2022 CURE Epilepsy Program Service Accomplishments:

CURE Epilepsy Background:

Citizens United for Research in Epilepsy (CURE Epilepsy), is the leading nongovernmental agency fully committed to funding research in epilepsy. Our mission is to find a cure for epilepsy, by promoting and funding patient-focused research.

The organization was founded by Susan Axelrod and a small group of parents of children with epilepsy who were frustrated with their inability to protect their children from seizures and the side effects of medications. Unwilling to sit back, they joined forces to spearhead the search for a cure.

Since its inception in 1998, CURE Epilepsy has raised more than $90 million to fund epilepsy research and other initiatives that will lead the way to cures for the epilepsies. CURE Epilepsy awards grants for novel research projects to prevent epilepsy related to pediatric epilepsy, post-traumatic epilepsy, treatment-resistant epilepsies, Sudden Unexplained Death in Epilepsy (SUDEP), Jeavons Syndrome and sleep and epilepsy advancing the search for a cure, eliminating treatment side effects, and reversing deficits caused by frequent seizures. CURE Epilepsy funds grants for young and established investigators and to date has awarded more than 285 cutting-edge projects in 18 countries around the world.

CURE Epilepsy has led a dramatic shift in the epilepsy research community from simply treating seizures to enhancing understanding of underlying mechanisms and causes, so that cures and preventative strategies can be found. CURE's research program is cutting-edge, dynamic and responsive to new scientific opportunities and directions through both investigator-initiated grants and unprecedented scientific programs and initiatives.

2022 Financial Metrics:

Total Revenue	$6,231,376
Total Expenses	$5,793,113
Awareness	$1,064,639
Research	$3,943,069
Program Expenses	$5,007,708
Fundraising	$460,931
Administration	$324,474
12/31 Net Assets	$6,150,686

CURE Officers:

Beth Dean - Chief Executive Officer

Laura Lubbers – Chief Science Officer

John Anderluh – Chief Financial Officer

CURE Board of Directors:

Kelly Cervantes – Chair

Lisa Cotton – Chair Elect

Kathy McKenna – Treasurer

Shalee Cunneen – Secretary

Other Board Members – Marilynn Gardner, David Reifman, Kimberly Borden, Carrie Garman, Matt Schneider, Steve Austin, Mike Axelrod, Justin Gover, Tina Sacks & Hannah Whitten

Program Research Focus Areas:

Epilepsy Genetics Initiative:

Made possible by a generous contribution from the John and Barbara Vogelstein Foundation, Epilepsy Genetics Initiative (EGI), a Signature Program of CURE Epilepsy, is advancing our understanding of the genetic causes of epilepsy. The vision is to improve the ways we prevent, diagnose, and treat this devastating disease. EGI is an initiative created to bridge the gap between people with epilepsy, clinicians, and researchers, and to advance precision medicine in epilepsy. EGI's centralized database holds the genetic (exome) data of people with epilepsy, and the data will be analyzed and reanalyzed until the cause of the patient's epilepsy is found. Findings will then be reported to the patient's treating physician and the data will be made available to advance cutting-edge research projects.

See "Our Impact/Signature Programs" on our website for further details & findings

Post-Traumatic Epilepsy:

With the help of a $10 million grant from the U.S. Department of Defense, CURE Epilepsy has implemented a research program focusing on post-traumatic epilepsy as a result of traumatic brain injury (TBI). This multi-disciplinary program devotes significant resources towards research benefiting veterans affected by traumatic brain injury (TBI) and resulting post-traumatic epilepsy (PTE). The goal of CURE Epilepsy's PTE Initiative is to establish a multi-center, multi-investigator research team to improve ways to study PTE in a laboratory setting, develop biomarkers, and understand risk factors that will help us predict who will develop PTE following TBI. In this way, we will lay the groundwork for the creation of novel therapies to prevent the development of PTE.

