individuals with Angelman syndrome

# THERAPEUTIC APPROACHES: Gene therapy




https://en.wikipedia.org/wiki/Gene_therapy

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# ASF funded first gene therapy study for AS

- Which form of UBE3A is best for maximal benefit?
- What are expectations for recovery based on intervention age?
- Do we need to target the whole brain or is one region sufficient?
- What percentage of neurons must be infected?
- What are dangers of too much UBE3A, and how do we limit chances of this?

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# Featured at 2017 ASF Scientific Symposium

## UNC's Steven Gray featured in CBS News report on a new gene therapy approach to treat rare diseases

*On October 16, 2015, CBS Evening News aired a story on Lori Sames' search for a cure for her daughter, Hannah, who suffers from Giant Axonal Neuropathy disease (GAN), a rare disease which causes nerves to die and muscles to stop working. Lori and her husband, Matt, founded Hannah's Hope to raise money to fund the research to find a cure.*

Now, after several years and an enormous level of dedication, the first gene therapy clinical trial for GAN is underway, with the research headed by Steven Gray, PhD, at the UNC Gene Therapy Center and the trial being conducted by Carsten Bonnemann. MD, at the NIH. Read and watch the CBS story here. Read more about Gray's GAN research here.

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click to enlarge

Steven J. Gray, PhD

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# ASF funded both UBE3A unsilencing approaches

1. Small molecules that unsilence UBE3A (topotecan)


2. Antisense oligonucleotides (ASOs or AONs)


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# ASF funded both UBE3A unsilencing

doi:10.1038/nature10726

## Topoisomerase inhibitors unsilence the dormant allele of *Ube3a* in neurons

Hsien-Sung Huang[1]*, John A. Allen[2]*, Angela M. Mabb[1], Ian F. King[1], Jayalakshmi Miriyala[1], Bonnie Taylor-Blake[1], Noah Sciaky[2], J. Walter Dutton Jr[1], Hyeong-Min Lee[2], Xin Chen[3], Jian Jin[3], Arlene S. Bridges[4], Mark J. Zylka[1,5,6], Bryan L. Roth[2,5,6,7,8] & Benjamin D. Philpot[1,5,6]

LETTER

doi:10.1038/nature13975

## Towards a therapy for Angelman syndrome by targeting a long non-coding RNA

Linyan Meng[1]*, Amanda J. Ward[2]*, Seung Chun[2], C. Frank Bennett[2], Arthur L. Beaudet[1] & Frank Rigo[2]

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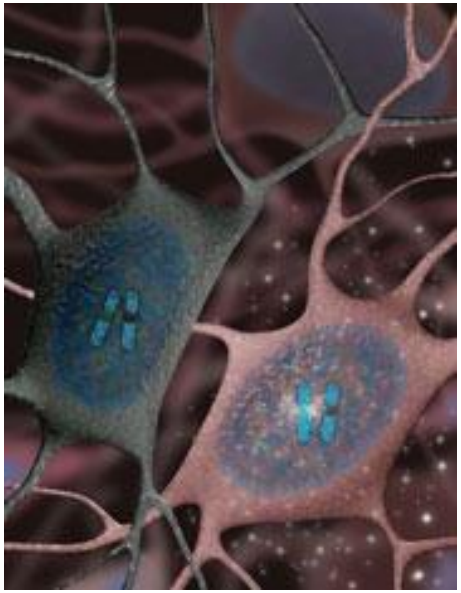
# UBE3A unsilencing approaches

- How long will *UBE3A* unsilencing last?
- What delivery methods are most appropriate?
- What level of unsilencing is necessary to achieve efficacy?
- Could a low level of unsilencing over a long period of time provide benefit?



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# Other treatments: cure vs treating symptoms

| Consistent | Frequent | Occasional |
|---|---|---|
| Functionally severe intellectual disability | Microcephaly with flat occiput/occipital groove | Scoliosis |
| Movement/balance disorder | Seizures | Hypopigmentation |
| Speech impairment | Abnormal EEG | Increased sensitivity to heat |
| Behavioral phenotype (easily excited, happy, frequent laughter, hypermotoric) | Gastrointestinal difficulties (feeding problems, gastroesophageal reflux, constipation) | Growth disturbance depending on genotype |
| | Fascination with water or crinkly items | Ocular problems (refractive and alignment errors) |
| | Mouthing behavior | |
| | Ankle pronation | |
| | Sleep disturbance | |

*Bird,2013*

# Phenotype-specific treatments

- How can we best target seizures?

