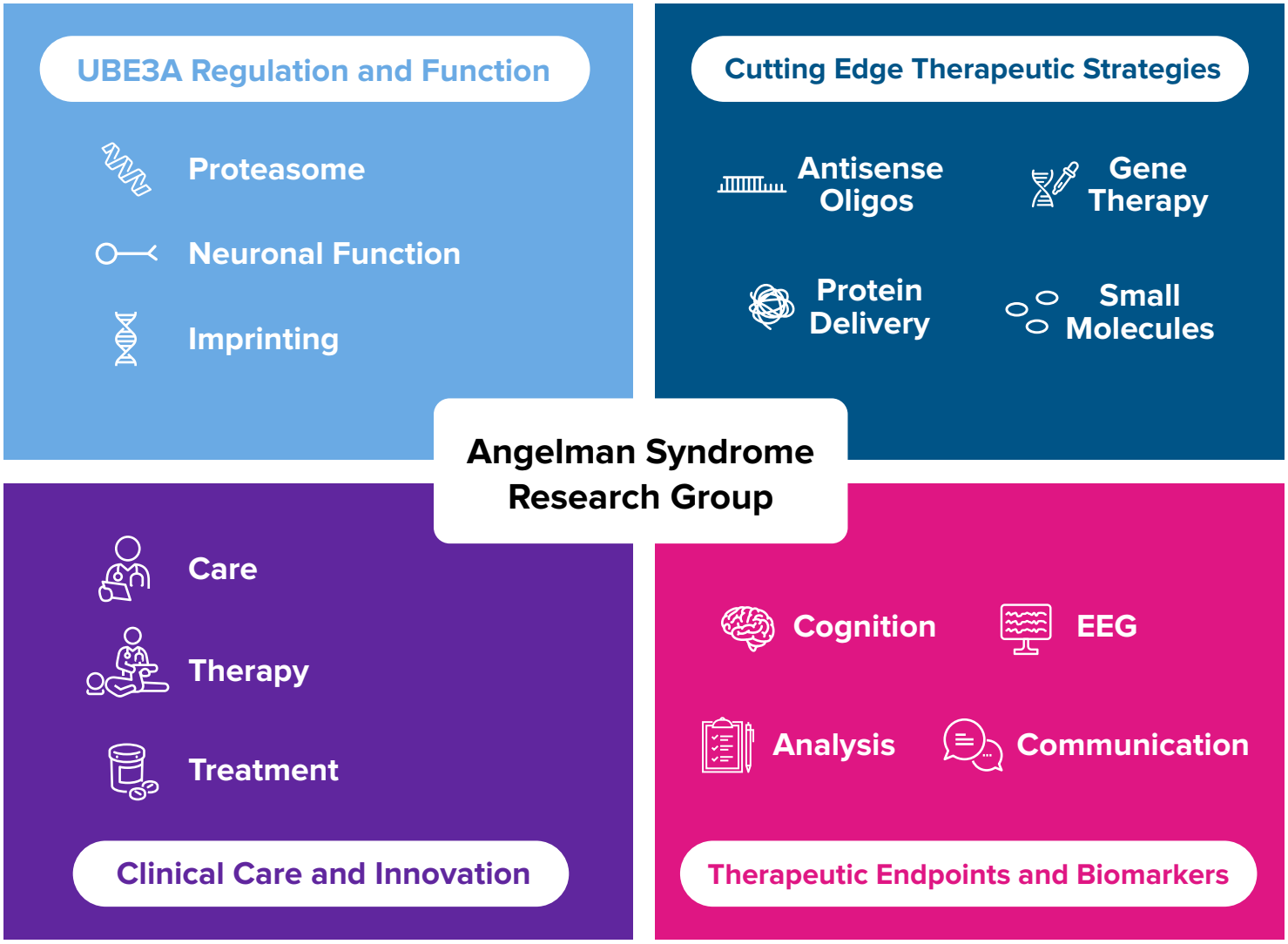
SCIENTIFIC ROADMAP

Established March 2025

angelman SYNDROME FOUNDATION

In March 2025, the Angelman Syndrome Foundation (ASF) established a new Research Roadmap to guide and prioritize our scientific investments with the goal of accelerating meaningful treatments and improving quality of life across the lifespan for individuals with Angelman syndrome. This updated roadmap reflects current scientific advancements, community needs, and strategic opportunities for impact. For additional information about how ASF has historically met our research goals, please see page 5 for a review of our 2009 Research Roadmap and the progress it helped catalyze over the past decade.



As graphically summarized, the following four pillars are proposed

- **UBE3A Regulation and Function**
- **Cutting Edge Therapeutic Strategies**
- **Therapeutic Endpoints and Biomarkers**
- **Clinical Care and Innovation**

UBE3A Regulation and Function

Goal: Continue to fund rigorous research towards understanding how UBE3A expression is regulated and how UBE3A functions in protein homeostasis and in neuronal function.

Objective: Deepen our understanding of the role of UBE3A. This includes but is not limited to:

- The roles of UBE3A in protein regulation
- Nuclear versus cytoplasmic roles of UBE3A
- Neuronal function in the absence of UBE3A
- Cell-type specific deficits in absence of UBE3A
- Impact of UBE3A loss on different brain regions
- Impact of haploinsufficiency of non-imprinted genes in Angelman Syndrome pathophysiology

Actions:

- Support investigations exploring the molecular mechanisms underlying UBE3A function and dysregulation.
- Foster collaborations between molecular biologists, geneticists, and neuroscientists to elucidate the complex interactions within the AS genetic landscape.
- Prioritize the funding of research projects aimed at identifying potential therapeutic targets and pathways affected by UBE3A deficiency and non-imprinted gene haploinsufficiency.

Cutting Edge Therapeutic Strategies

Goal: Support the study and development of new therapeutic approaches and the translational studies required for their advancement to the clinic.

