KCNT1 EPILEPSY
HOPE IS ON THE HORIZON

2022 Year-End Update

To fellow KCNT1 Epilepsy family members;

As 2022 comes to an end, I would like to take a moment to thank you for your support.

As many of you know, the KCNT1 Epilepsy Foundation is run by parents. None of us are experts in this field; we are joined together by the circumstances our children face and our determination to make a difference. We initiate and manage dozens of initiatives while working full time jobs, raising sick children, and trying to provide relatively normal lives to our healthy children. Our Board of Directors and Executive Director are not all parents of children with KCNT1 — yet they still volunteer many hours to this cause, all in an effort to help our KCNT1 community. Some of our most generous donors do not have children or family members impacted by KCNT1, but support us because of the personal interest they have in the children and families in our community, a desire to support the scientific efforts which will have impact on the world beyond our community, and a belief in our vision. For this and so much more we are grateful going into 2023.

With this in mind, let's review some of the most important initiatives we are currently working on at the KCNT1 Epilepsy Foundation. I am proud so share that we have made meaningful progress in the three years since we first embarked on this journey. The Foundation has made considerable efforts at putting KCNT1 on the radar of as many drug discovery teams around the world as possible. During the last two years we have seen an expansion from 4 to 13 drug discovery programs. The pharma industry is well aware of KCNT1 at this point. We also have all the tools in place to help prepare our community for clinical trials when they begin.

We spend considerable time collaborating with the foundation leaders of dozens of other rare disease organizations. Many of those have basic research programs being done for their disease. Some have one or two drug development programs underway. But I am not aware of a single rare disease foundation that has anything close to the number of active programs that we have.

The following is a summary of the drug discovery efforts for KCNT1 under way around the world. More than half of the programs initiated since 2020 are the direct results of efforts on the Foundation's part to bring more pharma teams to the table. Our strategy for increasing awareness of KCNT1 and maximizing the number of teams working to find new treatments is working.

Program 1: Since 2017 an academic group in the US has been working on a small molecule program for KCNT1. The timeframe for a program like this is 7-10 years to bring a drug to trial assuming all goes well. The Foundation has been collaborating with the Principal Investigator and team members for several years. This program has analyzed millions of compounds to see if any have the potential to be turned into a small molecule drug (pill). Numerous hits have been identified but there are still years of work left that would go into turning any of these into drugs that could be used in a clinical trial. Efforts by the Foundation ultimately helped bring in a major funding partner to this program.

The partner company had been interested in KCNT1 as a disease for several years. The executive team made it very clear that they had been waiting until we had a minimum of 150 patients in our databases (contact database and Patient Registry) to make the financial commitment. This is a perfect example for members of our community of just how critical participation is in the programs we are promoting: signing up for the contact database, participating in the Patient Registry, and signing up for a Citizen account. The more patients we can show the pharma world that are actively involved in our community programs, the greater their interest. And the greater our chances that someone will find a drug that improves the lives of our children.

Program 2: Praxis started working on their own small molecule program around the same time. We have been connected to their program since 2018/2019. As many of you are aware, UCB and Praxis just announced publicly that they will be working on the KCNT1 program together. This is an exciting development as UCB brings substantial funding capacity to the effort. The preclinical data for the program is promising, and a pill taken daily will likely be more appealing to some families than an injection near the spine every 2-4 months. We had the chance to meet with the UCB team at the AES meeting this month and feel that this new partnership with Praxis will be very beneficial to the program.

Program 3: In 2018 the first ASO program was initiated at Boston Children's Hospital.

Program 4: In 2020 Biogen made their ASO program public knowledge and engaged the KCNT1 Epilepsy Foundation to assist with the relevant NHS program. Without our participation, there would be no possibility of a clinical trial. Thank you to everyone who volunteered their time to participate.

Program 5: The Foundation initiated a gene editing program at a major academic center on the East Coast and facilitated a research pipeline between this group and another major academic center in the Midwest that was already doing basic science work on KCNT1.

Program 6: The Foundation initiated a program consisting of an AAV based gene editing approach combined with knockdown of a regulator of cellular function at a major pediatric research center in the US. We facilitated a collaboration between this team, a major KCNT1 researcher in the UK, and an academic center in the Midwest with KCNT1 assets.

