FAST
Foundation for Angelman Syndrome Therapeutics
CUREAngelman.org

Angelman Syndrome Roadmap to a Cure

The Need:

The Foundation for Angelman Syndrome Therapeutics (FAST) is focused on funding research that will lead to a cure for Angelman Syndrome (AS). There are almost half a million people worldwide suffering from AS, a single gene disorder that affects speech, cognition, movement, balance, sleep, and behavior and, in most cases, causes life-threatening seizures. Individuals with AS require continuous care and are unable to live independently.

The Knowledge:

- **We know exactly what causes Angelman Syndrome** in individuals - the function of one gene inherited from the mother, maternal UBE3A, is non-functioning. The copy of the *UBE3A* gene inherited from the father is present in everyone, but is silenced in the brain due to a genetic mechanism called imprinting. The fact that *UBE3A* is imprinted plays a very important role in the path to a cure.
- **We know that loss of maternal UBE3A does not affect neuronal development,** only neuronal function and we have evidence that neuronal functionality can be restored.
- **Angelman Syndrome has been cured in the laboratory using four separate strategies** ; drug activation of the paternal gene, protein replacement therapy, gene therapy and biologics. Cognitive and motor delays have been reversed in adult Angelman mice, suggesting that human therapeutics can achieve results at any age.

Gene/Protein Terminology:

The gene involved in human AS is the *UBE3A* gene. The protein this gene makes is **UBE3A.**

When referring to mice, the gene is *Ube3a* and the protein this gene makes is **Ube3a.**

The Roadmap:

FAST proposes that with **$20M, a cure for AS is achievable within five years.** Each of these strategies is purposefully designed to bring therapeutics to human clinical trial in the most efficient and expedient manner possible. Timelines and costs represent bringing therapeutics to the point where pre-clinical validation can occur.

