2020 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 $78 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), 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 260 cutting-edge projects in 16 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.

2020 Financial Metrics:

Total Revenue	$7,202,553
Total Expenses	$7,729,167
Awareness	$855,731
Scholarships	$50,000
Research	$5,864,267
Program Expenses	$6,769,998
Fundraising	$635,769
Administration	$323,400
12/31 Net Assets	$6,576,284

CURE Officers:

Beth Dean - Chief Executive Officer

Laura Lubbers – Chief Science Officer

John Anderluh – Chief Financial Officer

CURE Board of Directors:

Stacey Piggott – Chair

Kelly Cervantes – Chair Elect

Kathy McKenna – Treasurer

Mike Axelrod – Secretary

Other Board Members – Marilynn Gardner, David Reifman, Lisa Cotton, Blake Cunneen, Kimberly Borden, Carrie Garman & Brian Gorczynski

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

2020 Research Grant Awards

In 2020, CURE Epilepsy awarded over $4.7 million in 23 separate 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, and 5) Treatment-resistant epilepsies.

Manipulating Sleep-Wake Networks to Treat Epilepsy

Nigel Pedersen, MD, Epileptologist
Emory Epilepsy Center, Emory University

Evidence for the well-recognized relationship between sleep and seizures includes seizures occurring at a specific time in relation to sleep, increased seizures with sleep-deprivation, and critically, the increased risk of dying from seizures during sleep. However, the mechanism of the interaction between sleep and seizures is unknown. In this study, Dr. Pedersen and his team will first determine the relationship between sleep and seizure severity in a mouse model of medial temporal lobe epilepsy (MTLE). Next, the team will use novel techniques to manipulate specific brain regions and cell types to gain insights into the impact of sleep changes and the effect of manipulation of these key brain circuits on seizures. This clinically-informed research lays the groundwork for potentially transformative treatments for epilepsy.

Update March 2021: Moving forward Dr. Pedersen's study is being funded by NINDS. The CURE Epilepsy-related funds will be used for a new grant.

PI3K Signaling as a Novel Disease Mechanism-Based Target to Prevent or Reduce SUDEP

Christina Gross, Ph.D. - Steven Crone, Ph.D.

Cincinnati Children's Hospital

Sudden Unexpected Death in Epilepsy (SUDEP) affects 1 in 1,000 people with epilepsy each year. The mechanisms of SUDEP are not fully understood, but may include breathing abnormalities. Dr. Gross and Dr. Crone will use mouse models to test if alterations in a specific genetic pathway in cells, called the PI3K/mTOR pathway, lead to breathing abnormalities and SUDEP. They will also test weather blocking this pathway with a specific compound reduces breathing abnormalities and SUDEP. The PI3K/mTOR pathway is often altered in epilepsy, and this work could therefore be the first step towards a novel treatment to reduce the risk for SUDEP.

Defining Breathing Network Neuromodulatory Approaches for Prevention of Sudden Unexpected Death in Epilepsy (SUDEP)

Nuria Lacuey-Lecumberri, MD, PhD, Assistant Professor of Neurology

McGovern Medical School, The University of Texas Health Science Center at Houston

Sudden Unexpected Death in Epilepsy (SUDEP) usually occurs in patients with frequent convulsive seizures due to seizure-induced breathing failure. There are currently no technologies or devices available for directly preventing death in patients at high risk. The goal of this project is to improve the overall understanding of breathing control by identifying specific brain areas that are most important for breathing function and stimulation techniques that can be used to prevent seizure-induced breathing failure. The outcome of this research will pave the way for deep brain stimulation devices for breathing rescue as a targeted SUDEP prevention strategy.

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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). We encourage studies that will provide new directions for epilepsy therapy, prevention, and ultimately a cure, and that will allow applicants to collect the data necessary to support a further funding by the National Institutes of Health (NIH) or other agencies.