Objective: Develop and optimize therapeutic approaches such as gene therapy to restore UBE3A expression and mitigate the effects of non-imprinted gene haploinsufficiency. This includes but is not limited to:

- The development of new strategies to activate UBE3A given rapid advancements in RNA and DNA editing approaches
- Optimize current approaches to activate UBE3A
- Develop strategies for enhanced delivery, durability, and distribution of therapies within the brain
- Develop primate models of AS to test therapeutics approaches in the most relevant animal model.
- Optimize viral delivery modalities for treating neurological disorders
- Develop understanding of parameters required for effective gene therapy (e.g. percent cells targeted, brain regions targeted, minimum and maximum expression levels)
- Develop approaches to prenatal delivery of these therapeutic approaches

Actions:

- Invest in preclinical studies to evaluate the efficacy and safety of gene therapy interventions targeting UBE3A reactivation.
- Explore innovative gene delivery methods, such as viral vectors, nanoparticles, and CRISPR-based technologies, for precise and sustainable UBE3A restoration.
- Collaborate with industry partners to accelerate the translation of promising gene therapy strategies into clinical applications, while ensuring rigorous regulatory compliance and ethical standards.

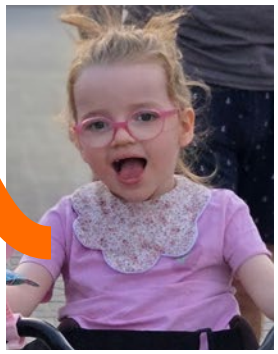
Clinical Care and Innovation

Goal: Enhance the quality of life and well-being of individuals with Angelman Syndrome through comprehensive and personalized clinical care approaches.

Objective: Expand the therapeutic toolkit for Angelman Syndrome to address the multifaceted nature of the disorder.

Actions:

- Support research into pharmacological interventions targeting specific molecular pathways implicated in AS pathogenesis, such as synaptic dysfunction, GABAergic signaling, and neuroinflammation.
- Investigate the potential synergistic effects of combining gene therapy with other therapeutic modalities, such as behavioral interventions, dietary supplements, and neuromodulation techniques.
- Advance the development and accessibility of symptomatic therapeutics in Angelman syndrome.
- Promote diversity in therapeutic development by encouraging studies that consider the unique genetic, phenotypic, and environmental factors influencing AS manifestation and response to treatment.
- Implement innovative care models, such as telemedicine and remote monitoring technologies, to increase accessibility and continuity of care for patients and caregivers, particularly in underserved communities.
- Foster partnerships between academic institutions, advocacy organizations, and healthcare providers to develop and disseminate best practices in AS clinical management, including early intervention strategies, symptom management protocols, and caregiver support programs.
- Ensure that the LADDER Learning Network is utilizing the database to input clinical outcomes in order to update, create and standardize care.
- Support the development of early detection methods, including pre-natal, and their implementation.



Therapeutic Endpoints and Biomarkers

Goal: Continue to fund studies to explore and develop endpoints and biomarkers to improve clinical trial design and measurement of response beyond physician and caregiver reported measures.

Objective: Establish objective measures of treatment response and disease progression to facilitate the evaluation of therapeutic interventions for Angelman Syndrome.

Actions:

- Collaborate with regulatory agencies, patient advocacy groups, and industry stakeholders to define clinically meaningful endpoints and biomarkers for use in AS clinical trials.
- Invest in the validation and standardization of outcome measures assessing key domains of AS symptomatology, such as motor function, communication skills, cognitive abilities, and behavioral profiles.
- Support the development of novel biomarkers, including neuroimaging markers, electrophysiological assays, and molecular signatures, to improve diagnostic accuracy, monitor disease progression, and predict treatment outcomes in individuals with AS.
- Maximize the utilization of LADDER data in all research initiatives. This goal aims to enhance the visibility and usability of LADDER data, ensuring it becomes a foundational element of the research community's efforts, aligned with the initial investment and strategic vision of the research roadmap.

By pursuing these research directions and collaborative initiatives, the Angelman Syndrome community can advance scientific knowledge, accelerate therapeutic development, and ultimately improve the lives of individuals affected by this rare neurodevelopmental disorder.

Background

The Angelman Syndrome Foundation was formally established in 1992 and began supporting AS research efforts in the mid 1990's. The first research grant was awarded by the foundation in 1996 ($10,000) to Dr. Joseph Wagstaff to study "Melatonin and Sleep in Angelman Syndrome", with the results published in 1999 (Journal of Pediatric Endocrinology & Metabolism, 1999, 12, 57-67). Between then and 2009, 59 grants, totaling ~$3.6 MM, were awarded. The studies supported during this period were wide ranging *(See Table I)* and a reflection of where the science of AS was at that time.

The 2009 ASF Scientific Roadmap

In 2008 the ASF assembled a task force to develop a Scientific Roadmap for the foundation. The task force was chaired by Charles Williams, the presiding chair of the ASF SAC. The task force members were Aaron Ciechanover, Evan Snyder, Dan Harvey, Steve Katz, and Fred Pritzker. The objective of the task force was to develop a roadmap (strategic plan) to guide the future scientific activities of the foundation and to ensure the efficient and productive use of its research dollars. The plan had the following three broad goals:

1. Aggressively support therapies to correct the UBE3A gene defects in AS

2. Develop new therapeutic strategies in AS to ameliorate and/or cure the problems of:
   - Seizures
   - Movement disorders
   - Language disability
   - Cognitive impairment

3. Identify "best practices" for improvement of the health, behaviors and life skills of those with AS

For each goal, short and long-term objectives (action plans) were defined *(See Figure 1)*.

