IN THE BEGINNING

For decades, small non-profit disease organizations modeled their funding philosophies after the National Institutes of Health (NIH). They would budget 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 then just…hope for results.

This slow, linear approach was barely working for diseases with millions of afflicted patients, and patient organizations with budgets in the hundreds of millions. It hardly seemed like it would yield promising fruit for Angelman syndrome, a rare syndrome which was then thought to affect only about 1 in 15,000 people worldwide, and which was garnering little to no attention in the research community.

Rather than sit on the sidelines of the research and development game, throwing money here and there at those on the field, FAST, established by founder Paula Evans, decided to insert itself as an active player in the process. Driven by an all-volunteer board of AS parents—including founding board members Elke Sprow, Reggie Hamm, Becky Burdine, Sharon Claridge, Maiddy Dunigan, Melissa Elkins, Kena Richert, Erin Sheldon, Terry Sullivan, Karen VanPuyenbroeck Doyle, and Sharon Weil-Chalker—FAST adopted a business model that enabled it to assess the landscape of potential research areas related to AS; seed that landscape through generous grants; and, if and when lightning struck, shepherd new insights or technologies from the academic space to the pharmaceutical one—all the while maintaining input and control over the direction of the research.

Conscious that parents worldwide were seeking therapeutics for their children and wanted to contribute to the search for a cure, FAST began to seek partners across the globe. In 2010 FAST Australia joined the FAST family. Later, affiliates from the United Kingdom, Canada, Italy, France, Latin America, and Spain joined FAST—creating a truly global force.

One of the early insights, which began to drive all of FAST's work, was that successful treatments are never discovered on their own; the more efforts underway in a given field—and the more diverse—the more likely it would be to find truly effective therapeutics, and eventually one that could be considered a cure.

In 2013, with the support of the Azout Family, the FIRE (FAST Integrative Research Environment) team was born. Conceived by Dr. Becky Burdine, this concept—which was ahead of its time—brought together scientists from different academic institutions to work together instead of in their own silos. The team was led by Dr. Ed Weeber, and included Drs. David Segal, Scott Dindot, Anne Anderson, and Kevin Nash. Over time, it grew.

In 2015, Dr. Allyson Berent joined the board of directors at FAST, and in 2016 became the Chief Science Officer. With a focus and expertise in translational research as a clinical researcher herself, Allyson began working closely with the board of directors and the FAST FIRE team, as well as investigators not yet working on Angelman syndrome research, to help ignite progress, and revamp FAST's "Roadmap to a Cure"—updating it into a step-by-step plan outlining the details of what it would take to bring proof-of-concept data in cell lines or animal models to human candidates for clinical trials. This new roadmap had three features: a clear need, a clear path, and a clear price tag. It outlined six disease-modifying strategies that, at the time, seemed to hold the most promise for AS—each one of which had its own price tag. The total for all of them was $5.8 million.

Based on the precision and strength of this plan, in 2016 FAST secured a monumental gift from the Marnier Lapostolle Foundation, founded by the family responsible for Grand Marnier liqueur, who were inspired by a family member with AS. The amount? The full $5.8 million.

It's hard to overstate the importance of that gift in the history of AS. In one fell swoop, six disease modifying strategies, in addition to other initiatives, were supported to be able to get from proof-of-concept in cell lines or animal models to human drug candidates. Six! To put this into perspective, most rare diseases have one or two options to consider, and very few ever reach human candidate drugs. In an instant, the Angelman syndrome community got not one or two, but six shots on goal to move closer to patients. At these early stages, there is limited data just on rodents—and that data doesn't predict what risk or benefits will ultimately be seen in human patients. Having this many options, and the funds to support them, was a dream come true.

One of those early grants bore fruit, in the form of an investigational antisense oligonucleotide drug. To make sure it moved securely through the initial developmental process, FAST founded its own biotech company called GeneTx Biotherapeutics. This summer, based on promising interim data, Ultragenyx Pharmaceutical acquired GeneTx—putting this large and exciting company in the driver's seat for a promising potential AS treatment.