Program 7: The Foundation initiated a drug repurposing screen of the FDA approved drug library with an academic center in the US. Multiple SLACK channel inhibitors were identified and validated in KCNT1 models. We are currently working with teams in three states to develop a trial protocol that we hope children in our community will be able to participate in next year.

Program 8: A separate drug repurposing screen was conducted overseas looking at the list of approved medications in the European Drugbank Library. Multiple SLACK channel initiators were identified. They are now being tested in animal models and the Foundation is collaborating with the investigators to support preclinical work and assist with trial initiation if a safe and effective candidate is selected. We have also facilitated collaborations between this group and the group doing repurposing work in the US in an effort to cut down the time to clinical applications.

Program 9: A third repurposing effort is going on with a different European team. We do not communicate regularly with this team, but from what we are told there is at least one drug of interest that is being considered for clinical use.

Program 10: A team from several countries in Europe is collaborating on development of a small molecule for KCNT1. They have preliminary preclinical data that shows some potential, but there is considerable work yet to be done to develop a drug that could enter trials.

Program 11: A team in the US is working on a gene therapy strategy that is similar to an ASO. They have some compelling preclinical data but there is much work to be done before a trial would be considered. We are collaborating with this team on preclinical testing in support of their efforts.

Program 12: A third team in the US is working on an ASO strategy for KCNT1. This is a smaller company that will likely need financial assistance from an outside source if they decide to continue working on their candidate. The Foundation and our scientific consultants will be reviewing the preclinical data soon to decide whether the work merits funding.

Program 13: In October the Foundation was approached by yet another company in Europe with an ASO for KCNT1. We are in discussions now about facilitating a clinical trial in the US. The Foundation has been asked to support this program in their efforts to get approval from the FDA.

The top goal of our Foundation has always been to have as many companies as possible working on KCNT1. Experts in the drug industry continually express the importance of having multiple "shots on goal." The sad truth about drug discovery is that 90% of drugs in clinical trials fail. To increase the odds that our children will one day have access to a treatment that is both safe and effective, we have focused on supporting as many programs as possible. But our work does not stop there.

There are additional essential initiatives the KCNT1 Epilepsy Foundation has started, or is currently managing, on behalf of our community:

KCNT1 Family Contact List: This list not only allows us keep in touch with all of you, it also is our running census of families around the world. This is very important because when we meet with pharmaceutical companies, one of the first questions they always ask is, 'how many patients are in your community' and 'how many do you communicate with'. Too small of a number and they may move on to the next disease. Currently we have 206 families in our list from 22 countries. It is helpful to know your country, age of your child and your child's variant. More patients translates to more interest in our community. If you are not currently in our Family Contact List, please stop reading this for a moment update our list here.

The Patient Research Registry: Any patient in the world can participate in the KCNT1 Patient Research Registry and health surveys hosted on the LunaDNA platform. The more who register the better. For us to have hope for a treatment or cure, our community members must sign up for and participate in programs like the Registry so that pharma sees that we have not only the right number of patients, but that we have families who are actively engaged and hoping to get access to trails when a new drug becomes available. Pharma teams only want to take on disease groups who are willing and able to participate in drug trials. If you do not have an account set up for your child on LunaDNA, please plan to do this in January. New surveys are being released in the coming weeks and many are available in several languages.

Biogen Natural History Study (NHS): The Foundation helped develop the remote/in-home natural history study (NHS) program to make it significantly easier for parents to participate. Without this data, Biogen would not be able to get approval for a drug trial. They must have a clear understanding of how the disease progresses over time (the "natural history" of it) in order to attribute improvements to the administration of the drug. The NHS is set to conclude this summer. Per conversations with Biogen, the data that has been gathered appears to be sufficient to support their IND filing with the FDA. A Natural History Study of this magnitude costs close to one million dollars. Companies like Biogen only initiate these studies once they have convincing evidence that the therapy they are developing has a high probability of working in patients.