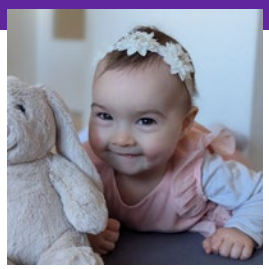


***Figure 1* – Summary of the Goals, short-term and long-term objectives of the 2009 ASF Research Roadmap**

Goals	Short-Term Action Plan	Long-Term Action Plan
Aggressively support therapies to correct the UBE3A gene defects in AS	• Delineate UBE3A regulatory aspects, including Imprinting Center mechanism of action • Attempt UBE3A delivery / regulation in the animal model • Conduct stem cell therapy studies	Support human trials for: • UCE3A replacement / activation • UBE3A gene / cell therapies
Develop new therapeutic strategies in AS to ameliorate and / or cure the problems of: • Seizures • Movement disorders • Language disability • Cognitive impairment	• Identify relevant UBE3A targets • Better define neuronal-UBE3A physiology • Identify critical areas in brain for UBE3A action • Conduct animal model treatments • Support alternative therapy research	Support human clinical trials for: • UBE3A druggable targets such as new anticonvulsant drugs. • Support novel therapies / alternative therapies
Identify "best practices" for improvement of the health, behaviors and life skills of those with AS	• Better define natural history • Support behavioral intervention research • Identify effective clinical outcomes • Identify emerging adult and end-of-like issues	Promote and disseminate information about best practices for care, treatment and amelioration

The 2009 Road Map envisioned achieving these goals through the establishment of an Angelman Treatment and Research Institute (ATRI). The ATRI was anticipated to position the ASF as an international hub for collaboration on translatable research targeted to improve the symptoms and lifestyle difficulties for those with ASF. The ATRI was envisioned by the road map committee to be part of the ASF but supported by its own staff and structure. Once fully operational, the ASF SAC was expected to be brought under the ATRI umbrella.

Additionally, the 2009 roadmap committee defined what would constitute a cure for AS and the theoretical ways at that time that such a cure might be achieved. It also acknowledged that such potentially curative treatments would most likely be best administered during fetal development or in the early postnatal period but recognized that there was insufficient knowledge at present to set an absolute time window for such treatments.

What has been accomplished since 2009?

Since development of the 2009 roadmap, considerable progress has been made in many areas. We will not attempt to present them all here but will summarize some of the progress made toward each of the three 2009 roadmap goals. The research grants funded during this period are provided in Table 1. From 2010 through 2023, 72 research grants totaling $12,138,141 were funded.

2009 Road Map Goal 1: Aggressively support therapies to correct the UBE3A gene defects in AS

Antisense Oligonucleotides (ASOs): In 2011 the ASF funded a proposal from Art Beaudet titled "The role of antisense RNA Ube3a-ATS in Ube3a imprinting and Angelman syndrome". In that proposal Dr. Beaudet stated:

> "Most of the Angelman syndrome patients have loss of UBE3A function due to maternal deletion, paternal uniparental disomy, imprinting defects or point mutation within UBE3A. No matter which class a patient belongs to, he/she usually has a normal copy of paternal UBE3A, which has the correct coding sequence, but is silenced under physiological conditions. **If this copy of UBE3A can be reactivated in Angelman syndrome patients, significant improvements and recovery from Angelman-syndrome phenotype should be anticipated".**

Their studies, some of which were done in collaboration with Ionis, were published shortly thereafter (PLoS Genet., **2013**, 9; Nature, **2015**, 518, 409-412) and demonstrated that antisense oligonucleotides (ASOs) could unsilence paternal Ube3a and, in an AS mouse model, were capable of ameliorating some of the cognitive deficits associated with AS. Subsequent investigations by Ionis and others led to the advancement of three ASO-based programs into the clinic by GeneTx/Ultragenyx (2020, Phase 1/2), Roche (2020, Phase 1), and Ionis/Biogen (2021, Phase 1/2). Phase 3 studies were initiated by Ultragenyx in Q4 2024 and are anticipated to be initiated by Ionis in H1 2025.

Gene Therapy: The foundation has also supported the development of gene therapy approaches. In 2007, prior to preparation of the 2009 roadmap, the foundation funded studies by Weeber et al, which were published in 2011 (PLoS ONE, 2011, 6, 27221) and demonstrated that an AAV-based approach could improve the cognitive deficits associated with AS in a mouse model. Subsequently, funding to support gene therapy investigations was provided to the labs of Dindot (2011), Zylka (2016, 2018), Gray (2017), Philpot (2020), and Butler (2022). Overall, these studies have demonstrated that gene therapy approaches to the treatment of AS are viable in animal models. Unfortunately, translation to human studies has been challenging, which is not unique to AS. Further investigations to move this area forward are in progress and additional development and pre-clinical efforts in this area are ongoing. Most promising is the announcement in November 2024 by Jim Wilson of GEMMA Biotherapeutics that IND-enabling studies of GTP-220 had been completed and that IND submission was expected in Q1-2025

Stem Cells: A short-term action plan under goal 1 was the exploration of patient derived stem cells. The first grant in this area was awarded to Eric Levine in 2011 with additional studies later supported in the labs of Chamberlain (2014), Morrow (2017), Doughty (2021), and Levine (2022). For a recent review of the extensive progress made in this area see Rocha et al. Front. Cell Dev. Biol. **2023**, 11, 1274040. The first AS induced pluripotent stem cells (iPSCs) were generated in the Chamberlain labs (PNAS, **2010**, 107, 17668-17673) and various other types of AS stem cell lines have subsequently been developed. Though still relatively new, induced pluripotent stem cells are now an important tool being used by many investigators to test and develop potential new AS therapeutic strategies.