*Epilepsia*, 53(9):1498–1502, 2012
doi: 10.1111/j.1528-1167.2012.03537.x

FULL-LENGTH ORIGINAL RESEARCH

## Low glycemic index treatment for seizures in Angelman syndrome

**Ronald L. Thibert, Heidi H. Pfeifer, Anna M. Larson, Annabel R. Raby, Ashley A. Reynolds, Amy K. Morgan, Elizabeth A. Thiele**

**Department of Neurology, Pediatric Epilepsy Program and Angelman Syndrome Clinic, Massachusetts General Hospital, Boston, Massachusetts, U.S.A.**

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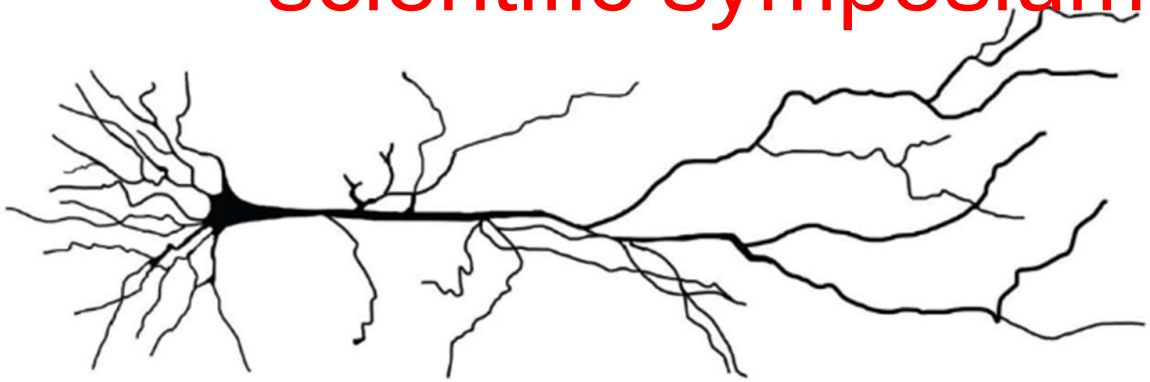
# Phenotype-specific treatments

- How can we treat anxiety?  What do we know about anxiety phenotype?

ASF funded Chris Keary,

talk by Anne Wheeler at 2017 ASF scientific symposium



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# Phenotype-specific treatments

- How might we treat motor problems?