We still have five other disease modifying platforms in the works from our original "Roadmap" that have not yet reached clinical trials, and since that time an additional four programs have also shown sufficient promise to be advanced toward human application—bringing us to a total of *ten* possible methods to treat AS. And we know more is coming as technology advances. FAST is committed to ensuring that all programs reach the right inflection point to know if each has a clear path forward. Some will and some won't. We cannot stop at the first or the second idea when it's our job to chase down every possible option for transformative treatments, and to filter out the absolute best ones for everyone around the world living with AS—regardless of genotype, and regardless of age.

FAST GOING FORWARD

This is an incredible moment—one we must meet responsibly, ambitiously, and transparently. To do so, I see FAST in this new era as committed to three pillars:

- Setting the agenda for advancement of AS therapeutics

- Accelerating and helping to broaden the therapeutic landscape for AS
- Effectively communicating to and educating the AS community about all significant research developments as they manifest themselves in concrete and legitimate ways

Setting the agenda for AS drug development

- Roadmap to a Cure: The blueprint, which guided us to this moment, remains the spine of our work. But a lot has happened since then! This year at the FAST Science Summit we will launch a 2.0 model, which will include information about all of the pathways now being explored. This also directly relates to the funds accrued to FAST from the sale of GTX, as the new Roadmap will delineate exactly where and how they will be spent.

- The Angelman Syndrome Biomarker and Outcome Measure Consortium (ABOM): How can we tell that a treatment is actually working? It may seem obvious to us parents, but science requires metrics—outcomes that are clearly defined in advance, measurable, replicable, and most important meaningful. We call these "outcome measures." If a drug provides a transformative benefit, we want it to be easily determinable, because this, in turn, helps support drug approvals. The ABOM is a pre-competitive consortium of pharmaceutical companies, clinicians, translational research teams, and patient advocacy groups, all brought together to develop endpoints and biomarkers. The team put together a list of priority symptoms experienced among individuals living with Angelman syndrome that drug companies should be focused on trying to improve, including: challenges faced by patients in areas of communication, gross motor and fine motor skills, behaviors, sleep, seizures, cognition, independence/activities of daily living, and patient and caregiver quality of life. FAST has funded consortium events and grants identified by the consortium since 2017, and in 2021 committed a million dollars to the project.

- The Global Angelman Search and Rescue Initiative is working closely with our FAST Global organizations as well as many other Angelman syndrome associations around the world. This initiative aims to address the underdiagnosed, misdiagnosed and unconnected individuals around the world living with Angelman syndrome. We all know that a diagnosis is imperative in order to participate in clinical trials and eventually have access to different drug treatments. In addition, community is so important to the growth and well being of our families as we live with Angelman syndrome. Identifying our global community allows each family the ability to connect with local and international families for support as well as the latest information on therapeutic treatments and research.

- The Global Angelman Syndrome Registry (GASR) The Global Angelman Syndrome Registry (GASR) is a global initiative to collect and collate data on individuals diagnosed with Angelman syndrome worldwide. Parents and caregivers drive data collection by contributing information on diagnosis, medical history, development, and more in a series of online modules. Modules can be modified and added to reflect the current needs and landscape, providing purpose-built data and reducing data duplication. Data is available to anyone with a desire to progress in understanding and outcomes for Angelman syndrome. The Angelman Syndrome Global Registry plays a key role in the Search & Rescue initiative to collect and disseminate data as it serves as the information touch point for all stakeholder families. It is also playing a key role in our initiatives to ensure all patients have access to therapeutics. The data that the community has so painstakingly entered is now bearing fruit, as it is and will continue to be widely used.