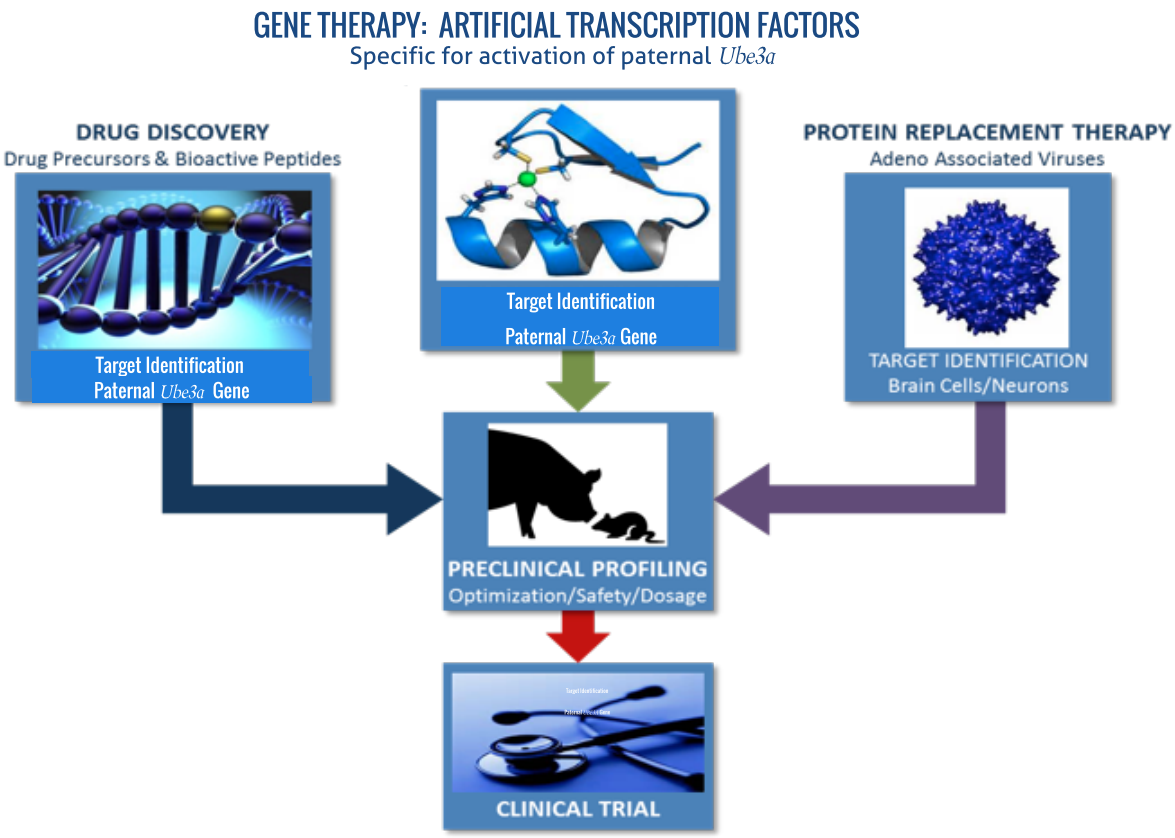

Figure 1. FAST Is Leveraging Multiple Paths to Identify a Cure in the Most Cost Effective and Rapid Methods Possible.

Drug Discovery:

FDA and Near-FDA Approved Drugs-

Identify pharmaceuticals that are, or are in the process of being, FDA approved. This category of drugs represents those that have passed rigorous testing for safety and tolerability and most have known mechanisms of action. Several potential drugs will be tested to determine their effectiveness in AS animal models to treat the 5 major areas of AS symptomology:

- Seizure control
- Cognitive rescue
- Motor coordination and movement
- Sleep patterns
- Synaptic function and neuronal morphology

New Drug Discovery

Identify small molecule precursors, proteins, or bioactive molecules to activate the silenced paternal *Ube3a*.

- We have employed a collaborative approach with different, yet complimentary, drug libraries and reporter / detection strategies to accelerate discovery. Collaborative cross-validation will reduce false positive results and time-consuming parallel paths of redundant pre-clinical development.
- We will share positive results to further expedite the discovery and validation by enabling concurrent evaluation of like drug/protein structures and families of small molecule precursors by multiple research groups.

Gene Therapy:

Animal research on the adult AS mouse model has shown proof-of-principle that gene therapy can reverse symptoms of AS. Specificity of this approach reduces potential negative side effects and increases likelihood of broad therapeutic benefit. We will engineer zinc finger-based artificial transcription factors to activate the paternal *UBE3A* gene.

- A FAST-funded scientist has developed zinc finger-based artificial transcription factors that cross the blood-brain barrier and promote widespread activation of the silenced *Ube3a* gene in the brain of the AS mouse model.

Protein Replacement Therapy:

Bioengineered Viruses (Adeno-associated viruses or AAV's) are now available to alter specific populations of neurons. These viruses can be used to replace the missing *UBE3A* gene, or turn certain cells into UBE3A protein factories to deliver to the rest of the neurons in the brain.

- A FAST funded scientist has already shown that recovery of the adult mouse model is possible using an AAV strategy.
- A FAST funded scientist has engineered an AAV to create Ube3a protein-producing cells and target the protein to be distributed throughout the brain.
- This strategy received Orphan Drug Designation from the FDA in 2015.