Small molecule "unsilencers": In 2009, funds were provided to the Philpot lab to identify novel compounds that could increase the expression of Ube3a in brain neurons. Using a high-content screen of a known drug collection, a group of compounds known as topoisomerase inhibitors were found to unsilence the paternal Ube3a allele (Nature, **2011**, 481, 185-189). Additional funds were provided to the Philpot and Zylka labs in 2011 to support additional preclinical studies in this area. The inherent toxicity and poor CNS penetration of this compound class precluded their advancement to the clinic, but these studies provided further evidence that unsilencing of paternal UBE3A is a viable approach to AS therapy development. Funding to identify additional small molecule unsilencers of Ube3a was provided to the Philpot team in 2017. These studies identified a new class of small molecules outside of the topoisomerase chemistry space that can induce paternal Ube3a expression in mice, and paternal UBE3A expression in human iPSC derived neurons. The results of these studies were recently published (Nat Commun, **2024**, 15, 5558) and represent a significant step forward in the development of a small molecule treatment for AS.

2009 Roadmap Goal 2 – Develop new therapeutic strategies in AS to ameliorate and/or cure the problems of: Seizures, Movement disorders, Language disability and Cognitive impairment.

Activities in this relatively broad area have been extensive and a few are highlighted here.

Gaboxadol – In 2012, Egawa and colleagues reported preliminary studies of the ability of 4,5,6,7-tetrahydroisothiazolo-[5,4-c)pryidin-3-ol (aka THIP, Gaboxadol), an extrasynaptic GABAA receptor agonist, to decrease tonic inhibition in various AS models. As clinical studies of gaboxadol had previously been completed and considerable safety data was available, clinical studies of gaboxadol as a treatment for AS were pursued by Ovid Therapeutics. In 2017, the foundation supported additional studies of gaboxadol by Egawa (Egawa, 2017) to develop a deeper understanding of the basis of this therapeutic approach. An initial phase 2 open-label trial suggested a positive response but, unfortunately, in a phase 3 blinded study, gaboxadol did not perform significantly better than placebo.

Cannabidiol – CBD, a major component of cannabis has shown significant antiseizure activity and, based on community reports, is frequently being used to treat individuals with AS. In 2017, the ASF provided support to Carney and colleagues to conduct a preclinical assessment of CBD as a treatment for AS. These studies, published in **2019** (J. Clin Invest, 2019, 129, 5462-5467) provided "critical preclinical evidence supporting CBD treatment of seizures and alleviation of EEG abnormalities in AS", thus justifying its clinical use.

Identification of relevant UBE3A targets – Identifying the downstream targets of UBE3A is of critical importance to expanding our understanding of the biochemistry of AS and the future development of rationally designed treatments. The ASF has funded downstream target studies in several labs (Howley, 2009; Klann, 2009; Greenberg, 2011; Lismann, 2013; Shepard, 2013; Kaphzan, 2015; Doughty, 2021). The targets studied by these groups include but are not limited to NRB-a/ErbB4, Dopamine D4 Receptors, Arc, Ephexin5, CaMKII and Alpha1-NaKA. These studies have not yet clearly identified a downstream druggable target but, in total, have greatly expanded our understanding of the extensive network of biochemical pathways influenced by the UBE3A gene.

Seizures – In addition to the cannabidiol studies mentioned above, several seizure-related awards have been made. In 2008, as the 2009 roadmap was being developed, funding was provided to Ron Thibert to study "The Significance of EEG Findings in AS" and in 2010, funds were provided to Althea Robinson to evaluate EEGs and their relationship to sleep and behavior in children with AS. More recently, several funded studies have demonstrated that EEGs are a potential useful biomarker in AS clinical trials. Additional funding to study nonepileptic myoclonus in AS has been provided to Robert Carson. Overall, our understanding of how various types of seizures present and manifest in EEGs, as well as the importance of aberrant spectral power to AS, has been significantly expanded.

Language/Communication – Grants to support language and communication research have been relatively limited (Sadhwani, 2015; Sennott, 2016) but extensive effort has been made by the foundation towards the development of language/communication training and education resources. In particular, a Communication Training Video Series, comprised of 43 sessions covering a wide area of communication related topics, was developed. More recently, "Stepping into AAC", a 20-part program supporting the use of Augmentative/Alternative Communication (AAC) devices has been produced in collaboration with PrAACtical AAC.

Goal 3: Identify "best practices" for improvement of the health, behaviors and life skills of those with AS

Key efforts in this area have been the AS Natural History Study, the creation of a network of AS Clinics and the development of the LADDER database.

The AS Natural History Study, which was started in 2006 and currently incorporates data collected on more than 544 individuals with AS, is now a critical resource for the AS clinical research community. For example, data from the AS Natural History Study was recently used to analyze the achievement of daily living skills and developmental milestones (Journal of Neurodevelopmental Disorders, 2024, 16, 32). The availability of such data is extremely useful to establish a baseline of achievement for ongoing and upcoming clinical trials, particularly those in which a concurrent placebo arm would be inappropriate or too challenging. Initial funding for the study was provided by the NIH. The study is currently supported through the Angelman Syndrome Biomarkers and Outcome Measures Consortium (ABOM) with funding provided by the ASF, Ionis, Roche, Ultragenyx, and FAST. Annual funding is approximately $500K.

The ASF Clinics, now part of the **L**inking **A**ngelman and **D**up15q **D**ata for **E**xpanded **R**esearch (LADDER) Learning Network (LLN), began with two sites in Chapel Hill, NC and Boston, MA in 2012. The network now encompasses thirty-five clinics, twenty-three throughout the United States and twelve international. Seventeen of these clinics also support Dup15q syndrome research and treatment. These clinics provide individuals with AS access to the highest quality, evidence-based medical care covering a broad range of disciplines. Additionally, they provide critical experience and expertise in AS to support current and future clinical trials.

The LADDER Learning Network aims to meet the following guiding objectives:

- **Increase access** of families with Angelman syndrome (AS) and Duplication 15q syndrome (Dup15q) to comprehensive multidisciplinary clinical care at specially designated ASF/Dup15q clinic sites.
- **Facilitate communication and collaboration** among US and international AS/Dup15q experts to share knowledge, discuss challenging cases, and work together on publications to benefit both communities.
- **Promote clinical and translational research** through the LADDER database and support clinical trials to better understand both conditions and contribute to therapeutic development.