Invitae/Ciitizen Digital Natural History Study: The main drawback of the Biogen natural history study (NHS) is that no other drug company will have immediate use of the data they collected. Historically, rare disease groups have had to do a new NHS for every new drug that gets developed. Participating in a natural history study is not difficult but it does take a lot of time to complete the tasks. Most parents are not likely to participate in a second, or third NHS.

The Invitae/Ciitizen program collects some of the same clinical information as a traditional NHS. But there is a key difference: the data that you provide when you sign up (takes 15 minutes) can be used by any research or pharma team interested in working on KCNT1. This means that when the second, third, and fourth drug companies go to the FDA to propose a drug trial, we will not have to set aside the time to essentially do the same study all over again. And more importantly, we will not have to spend 2+ years doing it. Which significantly reduces the time we wait for future trials. It also ensures interest from a wider variety of pharma teams who will not have to invest one million or more dollars into a traditional NHS.

Our participation in the Invitae/Ciitizen program is a direct result of work done by the Foundation to make sure we were one of the first diseases included in the program, and the time spent educating our pharma collaborators about this option encouraged them to help fund our enrollment. Currently the program is open to U.S. based families with medical records in English.

Biobank: As I mentioned earlier, many of us in this community have provided blood and skin samples to generate fibroblasts and iPSCs for researchers to study and drug developers to test potential therapeutic agents. This year the Foundation opened a biobank with CombinedBrain that can collect and process samples from any patient in the US.

Why create a biobank if researchers already have cell lines? When we send samples from our children to academic or pharma collaborators, we release our rights to those samples and anything that is created from them. Those samples are therefore only useful to the program who we sent them to. If a new researcher is interested in studying KCNT1, or a new pharma company decides to try to develop a drug for us, they have two choices: They can develop their own cell lines which takes 3-6 months, (Pharma cannot contact patients and ask for samples, so developing a cell line also requires that patients reach out to pharma and request to have samples sent.) or, the other option is for the Foundation to facilitate introductions and collaborations between new researchers/pharma and those with existing cell lines. However, the teams with our cells have no obligation to share them. Despite this, we have been successful in many cases with getting access to these assets. But it takes time, typically several months, for these groups to negotiate contracts that dictate the terms of sharing these cells.

Something we can all agree on is that speed is important. The longer our kids go without targeted therapy, the less likely they are to benefit when a drug does become available. In the interest of being efficient, we have started gathering patient samples for the biobank. My son, Andrew, was the first to have a blood sample sent. We are inviting any interested U.S. families to participate. Fill out the interest form if you are able to contribute.

We have arrangements in place to have those cells turned into iPSCs. We will also be looking at generating other KCNT1 assets including new mouse models and an organoid. These assets will be made available to any interested researcher or pharma team with a legitimate proposal for working with them.

We see many advantages to a foundation-managed asset library:

This will ensure that any legitimate researcher or pharma team can **get the assets they need to conduct their work** on our behalf.

This will **reduce the time** to get an asset to an investigator. We can achieve in 48 hours what institution to intuition transfer agreements do in 4-6 months. This means less time waiting for our children.

This will **expand the library of variants available** to test. Our goal is to focus on the variants that are seen most commonly in our community. If we have the right variants in the library we can have models that cover 50% of the patient population. Since variant-specific reponse to drugs has been brought up as a possible explanation for why some children respond better to a drug than others, a diverse asset library will allow pharma to test a boarder range of variants and give our community more information about how likely a drug is to work for an individual patient.

Perhaps most importantly, an asset library of the magnitude will help us **attract more researchers and pharma teams** looking for new diseases to study. I mentioned earlier that the first question most pharma teams ask is **how many patients** are in our community. The second question is usually about **what assets** (cell lines, animal models, data, etc) we have access to.

Our community will continue to stand out among the thousands of other rare disorders as one to be interested in if we have an immediately available, well-structured biobank and accompanying health data.

Other Programs and Initiatives

Co-sponsor of Grant with Cure Epilepsy. The Foundation made a grant in 2022 to University of Vermont, to KCNT1 researcher, Dr Willie Tobin, who is working on the selective targeting of brain tissue with therapeutics for KCNT1. The goal is to determine if drugs can be designed to only treat compromised areas of the brain. By avoiding the regions of the brain not impacted by the KCNT1 mutation, it is possible that we may see a decrease in side effects which can be a substantial problem with any drug in the central nervous system. The Foundation also facilitated a collaboration between this researcher and a pharma team working on a novel approach to treat KCNT1.