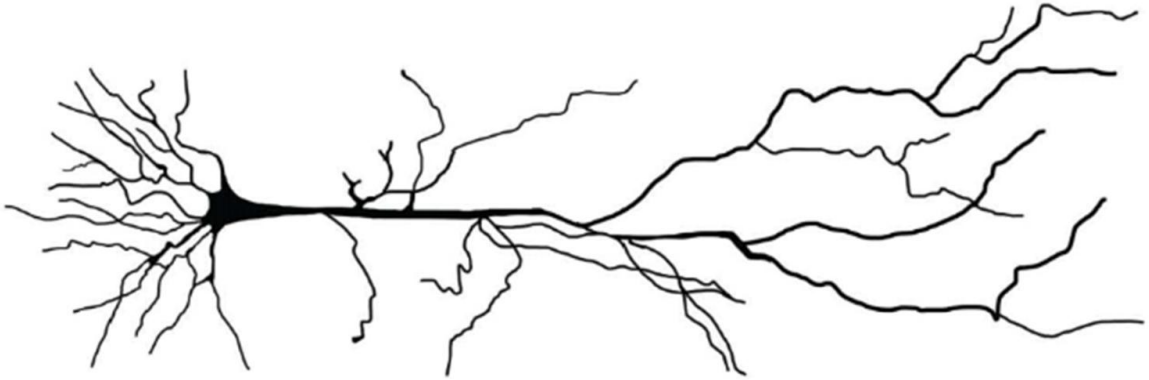
The Journal of Clinical Investigation

RESEARCH ARTICLE

## Dissociation of locomotor and cerebellar deficits in a murine Angelman syndrome model

Caroline F. Bruinsma,[1,2] Martijn Schonewille,[1] Zhenyu Gao,[1] Eleonora M.A. Aronica,[3] Matthew C. Judson,[4] Benjamin D. Philpot,[4] Freek E. Hoebeek,[1] Geeske M. van Woerden,[1,2] Chris I. De Zeeuw,[1,2,5] and Ype Elgersma[1,2]

[1]Department of Neuroscience and [2]ENCORE Expertise Centre for Neurodevelopmental Disorders, Erasmus MC, Rotterdam, Netherlands. [3]Department of (Neuro)Pathology, Academic Medical Center, Amsterdam, Netherlands. [4]Department of Cell Biology and Physiology, Neuroscience Center, and Carolina Institute for Developmental Disabilities, University of North Carolina, Chapel Hill, North Carolina, USA. [5]Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, Netherlands.



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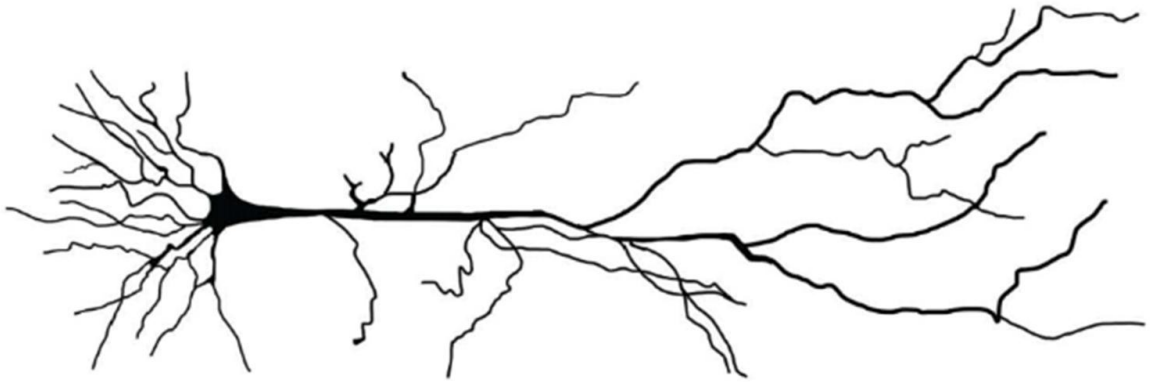
# Phenotype-specific treatments

- Many other domains could be targeted:  intellectual disability, sleep, communication, drooling, etc.

## ASF funded melatonin study, communication studies



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# Treating a specific neuron deficit: OV101

STARS clinical trial by Ovid uses a drug called OV101

- OV101 is thought to reverse a deficit in tonic inhibition. We're not entirely sure which phenotypes this is important for.

- One brain region in AS mice have deficits in tonic inhibition. Other brain regions are being studied

- Safety studies have been previously done (in typical individuals), so clinical trial is already going on.

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# Treating a specific neuron deficit: OV101

**RESEARCH ARTICLE** | NEURODEGENERATIVE DISEASE

## Decreased Tonic Inhibition in Cerebellar Granule Cells Causes Motor Dysfunction in a Mouse Model of Angelman Syndrome

Kiyoshi Egawa[1,*,†], Kyoko Kitagawa[2], Koichi Inoue[1], Masakazu Takayama[1], Chitoshi Takayama[3], Shinji Saitoh.