Evaluating the Role of Repeat Expansions as a Genetic Cause of Epilepsy

Mark Bennett, Ph.D.

The Walter and Eliza Hall Institute of Medical Research, Australia

Genetic factors can impact a person's risk of developing epilepsy. 'Repeat expansions' are genetic changes that occur when repeated segments of DNA are copied many times. They have been linked to neurological (brain) disorders, including several types of epilepsy.

Dr Bennett will investigate the contribution of repeat expansions to the genetics of epilepsy. He will use cutting-edge computational methods to analyse data from one of the largest genetic studies of epilepsy and aim to discover repeat expansions that are linked with epilepsy. This research will provide new insights into the genetic causes of epilepsy, which he hopes will lead to better treatment options.

Restoration of Circadian Function as a Novel Therapy for Epilepsy

Cristina Reschke, Ph.D.

Royal College of Surgeons in Ireland

There is increasing evidence that seizures in some people occur in predictable patterns. This raises the possibility of a link between the body's 24-hour rhythms called circadian rhythms and epilepsy. However, it is unknown whether genetic mechanisms that control circadian rhythms are involved in the process of epileptogenesis.

In this project generously funded by The Cameron Boyce Foundation, Dr. Reschke will study how disruption of circadian rhythms could affect gene expression during epileptogenesis. She will also develop a gene therapy approach to restore proper function of a central gene that is involved in regulating circadian rhythms. Finally, Dr. Reschke proposes to explore whether "adjusting the clocks" represents a potential approach for disease modification by testing the gene therapy in mice with drug-resistant epilepsy.

Together, these findings will explore an important potential mechanism influencing epilepsy development and may lead to new strategies for the next generation of treatments for epilepsy.

Utilizing Patient Derived Brain Organoids to Model the Differential Effects of SCN8A Mutation on Cortical and Hippocampal Neural Networks

Ranmal Samarasinghe, M.D., Ph.D.

University of California, Los Angeles

The goal of Dr. Samarasinghe's project is to develop and utilize human brain organoids to enhance our understanding and treatment of epilepsy. Human brain organoids are 3D brain-like structures derived from human cells. Dr. Samarasinghe has made brain organoids from the cells of patients with severe epilepsy due to a mutation in the SCN8A gene. He developed these organoids to model different regions of the human brain and observed unique patterns of neuronal activity. For his CURE Epilepsy project, Dr. Samarasinghe will try to uncover the cellular changes that account for these differences in activity and will use the organoids as a model to test anti-seizure medications.

Personalizing Seizure Treatment After Acute Brain Injury Using EEG

Edilberto Amorim de Cerqueira, M.D.

University of California, San Francisco

Acute brain injury from trauma, stroke, or a lack of brain oxygenation are among the most common causes of acquired epilepsy in adults and children worldwide. Unfortunately, we still do not know which patients are likely to benefit from early medication use for seizure prevention or which medications are most effective for individual patients.

Dr. Amorim's research is using non-invasive brain monitoring with electroencephalography (EEG) to predict, prevent, and treat seizures in critically ill patients. He is designing algorithms that can determine seizure risk after acute brain injury as well as measure the individual's response to anti-seizure drugs. Dr. Amorim hopes that a data-driven approach to seizure physiology will pave the way to personalized treatments to prevent epilepsy development after acute brain injury.

Optogenetic Rescue of Seizure-Induced Apnea

Ian Wenker, PhD

University of Virginia

There is increasing evidence that respiratory arrest is the primary cause of death for many cases of sudden unexpected death in epilepsy (SUDEP). In a novel mouse model of SUDEP, Dr. Wenker observed that death is due to respiratory arrest that originates during the tonic phase of seizures. He hypothesizes that breathing recovery is possible once this tonic activity subsides.

In this study, Dr. Wenker proposes to activate specific neuronal populations of the brainstem that either inhibit or stimulate inspiratory activity (inhalation) to recover breathing. The results will provide insight into how the brain's control of breathing is altered during seizures and identify therapeutic targets for SUDEP.