Overall, during the 2012-24 period, the ASF has provided $2.04 MM of support to the ASF Clinics and the Ladder Learning Network.

The LADDER Database, is a strategic collaboration between the ASF and the Dup15q Alliance. It brings together information about AS and Dup15q collected from sources all over the world including:

- The Angelman Natural History Study
- Patient visits to the Clinics in the LADDER Learning Network
- The Global Angelman Syndrome Registry
- Research Studies done on AS and Dup15q

Recently, a number of studies that have mined the data available through the LLN have been published. During the 2020-24 period, the ASF has provided $1.7 MM of support to this effort.

A number of activities of importance that were not explicitly envisioned in the 2009 Roadmap have also been pursued. One of some significance is the involvement of the ASF in the Angelman Biomarkers and Outcome Measures (ABOM) Alliance. In 2016 it was clear that a significant number of therapeutic approaches to the treatment of AS were going to be ready for clinical studies in the coming years. In March of that year, an initial meeting of representatives from family support groups, academic investigators and several pharma companies that were at an early stage of developing AS therapeutics was held to discuss what needed to be done to ensure that the anticipated clinical studies had the greatest chance of success. This meeting led to the creation later that year of ABOM. The alliance included patient foundations, such as the ASF, pharma companies (Ovid, Agilis, Roche, Ionis and others) and various academic investigators with clinical expertise. The focus of the alliance was the pre-competitive space wherein pharma companies are generally more willing to share information. A steering committee was formed and a diverse array of topics were explored, including, but not limited to, communication, gross motor, fine motor, cognition, sleep, seizures, behavior, quality of life/activities of daily living, Clinical Global Impression rating scales, and biomarkers derived from blood/body fluids. Through the efforts of this alliance, numerous collaborative projects were initiated, many of which supported the foundational clinical trials recently completed.

Grant Year	First	Last	Title	Institute	Amount Funded
1996	Joseph	Wagstaff	Melatonin and Sleep in Angelman Syndrome	Boston Children's Hospital	$10,000.00
1997	Richard	Olsen	GABA beta3 Deficient Mice		$10,000.00
1998	Nicolay	Walz	Behavioral Aspects of Angelman Syndrome	Cincinnati Children's Hospital	$3,213.00
1999	Stephen	Calculator	Use of Enhanced Natural Gestures and Angelman Syndrome	University of New Hampshire	$10,581.00
1999	Tim	DeLorey	GABA beta3 Deficient Mice		$10,000.00
1999	Richard	Olsen	GABA-A receptor beta 3 subunit knockout mice		$10,000.00
2000	Arthur	Beaudet	A Therapeutic Trial of Folate and Betaine in Angelman Syndrome	Baylor College of Medicine	$62,903.00
2000	Ethan	Bier	Molecular Genetic Analysis of the Drosophila Angelman Syndrome Gene	University of California San Diego	$25,000.00
2000	Louise/Jill	Tiranoff/Clayton-Smith	(1) History & Discovery: Dr. Harry Angelman's Observations, (2) Special Issues of Adolescence and The Transition to Adulthood	Other	$29,700.00
2000	Nicolay	Walz	Sleep Patterns and Autistic Symptomology in Angelman Syndrome: Further Delineation of the Behavioral Phenotype	Cincinnati Children's Hospital	$3,600.00
2002	Lynne	Bird	Folate Clinical Study SD Grant	University of California San Diego	$14,145.00
2002	Stephen	Calculator	Efficacy of Enhanced Natural Gestures for Young Children with Angelman Syndrome	University of New Hampshire	$11,541.00
2002	Soma	Das	Molecular Analysis of the Angelman Syndrome: The role of UBE3A deletions	University of Chicago	$25,000.00
2002	Joseph	Wagstaff	Role of the UBE3A Gene Product in Brain Protein Metabolism	University of Virginia	$45,547.00
2003	Lynne	Bird	Folic Acid/Betaine Clinical Study	University of California San Diego	$26,000.00
2005	Yong-Hui	Jiang	Dissecting the roles of Ube3a in synaptic plasticity by analyzing synaptic function at the single cell level and utilizing 'Network Analysis Proteomics' strategy'.	Baylor College of Medicine	$56,000.00
2005	Aaron	Razin	Control of monoallelic expression of the Angelman gene UBE3A	The Hebrew University - Hadassah Medical School	$50,000.00

Grant Year	First	Last	Title	Institute	Amount Funded
2005	Jane	Summers	Evaluating the effectiveness of ABA-based approaches for teaching functional skills to children with Angelman syndrome	McMaster Children's Hospital and McMaster University	$47,000.00
2005	Joseph	Wagstaff	Testing for Correction of the Angelman Syndrome Phenotype of UBE3A-Maternal-Deficient Mice by UBE3A Transgene	Carolinas Medical Center	$47,000.00
2006	Terry Jo	Bichell	Alphabet Therapy	Vanderbilt University	$31,300.00
2006	Stephen	Calculator	Communication/Educational programs for students with Angelman Syndrome in inclusive classrooms: A look at best practices.	University of New Hampshire	$31,087.00
2006	Benjamin	Enav	A Prospective Pilot Study of Gastric Myoelectrical Activity in Children with Angelman Syndrome	UCLA	$30,000.00
2006	Fen-Ben	Gao	Genetic dissection of the Molecular Pathways Underlying the Pathogenesis of Angelman Syndrome.	Gladstone Institute of Neurological Disease	$85,000.00
2006	Michael	Greenberg	Investigation of UBE3A in the role of Synapse Development	Boston Children's Hospital	$85,000.00
2006	Peter	Hammond	Facial phenotype-genotype correlations in Angelman Syndrome	UCL Eastman Dental Institute	$10,500.00
2006	Gentry	Patrick	Elucidating the function of the E6AP ligase at mammalian CNS synapses	University of California San Diego	$50,000.00
2006	Lowell	Rayburn	Effect of premature truncation of the Ube3a antisense transcript on Ube3a imprinted expression	Carolinas HealthCare System	$82,255.00
2007	Arthur	Beaudet	A rigorous test in the mouse of whether increased DNA methylation can activate neuronal expression of the paternal Ube3a allele	Baylor College of Medicine	$80,000.00
2007	Margaret	Bradley	Brain potentials of cognition and emotion in individuals with Angelman Syndrome	University of Florida	$35,000.00
2007	Aaron	Ciechanover	The Ubiquitin Ligase E6-AP Targets the Polycomb Repressive Complex Proteins ring1b and bmil to Ubiquitination and Subsequent degradation: Structural and functional Implications and Possible Relationship to the Pathogenesis of Angelman Syndrome	Technion-Israel Institute of Technology	$95,000.00
2007	Michael	Ehlers	Ube3a and Altered Neuronal Trafficking in Angelman Syndrome	Duke University	$75,000.00