+ See all authors and affiliations

*Science Translational Medicine* 05 Dec 2012:
Vol. 4, Issue 163, pp. 163ra157
DOI: 10.1126/scitranslmed.3004655

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# CLINICAL TRIALS

Ongoing

- Ovid:  OV101

Upcoming

- Ionis—antisense oligonucleotides
- Agilis, UPenn Orphan Disease Center—gene therapy
- Roche—

Perhaps interested, but not providing details

- Vertex, Fulcrum, Nestle, Alexion, Cydan

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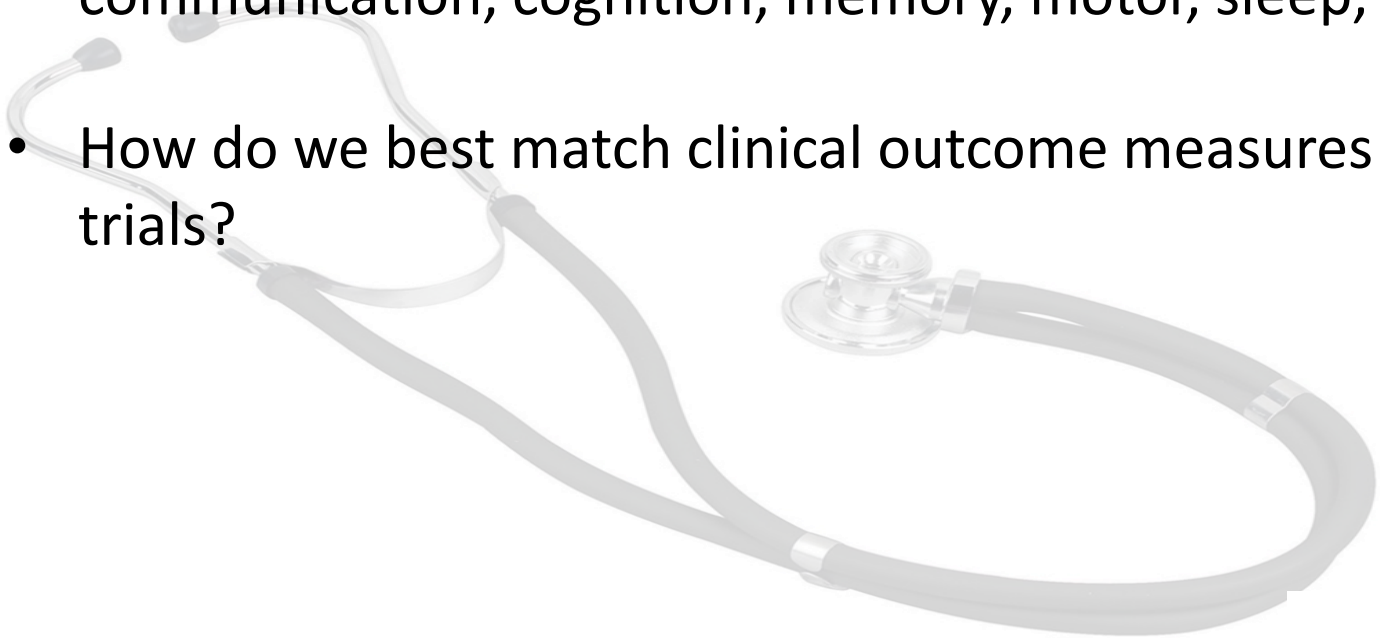
# Biomarkers

- What biomarkers are clinically relevant and can be measured in a relatively non-invasive manner?
- EEG, seizures, MRI/DTI, body fluids (blood, urine, spinal fluid), communication, cognition, memory, motor, sleep, etc.
- How do we best match clinical outcome measures to clinical trials?