CURE Epilepsy's PTE Initiative assembles thought leaders in the field to address questions with a peer-reviewed approach. An External Advisory Council also provides scientific and logistical oversight over the selected investigative team. As science drives the initiative, it adapts to make outcomes as impactful as possible, with the key aim of positively affecting the lives of those affected by TBI and PTE.

See "Our Impact/Signature Programs" on our website for further details & findings

Sudden Unexpected Death in Epilepsy:

Sudden Unexpected Death in Epilepsy (SUDEP), which occurs when a seemingly healthy person with epilepsy dies for no known obvious reason, is perhaps the most devastating possible consequence of epilepsy. SUDEP can happen to anyone with epilepsy, although certain individuals are at a greater risk. While certain steps can be taken to reduce this risk, there is a critical need for continued SUDEP research to understand the underlying mechanisms in order to prevent SUDEP.

In response to bereaved families looking for answers, CURE Epilepsy, in 2004, launched the first ever private US research program dedicated to advancing understanding of SUDEP and its prevention. Since this time, CURE Epilepsy has been the leading private funder of SUDEP research, supporting over 40 investigators who have dramatically changed our understanding of this phenomenon. Simultaneously, CURE Epilepsy, in partnership with families, other non-profits and governmental agencies, have created a strong movement driving research, awareness, advocacy and increased funding to tackle this problem. CURE Epilepsy remains committed to unraveling the mysteries of SUDEP. We will continue to work closely with families and the research community to identify pressing needs while pushing for innovative solutions that ultimately lead to SUDEP prevention.

See "Our Research/Signature Programs" on our website for further details & findings

Infantile Spasms Initiative:

Infantile spasms are a rare and particularly severe epilepsy syndrome that typically begins within the first year of life. Infantile spasms are characterized by subtle seizures which can have large neurological effects and an atypical EEG pattern; these symptoms can lead to large developmental delays and cognitive and physical deterioration. The exact mechanisms underlying infantile spasms are not completely understood.

Sadly, many primary care doctors and parents alike are not familiar with the signs and symptoms of infantile spasms. So, many children with infantile spasms do not receive treatment during the critical window within the weeks and months after the emergence of symptoms. Many other children do not respond to available treatments for infantile spasms or these treatments have substantial adverse side effects, giving these children a dire prognosis.

CURE Epilepsy has made infantile spasms research an important part of our mission to address gaps in the field. Since 2011, CURE Epilepsy has funded cutting-edge infantile spasms research, and in 2013 awarded grants to a team of investigators through a groundbreaking, multidisciplinary 'team science' initiative to advance front-of-the-line research to find a cure for infantile spasms. Collectively, the investigators studied the basic biology underlying IS, searched for biomarkers as well as novel drug targets, and developed improved treatments.

See "Our Impact/Signature Programs" on our website for further details & findings

2022 Research Grant Awards

In 2022, CURE Epilepsy awarded $2.8 million in 23 research grants across our portfolio of research opportunities.

1) **CURE Epilepsy Awards**: Two-year, $250,000 awards focusing on scientific advances that have the potential to truly transform the lives of those affected by epilepsy, with prevention and disease modification as critical goals. Priority areas include: 1) Basic mechanisms of epilepsy, 2) Acquired epilepsies, 3) Pediatric epilepsies, 4) SUDEP, 5) Treatment-resistant epilepsies and 6) Sleep and Epilepsy

Implication of the Pedunculopontine Nucleus in Comorbid Sleep Disorders

Annaelle Devergnas, PhD
Emory University

Sleep is critical for our well-being. Too little, fragmented, or poorly structured sleep negatively impacts daytime function. While it has been known for years that sleep quality and epilepsy are interconnected, the mechanisms are still unclear. A brain structure called the pedunculopontine nucleus (PPN) is known to control arousal and regulation of rapid eye movement. The hypothesis for this project is that frontal seizures disrupt the normal function of the PPN, leading to changes in sleep, and that manipulating PPN activity might restore normal sleep activity. This study will be performed in a non-human primate model that shows similar sleep disruptions and has similar anatomy in the PPN as seen in humans.