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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.

Adenosine Kinase Inhibitors for Antiepileptogenic Therapy

Detlev Boison, PhD

Rutgers University

Epilepsy prevention is the ultimate goal in therapy development. In 25 years of research, Dr. Boison's team found that a pathological reduction in adenosine, which is the brain's own seizure terminator, not only triggers epileptic seizures, but also is a key factor in the development and progression of epilepsy. Therefore, increasing adenosine in the brain is a logical approach for the prevention of epilepsy. Therapeutic increases in adenosine can most effectively be achieved by using a drug, which blocks the major adenosine removing enzyme, adenosine kinase (ADK).

This project builds on a prior CURE-funded and published study, in which the team demonstrated robust epilepsy prevention in mice through the use of a small molecule ADK inhibitor. Our goal in this project is to optimize and test a new epilepsy preventing drug, which meets criteria for future clinical development. The development of such a disease-modifying therapy would likely transform our treatment options for epilepsy.

Preclinical IND Enabling Studies of TrkB Peptide

James O. McNamara, MD

Duke University

Temporal Lobe Epilepsy (TLE) is a common form of epilepsy with an estimated 35% of patients having recurrent seizures despite treatment with anticonvulsants. Dr. McNamara and other researchers previously discovered that proteins in the brain called BDNF and TrkB play an important role in the development of TLE in animal models. Dr. McNamara's team further found that BDNF/TrkB can cause epileptogenesis through activation of another protein called PLCgamma1. This led to their discovery of a novel peptide, pY816, which blocks the activation of PLCgamma1 and prevents epileptogenesis in animal models.

The goal of this translational research project is to conduct key studies to advance pY816 to human clinical trials for TLE. Specifically, the team will develop an assay to reliably detect pY816 in the blood of treated animals and conduct studies to determine the best dose which causes minimal toxicity in the animals.

In a previous grant funded by CURE Epilepsy, Dr. McNamara studied the role of TrkB in post-traumatic epilepsy in animal models. For his Catalyst Award, his current set of studies will focus on advancing the development of pY816 as a novel therapy for drug resistant TLE.

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4) **The Epilepsy Research Continuity Fund (ERCF):** This grant will provide reimbursements of up to $15,000 for research related expenses incurred as a result of institutional shutdowns during the COVID-19 pandemic and for which institutional support was not available or provided. This program is made possible through a gift from the Cotton Family in honor of Vivian Cotton. In 2020, CURE Epilepsy funded 13 individual grants for a total of over $206,000

5) **2020 CURE Sponsored Research Conferences:** Typically, CURE Epilepsy will sponsor conferences that bring together epilepsy researchers and enable learning opportunities and information sharing. These were not possible in calendar 2020 due to the COVID-19 pandemic. Investment will return in 2021.

Other 2020 CURE Epilepsy Program Service Accomplishments:

EDUCATION ENRICHMENT FUND SCHOLARSHIP

This program is a one-time scholarship (up to $5,000) for those living with epilepsy, family members, or caregivers. These scholarships support coursework in scholars' chosen fields, so they can use their knowledge and skills to become agents of change in the epilepsy community. In 2020, ten scholarships were awarded for a total of $50,000 that are detailed on our website.

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 2020, 24 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 2020 Webinars (see our website for more details):

- Disparities in Epilepsy: Overcoming barriers to improve care and treatment outcomes
- Breathing and SUDEP: Research and the influence of seizures on the respiratory system
- Fenfluramine for Dravet: An old drug with a new purpose
- Transforming data into seizure control with learning healthcare systems
- The Epilepsy – Autism connection: Research, diagnosis and treatment
- The ABCs of EEGs: An evolving tool for Epilepsy diagnosis

Awareness

CURE Epilepsy invested over $850,000 in 2020 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.