Grant Year	First	Last	Title	Institute	Amount Funded
2007	Yong-Hui	Jiang	Explore the therapeutic potential of levodopa to treat Angelman syndrome in mouse model	Baylor College of Medicine	$50,000.00
2007	Brian	Kuhlman	Redesigning the Ubiquitin Pathway to Identify the Substrates of E6AP	University of North Carolina, Chapel Hill	$80,000.00
2007	Sarika	Peters	Neuroimaging Studies in Angelman Syndrome	Baylor College of Medicine	$85,000.00
2007	Benjamin	Philpot	Importance of Ube3A for Experience-Dependent Modifications of Cortical Synapses	University of North Carolina, Chapel Hill	$70,000.00
2007	Michael	Stryker	The role of UBE3A in development of excitatory-inhibitory balance in neocortex	University of California San Francisco	$80,000.00
2007	Jane	Summers	Developing an assessment battery to study learning, memory and motor performance in children with Angelman syndrome	McMaster Children's Hospital and McMaster University	$30,000.00
2007	Ronald	Thibert	Low Glycemic Index Therapy for the Treatment of Epilepsy in Angelman Syndrome	Massachusetts General Hospital	$28,850.00
2007	Elizabeth	Thiele	Seizure Survey	Massachusetts General Hospital	$10,000.00
2007	Edward	Weeber	Therapeutic effectiveness of levodopa in the treatment of seizures and motor defects using the Angelman Syndrome mouse model	University of South Florida	$50,000.00
2007	Edward	Weeber	Identifying Potential Therapeutic Strategies for the Treatment of Angelman Syndrome	University of South Florida	$62,200.00
2008	Lynne	Bird	Levodopa/Carbidopa Treatment of children with Angelman Syndrome	University of California San Diego/UCSF	$72,855.00
2008	Michael	Ehlers	Restoration of Neocortical Plasticity in a Mouse Model of Angelman Syndrome	Duke University	$95,000.00
2008	Ype	Elgersma	Are the neurological symptoms of Angelman Syndrome reversible? An inducible mouse model for Angelman Syndrome	Erasmus University Medical Center	$76,600.00
2008	Yong-Hui	Jiang	Explore epigenetic therapy of using histone deacetylase inhibitors in the Angelman syndrome mouse model	Duke University	$98,450.00
2008	Eric	Klann	Neuregulin-dependent Alterations in Glutamate Receptor Function and LTP in Angelman Syndrome Model Mice	New York University	$78,788.00

Grant Year	First	Last	Title	Institute	Amount Funded
2008	Chris	Oliver	Establishing the basic principles of effective intervention for difficult behaviour in Angelman syndrome.	University of Birmingham	$78,497.00
2008	Benjamin	Philpot	Restoration of Neocortial Plasticity in a Mouse Model of Angelman Syndrome	University of North Carolina, Chapel Hill	$95,000.00
2008	Lawrence	Reiter	A combined molecular and electrophysiological approach to understanding cerebellar defects in Angelman syndrome	University of Tennessee Memphis	$77,866.00
2008	David	Segal	Towards Gene Therapy for Angelman Syndrome Using Artificial Transcription Factors.	University of California Davis	$76,055.00
2008	Ronald	Thibert	The Significance of EEG Findings in Angelman Syndrome	Massachusetts General Hospital	$58,256.00
2009	Keith	Allen	Evaluation of a Standard Behavioral Protocol in the Treatment of Sleep Problems in Children with Angelman Syndrome	University of Nebraska Medical Center	$64,269.00
2009	Scott	Dindot	Determining the Role of the E6-AP Isoforms in Synaptic Maturation	Texas A&M University	$94,563.00
2009	Peter	Howley	Identification of UBE3A Ligase Substrates	Harvard Medical School	$200,000.00
2009	Yong-Hui	Jiang	Novel Ube3a Isoform and Angelman Syndrome	Duke University	$99,425.00
2009	Eric	Klann	NRB-a/ErbB4 and Dopamine D4 Receptors as Therapeutic Targets to Treat Cognitive Deficits in Angelman Syndrome	New York University	$197,580.00
2009	John	Marshall	Rescue of Angelman Syndrome Learning Deficits by an Investigational New Drug	Brown University	$198,899.00
2009	Sarika	Peters	Use of Conventional and Complementary and Alternative Treatments for Problem Behaviors in Angelman Syndrome	Vanderbilt University/Baylor	$40,269.00
2009	Benjamin	Philpot	Novel therapeutics for Angelman syndrome by manipulating Ube3a expression	University of North Carolina, Chapel Hill	$199,972.00
2010	Althea	Robinson	Association of Sleep and Behavior in Children with Angelman Syndrome (RDCRN)	Vanderbilt University - RDCRN	$25,000.00
2011	Arthur	Beaudet	The role of antisense RNA Ube3a-ATS in Ube3a imprinting and Angelman syndrome	Baylor College of Medicine	$100,000.00