- Newborn Screening: An effort to fund the addition of chromosome 15 conditions, including Angelman syndrome, to Early Check, a framework developed to create the infrastructure for rare diseases to be included in the Newborn Screening Panel. The Newborn Screening Panel is the only population-based strategy to identify newborns who could benefit from early disease detection and treatment. Early Check is a collaboration among researchers, public health professionals and clinicians at RTI International, the University of North Carolina at Chapel Hill, Duke University, Wake Forest School of Medicine and the NC State Laboratory of Public Health. FAST, ASF, and others are funding this effort together. Additionally, FAST is supporting an effort in Wisconsin to both perfect the bloodspot science and enter their newborn screening program, and we are looking forward to participating in an ongoing Newborn Screening project in New York City—mapping the entire genome of a newborn. In addition, there are efforts underway in the state of California, the U.K. and Belgium to advance Newborn Screening Efforts there for Angelman syndrome.

- Patient Access to Drugs: For the last year, FAST has been building a strategy to help ensure patients have access to drugs (once approved). FAST has engaged a patient access consultant, who has successfully led these efforts for other rare disease drugs, as well as a health economics firm.

- INSYNC-AS: The International Angelman Syndrome Research Council (INSYNC-AS) brings together world experts outside of the Angelman syndrome space to help support advancing AS in all areas of drug development that we are not currently invested in. This has allowed us to gain knowledge and insight into new strategies that could benefit AS therapies, and leverage new relationships to get world renowned teams working on AS, where they were not before. Scientific discoveries are advancing rapidly, and this allows us to ensure that those for AS are doing the same.

- Translational Research Symposium (TRS): Once a year, just before the Global Science Summit & Gala, we invite dozens of scientists and experts from around the world working in the field to come to present their research live, updating the scientific community on their latest findings in order to encourage collaborations, relationships, and progress in Angelman syndrome translational research, both clinical and pre-clinical. This is an open forum, while remaining confidential and private to protect individuals' research data, so that people can ask questions, learn from each other and not duplicate efforts. This creates strong collaboration and open sources of information sharing among scientists and researchers, while allowing our pharmaceutical stakeholders to know what is happening on the research side, which could potentially benefit their programs as well.

Accelerating the drug pipeline

We do this in multiple ways, each of which bears explanation:

- Grants: In the last three years, we have averaged nine grants and $3.3 million a year in research investments. Unlike other organizations, we do not have a research deadline, but instead maintain a rolling application process—enabling us to scoop up promising ideas as soon as they surface, while being proactive and recruiting the best in the world with novel ideas to work on Angelman syndrome. Each proposal is sent to three members of our Scientific Advisory Board (SAB), made up of 25 individuals who are each subject matter experts in different areas. In addition, there are scientific consultants that volunteer to review for FAST, who we will leverage if the topic is in an area outside of the scope of members of the SAB, or there is any conflict of interest for members of the SAB. These individuals review and give constructive feedback in a standardized manner on the translational relevance, scientific rigor, track record and expertise of the investigator, proposed timeline and associated budget of the project, and overall feasibility and probabilities of the suggested research. This process is led by the chair of the Scientific Advisory Board, Dr. Barbara Bailus. At the same time, legal teams negotiate a contract to govern the grant and any advancements that may come from the grant. If and when all is ripe and the grant is approved by the chair of the SAB, the CSO, and the entire FAST Board of Directors, then the contract is signed and the work can begin immediately. Recent examples of FAST grants include powerful work: Dr. Jim Wilson (hUBE3a, miRNA, CRISPR AAV delivery for gene replacement or gene-editing); Dr. Bryce Reeve ORCA for the development of a novel communication endpoint for Angelman syndrome; Dr. Yong-hui Jiang, who created a biorepository to include all genotypes for AS cell lines; Dr. Albert Keung who developed landing pads in AS organoids to test drugs for all genotypes including large deletion (genes outside of UBE3A), mutation, UPD/ICD and mosaic; Drs. Jill Silverman, Dave Segal and Kyle Fink at UC Davis to create an AS animal testing facility for all pharma to ultilize in early stage POC studies, and more. Currently, FAST has over 20 research grants that are active and ongoing in different research facilities around the world.