Biomarker Program: The Foundation initiated a program with a major academic center in the US to look for specific signals in the EEGs of children with KCNT1 that could be used to demonstrate improvement during a drug trial. We look forward to having updates on this program for you in the new year. We encourage you to begin asking for digital copies of your EEGs in EDF format.

Home EEG Monitor: We all know how unpleasant it is for our children to have dozens of EEG leads glued to their heads and the struggle we go through to remove it from their skin and hair for a week after the study. The Foundation is currently working with a device manufacture that has developed a small forehead sensor that can be applied by parents at home. This device captures most of the electrical activity that a traditional EEG array does, but in a very simple, clean system. We will be the first disease community in the world to participate in a "wearability challenge" to demonstrate whether children will wear them overnight without removing them. We will also be among the first disease groups in the world to have the device for use in a clinical trial.

Alternative ASO Delivery: The Foundation has been in early-stage conversations with a team that has developed an improved delivery vehicle for ASOs and small molecule drugs directly to the brain through a small port that is accessed on the chest. For ASOs, this means that the drug could be delivered in an office setting by a neurologist rather than in the OR by a neurosurgeon into the IT space (area near the spinal cord where cerebrospinal fluid circulates between the brain and spinal cord). For small molecules, direct access to the brain means that we don't have to limit treatment options to the small group of drugs that can cross the blood brain barrier. In theory, any safe and effective drug could be delivered.

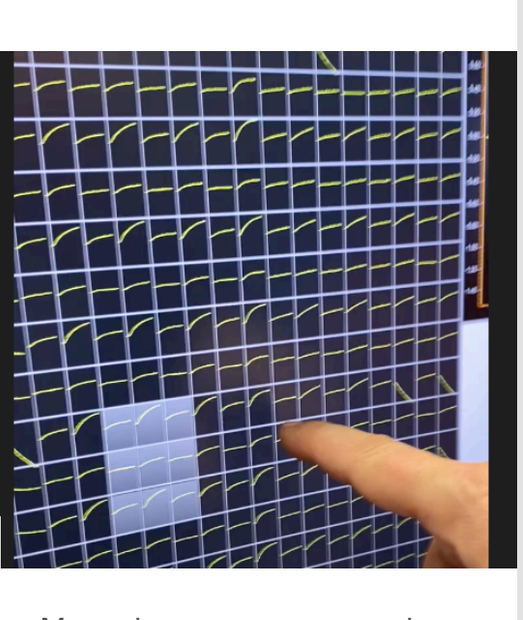
Treatment Recommendations Program: The Foundation has organized a group of experienced clinicians who manage large groups of KCNT1 patients to work on a formal set of treatment recommendations for our community. As of now, doctors around the world treat the few KCNT1 patients they encounter with whatever drug combination they personally feel might work best. Our goal is to gather hard data and have our clinicians identify trends in what drugs and drug combinations work best for the greatest number of patients. Your participation in our Registry surveys in 2023 will contribute to this effort. We expect to have these treatment recommendations in 2023 and hope to reach underserved areas of the world improving care for all patients with KCNT1 mutations.

ICD-10 Code: Many diseases or conditions have a specific diagnostic code. Insurance companies link these codes to specific treatments. As long as your doctor records the right code, your insurance company will generally cover the cost of the treatment for a given disease. Like most genetic epilepsies, there is no ICD-10 code for KCNT1. We have a generic epilepsy code that is not particularly useful. As KCNT1-specific medications come to the market, it will become important that our doctors have an ICD-10 code for our children. This will make it more difficult for insurance companies to deny coverage for what will likely be very expensive therapies. The Foundation is presently doing the groundwork to have an ICD-10 code assigned to KCNT1.