A better understanding of the neural circuits involved in epilepsy-related sleep disorders is necessary to develop new therapies that will improve care for people with epilepsy.

Nighttime Mechanisms for SUDEP

Gordon Buchanan, MD, PhD
University of Iowa Medicine

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in people with treatment-resistant epilepsy. SUDEP occurs commonly at night. This is often attributed to SUDEP occurring during sleep; however, emerging data suggest that time-of-day may play an independent role in SUDEP.

Dr. Buchanan's group will examine whether a signaling molecule called serotonin drives this time-of-day vulnerability to SUDEP. They will eliminate the body's 24-hour clock or remove serotonin in a mouse model of Dravet Syndrome, an epileptic encephalopathy that has a high SUDEP incidence, and study the effect of these manipulations on the timing of seizure-induced death.

Determining how time-of-day interacts with SUDEP may profoundly impact how SUDEP research is conducted and lead to the development of actionable strategies for reducing SUDEP.

This *CURE Epilepsy* Award is funded by the Joanna Sophia Foundation.

Targeting Maladaptive Myelination in Lennox-Gastaut Syndrome

Juliet Knowles, MD, PhD
Stanford School of Medicine

Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy in which seizures, such as atypical absence seizures, progressively increase despite treatment. Dr. Juliet Knowles and her team previously demonstrated that a change (known as plasticity) in the white matter or myelin of the brain contributed to the progression of typical absence seizures. Myelin is a substance that acts as a form of insulation around the nerve cells of the brain and is essential for the conduction of electrical impulses between neurons and for the proper functioning of the brain. They also showed that preventing this change with a type of drug called a histone deacetylase inhibitor (HDACI) significantly reduced the progression of these seizures. For this project, the team will study whether HDACIs can prevent myelin plasticity and seizure progression in a mouse model of LGS. These studies will help determine the therapeutic potential for targeting myelin plasticity in LGS.

This grant is co-funded with the Isaiah Stone Foundation.

Forecasting Seizure Cycles in People with Genetic Generalized Epilepsy

Maxime Baud, MD, PhD
University of Bern

Genetic generalized epilepsies are rare epilepsy syndromes characterized by the recurrence of life-threatening seizures in children, adolescents, and adults. Although they seem unpredictable, recent evidence suggests that in genetic generalized epilepsies, seizures preferentially occur at certain times (morning hours) with sleep deprivation being a potent trigger. This suggests that therapies might be targeted to periods of high seizure risk. However, this would require a reliable method for accurate seizure forecasting. Dr. Baud's group recently developed a method to forecast seizure risk over days in focal epilepsy – akin to weather forecasting – based on EEG recordings obtained with electrodes directly implanted in the brain. For this project, they would like to test whether similar results could be obtained for people with genetic generalized epilepsy using a novel, minimally invasive EEG system. In a proof-of-concept clinical trial, the team proposes to recruit a small, tractable cohort of 15 people living with genetic generalized epilepsy, who will be implanted with a CE-labeled EEG device between the scalp and the skull (i.e. minimally invasive) and monitor their epileptic brain activity over months. Daily and hourly forecasts will be provided in a user-friendly visual format based on established algorithms. The team will study the accuracy of seizure forecasting using this method as well as any adverse effects.

In the future, a larger trial could assess the usefulness of accurate forecasts in managing seizures and improving the quality of life of people with genetic generalized epilepsy.

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2) **Taking Flight Awards:** One-year, $100,000 awards that promote the careers of young epilepsy investigators, allowing development of a research focus independent of their mentor(s).

Massively Parallel Reporter Assays to Reveal Noncoding Variant Contribution in Epilepsy

Jeffrey Calhoun, PhD

Northwestern University

The genetic causes of common epilepsies are understudied despite their impact on the community. We know that many genetic variants are linked with epilepsy risk, but which one(s) are the biggest culprits is not known. Part of the challenge is that we do not have the tools to study many variants simultaneously. This research will develop a new method to rapidly determine which (if any) genetic variants near SCN1A, an important epilepsy gene, alter SCN1A gene expression. If successful, this method can be used to test variants in other epilepsy-associated genes. Increased knowledge of whether a specific genetic variant might increase or decrease the expression of an epilepsy-related gene could have an impact on diagnosis and clinical care.