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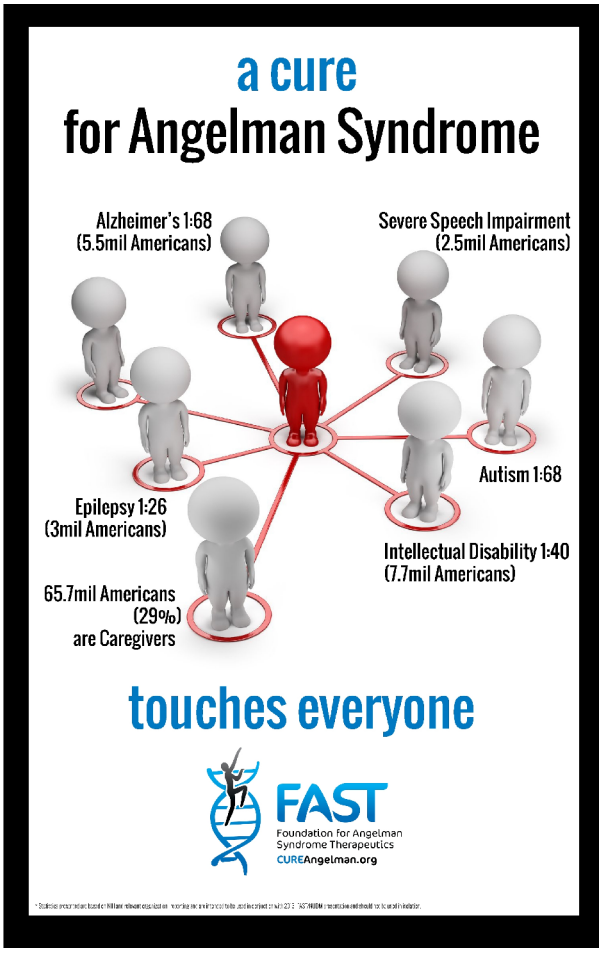
The Impact:

A cure for Angelman Syndrome will have a tremendous impact on society at large.

The gene that causes Angelman Syndrome has been linked to several other diseases and genetic disorders involving learning and memory and stands to be the gateway cure for many other devastating conditions.

- There is a known correlation between Rett Syndrome and Angelman Syndrome.
- There is a known correlation between Fragile X Syndrome and Angelman Syndrome.
- There is a genetic link between Angelman Syndrome and Autism.
- The AS protein UBE3A is decreased in Alzheimer's disease.
- Angelman Syndrome involves one of the most severe types of and one of the few known genetic causes of epilepsy.



Because we know exactly what causes AS and have already cured it in the laboratory, an investment in FAST is an investment of global proportion. You will realize a miracle in your lifetime...for millions of people around the globe.

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The Foundation:

FAST, a 501(c)(3) charitable organization, was formed as an all-volunteer organization in 2008 after AS was first cured in a mouse model.

For decades, small, non-profit disease research organizations like FAST have modeled their funding philosophies after the National Institutes of Health (NIH), where they budget their research dollars, put out a once-a-year call for applications, wait for scientists to come to them with ideas, select the most promising applications, and hope they actually see results. FAST is not at all interested in this slow, linear approach to funding research and, instead, adopted the innovative model of venture philanthropy, recruiting a stellar in-house team to work in partnership with leading scientists on ambitious, high-risk/high-reward study designs that will ensure promising therapeutics make it from the laboratory bench to the patient's bedside as quickly as possible.

Angelman Syndrome is currently one of the most promising fields of scientific research; relying solely on investigator-initiated research to identify and implement patient treatments is inefficient and short-sighted. Additionally, true collaboration of researchers is the best and most rapid strategy to accelerate "bench to bedside" science into therapeutics.

In May of 2013, FAST launched the most aggressive Angelman research initiative in history, bringing more than 25 researchers from 5 universities together in true collaboration to identify additional treatments and a cure for Angelman Syndrome. Through this initiative, not only have we have built a solid infrastructure for our own research agenda but have attracted additional pharmaceutical companies to engage FAST to assist with their pre-clinical research on potential therapeutics within their own pipelines. We have also conducted the research and development of potential therapeutics that have attracted additional pharmaceutical companies to focus on AS.

FAST has proven the success of our funding philosophy in a very short amount of time and with relatively little funding. We have partnered with three pharmaceutical companies for human clinical trials, two of which are scheduled to begin in 2016. It is not about how much you spend, but rather how you spend it. FAST is funding smarter, faster science and, with proper funding, a cure is now just within our reach.

To speak with a FAST representative regarding the impact of your gift, please call (866) 783-0078 or send an email to info@CureAngelman.org.