- Infrastructure: FAST paid for and developed a robust infrastructure for any researcher, biotech, or pharmaceutical company to utilize in order to test their drug. Our years of investment have yielded mice, rats, and pigs—all with AS—waiting to test curative treatments. This includes a full deletion mouse to understand what the genes deleted other than UBE3A are doing (or not doing as the case may be). Additionally, we have cutting edge cell lines and organoids (or "mini brains") for each genotype, through which therapeutics can be tested to help us understand how our loved ones' neurons will react to a therapeutic. We have also funded "landing pads" to test each gene or RNA—which may be under-expressed in deletion or over-expressed in ICD and UPD—to better understand the cause of that variance and the consequences of replacing or activating it.

- Engaging in the pharmaceutical space: Supporting the nonclinical and clinical development programs of numerous pharma companies.

  We engage aggressively in the pharmaceutical space to ensure potential therapeutics do not languish in the laboratory or beyond—especially in the "valley of death" of drug development, the period during which innovative medical research discoveries are made, generally in an academic lab, and yet somehow get blocked from becoming new therapies for humans, or even making it to clinical trials. In rare disease, where the profits to pharmaceutical companies may be considered smaller than that of more common disorders, this is unfortunately common.

  Or, more tragically, even after seeing positive results in humans, drugs can languish. This is of vital importance. If you want to read a horror story scarier than any "Nightmare on Elm Street" for a rare disease patient or family, see the Los Angeles Times article from last year, in which a cure for a rare and fatal disease was actually discovered and was in the process of being administered successfully to patients—until the biotech company awarded an exclusive license to develop and market the cure shelved it. Why? Not because of any misgivings about its safety or efficacy, but for "'business reasons,' meaning that it wanted to invest instead in treatments for more common diseases with more potential for profits." We know that no pharma wants to make this type of decision, but unfortunately, in companies the bottom line often comes down to finances and priorities. We can't let this happen to any promising AS treatment, and that means not counting on Angelman syndrome being the priority of anyone other than us, our community.

- Building our own companies: Sometimes, the best way to avoid losing a promising therapeutic in the "valley of death"—especially one we've invested in from its inception, via one of our grants—is to build our own company around it. This allows us to guardrail the treatment through the toughest terrain of the drug pipeline, namely from basic

> research through discovery and IND enabling studies into phases 1/2 clinical trials. If it succeeds through all of these, it will then be an attractive asset for a pharmaceutical company big enough to take it through the pipeline's most expensive final stages all the way to a possible FDA approval. Human data is more powerful than any cellular or animal data, and that gives Angelman syndrome the closest guarantee to attract the best partner to advance the therapy for all patients.
>
> Funds used in the establishment of for-profit entities initially are seeded by FAST, since we funded most of the work to get us there. The larger infusion of funds needed for the IND enabling studies and any potential clinical trial will generally come from outside investors, some of whom may have personal connections to AS (angel investors), and others who are not yet connected directly but believe in the science and see the potential. In many cases, as with GeneTx, these investors may request that specific representatives of FAST stay involved in the program for a period of time, which could result in them being on payroll at the new company, expressly for the purpose of ensuring that the new entity maintains its primary commitment to AS. This decision would be made by an independent board that is leading the company, not leading FAST. In no instance can board members or any FAST-affiliated individuals acquire independent control over intellectual property rights of any technology or project seeded by FAST.