This CURE Epilepsy *Taking Flight* Award is funded by the Joseph Gomoll Foundation.

Target Optimization in Precision Treatment of KCNT1-Related Epilepsy

William Tobin, PhD
The University of Vermont and State Agriculture

The discovery of epilepsy-causing gene variants has facilitated the development of precision medicines that target the molecular causes of disease. But to realize the full, side effect-free, therapeutic potential of these tools, they need to be targeted to the right cells and brain regions. Dr. Tobin will test strategies to optimize cutting-edge gene and drug therapies by selectively targeting the most severely affected cells and brain networks in a mouse model of KCNT1-related epilepsy. Each treatment will be evaluated not only in terms of seizure control but also in its ability to normalize brain activity – recognizing that our true goal is to holistically restore normal function in the epileptic brain.

This CURE Epilepsy *Taking Flight* Award is co-funded by the KCNT1 Epilepsy Foundation.

Mitochondria Function as a Target in Post-Traumatic Epilepsy

Gerben van Hameren, PhD
Dalhousie University

Traumatic brain injury can increase the risk of developing epilepsy, but how this may occur is poorly understood. An electrical wave of activity in the brain, known as spreading depolarization, can occur within minutes of a head impact, causing cellular damage and potentially increasing the production of damaging reactive oxygen species or ROS from the mitochondria within cells. Dr. van Hameren will study the damage to mitochondria caused by spreading depolarization and whether blocking this damage with a drug can prevent the development of post-traumatic epilepsy.

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3) **Catalyst Awards:** The CURE Epilepsy Catalyst Award (2 years / $250,000) supports nimble development of data necessary to attract larger commercialization funding opportunities and is not intended to replace those opportunities.

Preclinical Testing of Oral KCC2 Potentiator Drug AXN-006-01-3 to Rescue Phenobarbital-Resistant Neonatal Seizures

Shilpa Kadam, PhD
Axonis Therapeutics, Inc.

Neonatal Hypoxic Ischemic Encephalopathy (HIE) is a condition where the newborn brain does not receive enough oxygen or blood flow for a period. HIE, Hypoxic (lacking oxygen) Ischemic (restricting blood flow) Encephalopathy (affecting the brain), affects about 2-3 in every 1,000 full-term births, and is the most common cause of seizures in newborns. Unfortunately, first-line treatments, such as

phenobarbital (PB), fail to curb seizures in ~50% of newborns that suffer HIE brain injury. Therefore, HIE is a frequent cause of drug-resistant epilepsy in need of novel therapies. Dr. Kadam and her team at AXONIS Therapeutics are developing a novel anti-seizure medication that increases the function of KCC2 (potassium chloride co-transporter 2), an important protein in the brain involved in inhibiting brain excitability. This study will generate key data showing that AXONIS' brain-penetrating, KCC2-potentiating drug can treat refractory neonatal seizures and prevent epileptogenesis in a neonatal phenobarbital-resistant mouse model of HIE.

This grant is a Robert Withrow Wier Grant.

A Gene Therapy Approach to Treating Pharmacoresistant Epilepsy

Suzanne Paradis, PhD
Brandeis University

Neurons form circuits through sites of cell-cell contact called synapses: excitatory synapses promote information flow in circuits while inhibitory synapses prevent it. One way to stop the runaway excitation in neural circuits, that is a hallmark of seizures, is to introduce more inhibition into the circuit. Dr. Paradis and her team discovered a protein called Sema4D (Semaphorin 4D) that rapidly promotes formation of inhibitory synapses. The team will test the safety and efficacy of using gene therapy to deliver Sema4D as a novel therapy for drug-resistant epilepsy. The potential of Sema4D to bypass mechanisms of drug resistance, combined with its potential to treat different seizure types in a minimally invasive fashion has the capability to be a disease-modifying therapy for the treatment of epileptic disorders.