Student Volunteer Programs: The Foundation works with the Stanford University genetics program and the pre-med undergraduate program at Vanderbilt to get students involved in several of our initiatives. It exposes them to the world of rare disease advocacy work, the challenges of treating rare diseases and the operations of a nonprofit while helping us complete some important tasks. We are speaking with other universities as well. Our goal is to build a multidisciplinary team of ambassadors and interns from the neuroscience, genetics, computer science and other programs to assist with our scientific, educational and community building initiatives.

The Weaver Lab at Vanderbilt University

Justin West visits the Weaver Lab to see repurposing screening results



Many drugs were screened

Meetings and Conferences: The Foundation continues to increase our presence every year at epilepsy and rare disease conferences, events and lab visits. We have been to some key events and now our Foundation is well recognized by industry leaders, clinicians and researches in the genetic epilepsy space. This has helped garner more interest in KCNT1 which we have seen demonstrated by more teams initiating programs for us. Some highlights from the last year:

Orphan Disease Conference: We applied and were accepted to our first poster presentation of the KCNT1 Registry at this conference in Boston, sharing data insights from our Registry. Some of the data shared in the poster encouraged major institutions in the US to work on options for KCNT1.

Global Genes Conference: This conference included patients, patient organizations and industry. It gave us yet another opportunity to spread awareness for KCNT1 and present data from our registry.

Ultragenyx Boot Camp: The Foundation participated in two separate sessions of this invite-only conference focused on rare disease leader development. We had a chance to meet with some of the most productive foundation leaders who are advocating for their children and communities, and to present our KCNT1 program initiatives to investors, researchers and drug developers.

American Epilepsy Society: This is a key conference for all rare disease groups. We were able to attend and meet with the CEOs/CSOs/CMOs of multiple pharma teams - some current collaborators, and some who have expressed interest in adding KCNT1 to their pipeline of drug development. We also had the chance to tour the lab at Vanderbilt University where a large segment of drug discovery work is being performed by Dr. David Weaver and his incredible team.

WE ARE HARD AT WORK AND MAKING PROGRESS.

As we prepare for the New Year we have many reasons for hope for our children and families impacted by KCNT1.

Again, I'll cite the Biogen study as an example**.** When we first met with Biogen, their plan was to have a single clinical site in upstate New York that every participant in the NHS would have to travel to for on-site evaluations. We were able to convince them that this was not practical given the complexity of traveling with medically fragile patients. As a result, Biogen crafted their first fully remote NHS which is now the model for how other studies will be performed. The Foundation then was given the responsibility of educating the community about this program and facilitating patient enrollment. Without enrollment, Biogen would be unable to conduct their NHS. Without an NHS, Biogen could not get FDA approval for a trial. Without a pathway to a trial, Biogen would have dropped KCNT1 from their pipeline and looked for a more motivated disease group to treat. **Fortunately for our community, we had one of the fastest patient enrollments in Biogen's history**.

Without a dedicated drug, our children have little hope of anything approaching a normal life. If that is acceptable to you, we don't have much to offer.. But if you want the option for a better life for your child, for yourselves, for the rest of your family, for everyone impacted by this disorder, I hope that you will take the time to make contributions to our community.

Please sign up for the Patient Registry. Sign up for Invitae/Ciitizen. Attend the parent meetings and conferences. Contribute to the Biobank. Share your story. Volunteer. Help us raise money to fund the initiatives that we started to help your children.

My hope is that you will all support these efforts**.** If you have any questions about our work, please feel free to DM or email us any time. If you have any criticisms of what we are doing, I welcome them and simply ask that you frame them constructively. And please consider that a tremendous amount of work is being put into these efforts by our volunteer Foundation members and that without parents stepping up and doing this work, no one in this community will have the chance to benefit from a large-scale drug trial.

As a parent of a child with a rare disease you have two choices: give up and accept that there is nothing you can do, or you can fight. Fight for your child. Fight for yourself. Fight for your family. We have no way of knowing whether any of the drugs that are being developed now will work. But we do know that we are closer than we have ever been to the chance that our kids can have better lives. I urge you to become more involved when you have time. Help us complete the many initiatives we have developed on behalf of your children and families in our community. Help ensure that we can carry forward the good work we have started.

Thank you, and best wishes for the new year,

Justin West, MD. President, Co-Founder, KCNT1 Epilepsy Foundation
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