Drug research and development is a universe where risk, and challenges, abound. FAST makes investments in research nearly every day, and this includes taking on the licenses, or option to take the license, to technologies that are promising but not yet proven, so that we can ensure that they are advanced appropriately and quickly on timelines that make sense to those impacted daily. But this also means some will be successful, and some will fail. Go and no-go decisions will always have to be made, and if we must pivot away from one program it will be with the utmost care, scientific rationale and rigor. We are spending time and money to ensure that programs are safe, their results are solid, and they are able to be replicated. We will continue to be transparent about early research progress—which we transmit via the summit and its aftermath, on our site, in our newsletter, and so on. Once technologies progress beyond a certain point in the development pipeline, and especially in cases where outside companies become involved, the processes for disclosures change. We cannot make public every detail of every action taken at every moment it occurs, but must instead wait until clear paths toward legitimate success, or failures, emerge. The moment something is shown to be sound, or not, we will share it with the community—not a minute before, and not a minute later. We are not in the business of giving people false hope. Having a loved one with AS is hard enough.

We understand this kind of engagement, marked as it must be by risk, is not for everyone. Thankfully, AS is blessed with not one but two powerful organizations working, in different ways, for our community. We strongly encourage anyone for whom our work feels too unpredictable or speculative to devote their time and resources to the incredible Angelman Syndrome Foundation, which can be found here.

Effectively communicating to the AS community all significant research developments as they manifest themselves in concrete and legitimate ways

It is profoundly important that our community be deeply informed and ahead-of-the-curve when it comes to research and development. This is a large and complicated universe—made up of thousands of researchers from all over the world, hundreds of pharmaceutical companies, clinicians, investors, educators, policymakers, and more. We represent a rare disease in this competitive space; our ability to attract attention to our cause comes in part from the maturity and sophistication of our community. It is FAST's obligation to maintain a channel of the deepest and most up-to-date scientific information, and for it to be as accessible and engaging as possible for a diverse community.

We do so in a number of ways:

- Weekly newsletters: Each Tuesday, FAST sends out a newsletter giving recipients the latest science news, family spotlights, as well as a window into the organization itself—including Q&As with staffers and other significant figures. You can sign up for them here.

- Monthly fireside chats: All are welcome, as are all inquiries about FAST's current workings or future plans.

- Summit & Gala: The annual Science Summit & Gala is an opportunity for the Angelman community to get in-person, up-to-date information about science and pharmaceutical advancements, often directly from scientists themselves, while connecting face-to-face and raising funds to support vital AS research. Scientists share updates on research as well as clinical trials, while providing us with information about best practices in education and therapies. In addition to the in-person event, the Global Science Summit is broadcasted live to thousands more around the globe and is translated via an outside platform into 121 languages.

- Social media: In addition to Twitter and Instagram, we run two pages on Facebook:

  > FAST main page (public). This is the place to go for research updates, FAST news, clinical trials, leadership updates, staff updates, and the like. These items include information featured in our newsletter, and which may be pre-scheduled or posted by the social media team.

> FAST Family & Friends (private, actively moderated). This is the place to go for polite, reasonable discussion *around* all of the above. It's also where you'll find people sharing personal stories or information, either unprovoked or led by administrators to start positive discussions.

The FAST Board of Directors is a group of parents whose children live with Angelman syndrome. These parents are all professionals who have specific skill sets that contribute to and help drive the vision for the organization. They have always been, and remain, volunteers.

The board is advised by two cohorts, also volunteers: the Scientific Advisory Board, a group of scientists and clinicians who review grants, advise on new scientific ideas, and support ongoing programs in academia and in industry, as well as the FAST Advisory Council, which is made up of a group of individuals with the professional skill sets necessary to advance priority programs and initiatives being directed by the FAST BOD, like supporting government policy as it relates to state and national awareness of the needs of those living with Angelman syndrome, editing and writing scientific content for newsletters and blogs, supporting the Angelman Syndrome Biomarker and Outcome Measure (ABOM) Consortium, and creating an army of representative families to ensure we stay aware of the needs of everyone in our worldwide community.

It is the job of the president to maintain the smooth and transparent flow of information between the cohorts that make up the FAST universe: the board, our advisors, the staff, our global chapters, and the public.

You can write to us at info@cureangelman.org.