iPSC-Derived Hypoimmunogenic Human Migratory Cortical Interneurons to Treat Intractable Epilepsy

Sangmi Chung, PhD

New York Medical College

Dr. Sangmi Chung's team recently conducted studies showing that transplanting cells called cortical interneurons into the brains of mice with epilepsy efficiently suppressed seizures and associated comorbidities. Cortical interneurons are cells that typically inhibit excitatory signals in the brain. For their CURE Epilepsy Catalyst project, the team will conduct key studies needed to advance this promising therapy toward clinical applications. These include studies to 1) determine the minimal dose of cells needed to control seizures and 2) determine the best location in the brain where cells can be transplanted for optimal seizure control.

This grant is a Robert Withrow Wier Grant.

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4) Rare Epilepsy Partnership Award: The *Rare Epilepsy Partnership* Award (1 year / $100,000) will support the development of necessary research tools, techniques, model systems, and data collection platforms to stimulate and accelerate research on rare epilepsies. Each award will be co-funded by CURE Epilepsy and one or more of the rare epilepsy advocacy groups (partners)

Increasing KANSL1 Expression Through Modulation of Endogenous Anti-Sense RNAs

Hans von Bokhoven, PhD

Stichting Radboud Universitair Medisch Centrum (Radboudumc)

Koolen de Vries syndrome (KdVS) is caused by loss of one copy of the *KANSL1* (KAT8 regulatory NSL complex subunit 1) gene leading to reduced levels of KANSL1 protein, a protein important for DNA regulation. KdVS syndrome is characterized by intellectual disability, epilepsy, hypotonia, and a variety of congenital malformation abnormalities including brain-specific morphological changes.

Dr. von Bokhoven and his team propose to restore normal KANSL1 levels by increasing the activity of the other (normal) copy of the gene that is still present in

cells of people with KdVS syndrome. They propose to do this through different genetic techniques using cells obtained from the blood of people with KdVS syndrome. Subsequently, they will also investigate whether increasing KANSL1 levels in cells can also restore their ability to form neural networks similar to those of control individuals.

In partnership with the Koolen-de Vries Syndrome (KdVS) Foundation.

This grant is sponsored by the Robert Withrow Wier Fund.

Characterization of a Novel Dup(Atp10a-Tub5gcp5) 'Dup15q' Mouse Model with Varying Levels of UBE3A

Ype Elgersma
Erasmus University Medical Center (Erasmus MC)

Dup15q syndrome is a neurodevelopmental disorder caused by duplications of a region on chromosome 15, often resulting in intellectual disability and intractable epilepsy. Recent findings indicate that the symptoms may be caused by an interaction of the UBE3A (Ubiquitin Protein Ligase 3A) gene with other genes in the duplicated region. However, the precise interaction between UBE3A and the other duplicated genes is unclear.

Dr. Elgersma's team proposes to develop a new mouse model to study the interaction and dose effect of these genes. If successful, this project will generate a novel representative mouse model of Dup15q syndrome which will be an important tool to study the syndrome as well as to test potential therapies in the future.

In partnership with the Dup15q Alliance.

This grant is sponsored by the Robert Withrow Wier Fund

Reconstructing the Longitudinal Disease History in SCN8A-Related Disorders

Jillian McKee, MD, PhD
The Children's Hospital of Philadelphia

Genetic mutations in the gene SCN8A (Sodium channel protein type 8 subunit alpha) can result in early-onset developmental and epileptic encephalopathies. The SCN8A gene codes for a part of the sodium channel Nav1.6 which is essential for the proper functioning of neurons. Although many disease-causing variants in the SCN8A gene have been identified to date, the clinical impact of these on the progression of the disease has not been studied extensively.