Grant Year	First	Last	Title	Institute	Amount Funded
2011	Julie	Davidson	Rett Syndrome Disorders and Angelman Syndrome as genetic models for autism spectrum disorders (RDCRN)	Vanderbilt University - RDCRN	$25,000.00
2011	Scott	Dindot	Examining rescue of neurological deficits in Angelman syndrome mice by expression of the E6-AP isoforms	Texas A&M University	$84,011.00
2011	Ype	Elgersma	An inducible mouse model for Angelman Syndrome: follow up	Erasmus University Medical Center	$92,144.00
2011	Michael	Greenberg	Validation of Arc and Ephexin5 as Novel Therapeutic Targets for the Treatment of Angelman Syndrome	Harvard Medical School	$200,000.00
2011	Ian	King	Epigenetic regulation of *Ube3a* by a candidate Angelman syndrome drug (UNCilencer1) - Wagstaff Fellowship	University of North Carolina, Chapel Hill	$110,000.00
2011	Eric	Levine	Pathophysiology in a human stem cell model of Angelman syndrome	University of Connecticut Health Center	$120,000.00
2011	Benjamin	Philpot	Preclinical testing of a candidate Angelman syndrome therapeutic	University of North Carolina, Chapel Hill	$200,000.00
2011	Mark	Zylka	Molecular mechanisms and biomarkers of a candidate Angelman syndrome therapeutic	University of North Carolina, Chapel Hill	$200,000.00
2012	Dan	Glaze	Sleep study (RDCRN)	Baylor College of Medicine - RDCRN	$17,000.00
2013	Arthur	Beaudet	Ube3a-ATS targeted antisense oligonucleotides as therapies for Angelman syndrome	Baylor College of Medicine	$200,000.00
2013	Ype	Elgersma	Defining Treatment Parameters for Angelman Syndrome	Erasmus Medical Center	$200,000.00
2013	Craig	Erickson	Preclinical Validation of Behavioral, Molecular, and Electrophysiological Effects of Acamprosate in A Mouse Model of Angelman Syndrome	Cincinnati Children's Hospital Medical Center	$81,631.00
2013	John	Lisman	Identification and manipulation of the phosphatases that produce aberrant phosphorylation of CaMKII in AS	Brandeis University	$200,000.00
2013	Angela	Mabb	Epigenetic Regulation of Ube3a by Topoisomerases - Wagstaff Fellowship	University of North Carolina, Chapel Hill	$110,000.00
2013	Benjamin	Philpot	Defining Treatment Parameters for Angelman Syndrome	University of North Carolina, Chapel Hill	$200,000.00
2013	Jason	Shepherd	Investigating the causal role of Arc in Angelman Syndrome pathogenesis	University of Utah	$170,202.00
2013	Mark	Zylka	Studies to determine how Angelman syndrome-associated missense mutations disrupt UBE3A function	University of North Carolina, Chapel Hill	$200,000.00

Grant Year	First	Last	Title	Institute	Amount Funded
2015	Stormy	Chamberlain	Testing the efficacy of antisense oligonucleotides against UBE3A-ATS in human neurons	University of Connecticut Health Center	$200,000.00
2015	Ben	Distel	Identification and characterization of novel targets and activators of E6AP	Academic Medical Center	$197,685.00
2015	Heather	Hazlett	Validation of Biomarkers for Angelman Syndrome Clinical Trials	University of North Carolina Carolina Institute for Developmental Disabilities	$89,980.00
2015	Hanoch	Kaphzan	Validation of Alpha1-NaKA Inhibition as a Novel Therapeutic Strategy for the Mouse Model of Angelman Syndrome	University of Haifa	$200,000.00
2015	Shalaka	Mulherkar	Targeting Rho GTPase Signaling in Angelman Syndrome - Wagstaff Fellowship	Baylor College of Medicine	$110,000.00
2015	Ben	Philpot	Validation of Biomarkers for Angelman Syndrome Clinical Trials	University of North Carolina, Chapel Hill	$168,700.00
2015	Anjali	Sadhwani	Speech generating devices in children with Angelman syndrome: An effectiveness trial	Boston Children's Hospital	$198,948.00
2015	Ronald	Thibert	Validation of Biomarkers for Angelman Syndrome Clinical Trials	Massachusetts General Hospital	$37,380.00
2016	Ype	Elgersma	Deciphering the role of UBE3A isoforms, by using isoform-specific mouse models for Angelman Syndrome	Erasmus Medical Centre	$199,650.00
2016	Christopher	Keary	Anxiety in Angelman Syndrome	Massachusetts General Hospital	$181,800.00
2016	Eric	Levine	Synaptic plasticity deficits in Angelman syndrome patient-derived neurons	University of Connecticut Health Center	$200,000.00
2016	Sam	Sennott	Augmentative and Alternative Communication (AAC) Immersion Project for Individuals with Angelman Syndrome	Portland State University	$79,755.00
2016	Geeske	van Woerden	Identifying hippocampus-dependent learning tests for drug testing in AS mice	Erasmus MC	$122,650.00
2016	Mark	Zylka	Genome-scale CRISPR/CAS9 screen to identify new therapeutic targets for Angelman syndrome	University of North Carolina at Chapel Hill	$200,000.00
2017	Terry Jo	Bichell	ABOM salary	N/A	$27,600.00
2017	Paul	Carney	Preclinical assessment of cannabidiol as a treatment for Angelman syndrome	University of North Carolina at Chapel Hill	$200,000.00
2017	Kiyoshi	Egawa	Pathophysiological impact of diverse deregulation of tonic inhibition in Angelman syndrome	Hokkaido University Graduate School of Medicine	$149,990.00