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# Biomarkers

RESEARCH Open Access

## Delta rhythmicity is a reliable EEG biomarker in Angelman syndrome: a parallel mouse and human analysis

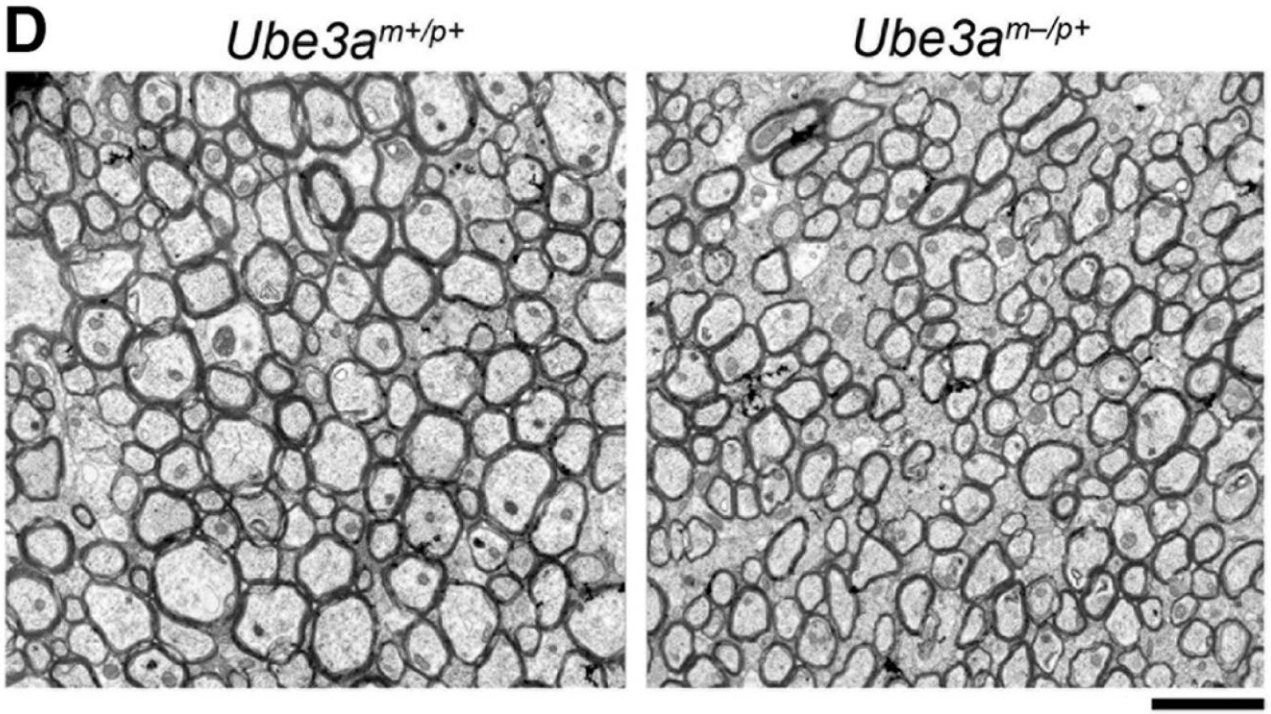
Michael S. Sidorov[1,2,3], Gina M. Deck[4,5,8], Marjan Dolatshahi[4,5], Ronald L. Thibert[4], Lynne M. Bird[6,7], Catherine J. Chu[4,5*] and Benjamin D. Philpot[1,2,3*]

# Biomarkers

## Decreased Axon Caliber Underlies Loss of Fiber Tract Integrity, Disproportional Reductions in White Matter Volume, and Microcephaly in Angelman Syndrome Model Mice

Matthew C. Judson,[1,2] Alain C. Burette,[1*] Courtney L. Thaxton,[1,2*] Alaine L. Pribisko,[1] Mark D. Shen,[2] Ashley M. Rumple,[3] Wilmer A. Del Cid,[1,4] Beatriz Paniagua,[3] Martin Styner,[3] Richard J. Weinberg,[1,5] and Benjamin D. Philpot[1,2,5]

[1]Department of Cell Biology and Physiology, [2]Carolina Institute for Developmental Disabilities, [3]Department of Psychiatry, [4]Postbaccalaureate Research Education Program, and [5]Neuroscience Center, University of North Carolina, Chapel Hill, North Carolina 27599



# Challenges facing therapeutic development

- How do we establish optimal ages of intervention? How does this vary by phenotype? --Elizabeth Berry-Kravis, scientific symposium

- What brain regions are necessary to reach to help with AS?

- How are we dealing with the variability of the patient population?

- How do we balance the desire to develop a total cure with with addressing the immediate needs of individuals with AS?

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# Challenges facing therapeutic development

- Which treatment strategies should we be devoting most of our time towards?
- How do we establish safety of clinical trials?
- How do we not overburden/overuse the patient population?

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# Keeping Our Research Goal in Mind

- To improve the lives of individuals with Angelman syndrome

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