Dr. McKee's project aims to understand the natural history and genetics of SCN8A-related disorders. Her team will use data from electronic medical records (EMR) to understand the full range of clinical features over time. Through analysis of this data the team proposes to identify previously unknown clinical subgroups, disease courses, and medication responses, to improve clinical care, medication choice, and aid in the design of clinical trials and targeted therapies.

In partnership with The Cute Syndrome Foundation.

This grant is sponsored by the Robert Withrow Wier Fund.

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5) **Federal Grant Research:** Investment continued with our U.S. Department of Defense research program focusing on post-traumatic epilepsy. In total, we invested an additional $0.5 million in post-traumatic epilepsy as a result of traumatic brain injury.

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6) 2022 CURE Sponsored Research Conferences: CURE Epilepsy sponsors conferences focused on communicating and advancing epilepsy research. We are dedicated to engaging the research community, promoting collaboration, and increasing epilepsy's visibility with

the goal of finding a cure. These conferences bring together epilepsy researchers and enable learning opportunities and information sharing. During 2022, CURE Epilepsy provided sponsorship to 7 individual epilepsy focused conferences with an investment of $40,000. See our website in the "for researchers" section to learn more specifics about the conferences we funded.

Other 2022 CURE Epilepsy Program Service Accomplishments:

RESEARCH SEMINARS

The CURE Epilepsy Frontiers in Epilepsy Research Seminar Series, generously supported by the Nussenbaum-Vogelstein Family, aims to help educate and expose young investigators to leading epilepsy research through seminars. The goal is to expose researchers, clinicians, and students to exciting epilepsy research and provide opportunities for young investigators to interact with leaders in the field.

In 2022, CURE Epilepsy funded 8 separate seminars with a total funding of $17,000.

SEIZING LIFE

Seizing Life® is a CURE podcast and videocast aiming to inspire empathy, offer helpful stories, and give hope as we search for a cure for epilepsy. Listen as guests share stories and insights on living with and battling epilepsy. In 2022, 26 individual programs were completed. Please visit our website to see what topics were covered and watch items of interest.

WEBINARS

Epilepsy experts discuss cutting-edge discoveries, research, and treatments in this free webinar series.

Available 2022 Webinars (see our website for more details):

- Advanced Imaging in Epilepsy: How MEG Can Assist in SurgeryPost-Traumatic Epilepsy and Cognitive Training: Improving Quality of Life Through HOBSCOTCH
- The Effects of Exercise on Epilepsy
- Speaking About SUDEP: Arming the Rare Epilepsy Community with the Latest Research
- Mental Health & Epilepsy: Improving Quality of Life
- Autoimmune Epilepsy Treatment Considerations
- Identification and Treatment of Autoimmune Epilepsy

CURE Epilepsy CARES Events

At CURE Epilepsy *CARES (Conversations Around Research in Epilepsy & Seizures)* events, leading experts answer your questions about epilepsy.

These free events happen across the country each year to give those impacted by epilepsy and their families the chance to learn from researchers and local physicians in an encouraging environment.

Awareness

CURE Epilepsy invested ~$1.1 million in 2022 on Epilepsy Awareness. CURE Epilepsy believes Epilepsy Awareness is a critical vehicle to increase the amount of funding available for Epilepsy research and to share key learnings and opportunities for those impacted by Epilepsy. CURE Epilepsy creates, sponsors and levers our website, webinars, seminars, podcasts, educational events and other digital communication to drive this critical awareness.

In 2022, a continued specific focus was investing in the information insights available on our website for epilepsy patients. Understanding Epilepsy is a tool for the epilepsy community that provides detailed information on epilepsy basics, diagnosing epilepsy, epilepsy treatments and therapies, available clinical trials, covid 19 and epilepsy and available epilepsy centers. Details can be found on our website at ***"understanding epilepsy".***

CURE Epilepsy has created an on-line store to help us provide opportunities for those familiar with all CURE Epilepsy does the opportunity to drive increased awareness of our mission and our impact. Check out our store on our website at ***"get involved/shop".***