Grant Year	First	Last	Title	Institute	Amount Funded
2017	Noelle	Germain	Investigating the efficacy of novel therapeutic approaches for restoring UBE3A expression in human Angelman syndrome neurons	UConn Health	$100,000.00
2017	Steven	Gray	Angelman Syndrome Gene Therapy	University of Texas Southwestern	$200,000.00
2017	Sasha	Key	ABOM research	Vanderbilt	$7,455.00
2017	H. A.	Moll	CompAS	Erasmus MC Sophia Children's Hospital	$131,618.00
2017	Eric	Morrow	Shared cellular mechanisms in Angelman syndrome and Christianson syndrome	Brown University	$200,000.00
2017	Ben	Philpot	Pilot study to validate three novel classes of small moelcules to unsilence the paternal UBE3A allele.	University of North Carolina at Chapel Hill	$200,000.00
2017	Anjali	Sadhwani	ABOM research	Boston Children's Hospital	$13,434.00
2018	David	Godler	Newborn screening for Prader Willi and Angelman Syndromes: A feasibility study on 50,000 newborns	Murdoch Children's Research Institute	$80,000.00
2018	Mark	Zylka	Validation of therapeutic guide RNAs targeting the UBE3A antisense transcript	UNC Chapel Hill	$200,000.00
2019	Ype	Elgersma	To what extent are striatal deficits underlying clinical features of Angelman Syndrome?	Erasmus Medical Centre	$199,650.00
2019	Karen	Erickson	The Prevalence and Form of CVI in Angelman Syndrome	UNC Chapel Hill	$93,648.00
2019	Gilles	Trave	Role of UBE3A-HERC2 complex in Angelman Syndrome: 3D structure and quantitative interactomics	CERBM	$100,000.00
2019	Jason	Yi	Structure-function studies to characterize UBE3A missense variants	Washington University in St. Louis	$200,000.00
2020	Charlott	DiStefano	EEG Biomarkers of Language in Angelman Syndrome	The Regents of UCLA	$199,928.00
2020	Holly	Fitch	Developmental UBE3A effects on language-related assessments in a mouse AS model	University of Connecticut Health Center	$197,000.00
2020	Bridgette	Kelleher	Piloting a Cusomized Telehealth-Based Caregiver Support Intervention in Angelman Syndrome	Purdue University	$50,000.00
2020	Ben	Philpot	Mapping UBE3A in Non-Human Primates to Inform UBE3A Gene Therapy and reinstatement Strategies to Treat Angelman Syndrome	UNC Chapel Hill	$95,102.00

Grant Year	First	Last	Title	Institute	Amount Funded
2021	Robert	Carson	Characterization of Nonepileptic Myoclonus in Angelman Syndrome	Vanderbilt University Medical Center	$103,342.00
2021	Martin	Doughty	Identifying UBE3A substrates targeted for proteasome degradation in human cortical neurons and their pathological importance in Angelman Syndrome	The Uniformed Services University of the Health Sciences	$150,000.00
2021	Ype	Elgersma	Better mice for better insights and treatments: an AS '15q11-13 deletion' mouse model	Erasmus Medical Centre	$198,000.00
2021	Brigid Anita	Kelleher Panjwani	Ingestive behaviors and gut microbiota in children with Angelman syndrome	Purdue University	$100,000.00
2021	Michael	Sidorov	Phenotyping mouse models of Angelman syndrome using multidimensional behavioral clustering	Children's National Hospital	$138,268.00
2022	Jamie Mark	Capal Shen	Recruitment and Deep Phenotyping of Infants with AS to Enable Early Treatment	UNC Chapel Hill	$199,000.00
2022	Ype	Elgersma	ASO Treatmet for a Better Understanding of AS Pathophysiology and Optimizing Therampeutic Efficacy	Erasmus Medical Centre	$199,100.00
2022	Joint w/FAST		Newborn screening for Prader Willi and Angelman Syndromes		$154,000.00
2022	Adam	Hantman	Pilot Study to Understand Skilled Motor Impairments in Angelman Syndrome	UNC Chapel Hill	$200,000.00
2022	Kara	Margolis	Angelman and the Gut	NYU	$250,000.00
2022	Ben/Mark	Philpot/Zylka Amaral	Pilot to assess feasibility of targeting maternal UBe3a allele-specifically in rhesus macaque blastocyts	UNC Chapel Hill, UC Davis	$95,201.62
2022	Anne	Wheeler	Development of the Angelman Syndrome Specific Neurodevelopment Training Manual" (PIXI)	RTI	$195,436.00
2023	Ryan	Butler	Support of the shRNA/AAV9 approach to treat AS	UTSW	$200,000.00
2023	Ype	Elgersma	Can individuals with ICD/UPD mutations participate in ASO trials: The effect of 2-fold UBE3A overexpression in an ICD/UPD mouse model	Erasmus	$99,000.00
2023	Eric	Levine	Contribution of hemizygous HERC2 deletion to Angelman syndrome pathophysiology	University of Connecticut Health Center	$200,000.00
2023	Wen-Han	Tan/FAST	Natural History Study	w/FAST	$235,572.16
2023	Anne	Wheeler	Development and Validation of an Angelman Specific Behavior Measure	RTI International	$290,362.00

Grant Year	First	Last	Title	Institute	Amount Funded
2023	Emily	Farrow	Development and Implementation of a Novel Comprehensive Panel for the Early Detection of Angelman Syndrome	The Children's Mercy Hospital	$199,362.00
2024	Mark	Zylka	Develop biosensor to quantify endogenous UBE3A activity in cells and predict variant pathogenicity	University of North Carolina at Chapel Hill	$200,000.00
2025	Elizabeth Wen-Hann Robert Jean-Baptiste	Berry-Kravis Tan Carson Le Pichon	Movement Disorder Analysis in Angelman Syndrome	Rush University MC Boston's Children's Hospital Vanderbilt University MC Children's Mercy Hospital	
2025	Ype	Elgersma	Establishing Phenotypic readouts in a novel mouse model of AS Type 1 deletion	Erasmus Medical Centre	$148,500.00