ICARE: Interagency Collaborative to Advance Research in Epilepsy
2021 Member Reports

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National Institute of Neurological Disorders and Stroke (NINDS), NIH

Primary Representative: Miriam Leenders, PhD, Program Director, Channels Synapses and Circuits Cluster, NINDS
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Mission: The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

Major Topics of Interest:

NINDS supports a broad range of research studies and training awards related to the epilepsies, and on the cognitive, behavioral, and emotional impairments that often accompany epilepsy. The majority of these studies are funded through the standard investigator-initiated application process, and include studies on basic mechanisms of the epilepsies, seizures and co-occurring conditions, translational projects to develop new therapeutics, and clinical studies and trials involving human subjects with epilepsy. All epilepsy related studies funded by NINDS (or other NIH institutes) can be found by searching the NIH RePORTER database at:

http://projectreporter.nih.gov/reporter.cfm or visit the Categorical Spending site and enter "Epilepsy".

- Basic mechanisms: NINDS supports studies on causes of the epilepsies, including genetics, infection, injury, metabolism, and structural defects. Basic mechanisms of epileptogenesis and ictogenesis are also major areas of study. Additional projects are focused on better understanding causes of co-occurring conditions and their relationship to epilepsy and seizures.

- Translational efforts: NINDS supports several translational efforts through the funding programs of the NINDS Division of Translational Research (DTR). These include Innovation Grants to Nurture Initial Translational Efforts (IGNITE), and the NINDS Cooperative Research to Enable and Advance Translational Enterprises (CREATE) program for biologics and devices, and the Blueprint Neurotherapeutics Network (BPN) Program. In recent years several epilepsy early translational projects have been funded in the IGNITE program to characterize new models of epilepsy for therapeutic development and optimize candidate therapeutics. And currently 3 epilepsy projects are supported by the BPN program for small molecule drug development. Furthermore, several projects are supported through the SBIR/STTR program. Additional information and a decision tree to help guide investigators to the appropriate funding opportunity can be found on the NINDS DTR homepage here: https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research.

The Epilepsy Therapy Screening Program (ETSP) is a long-standing contract supported by NINDS to provide assistance to academic or industry groups through free in vivo seizure model screening to identify promising anti-seizure agents. The ETSP is also incorporating new screening approaches to differentiate compounds that may be better tolerated than existing drugs, or more effective for the population of patients with medication-resistant epilepsy.

Clinical studies and trials: NINDS supports a number of observational clinical studies to evaluate the development of epilepsy in those at risk, to better localize the seizure onset zone and evaluate surgical risks and prognosis, to evaluate the effects of AED treatment on pregnant women and on the developing brain (MONEAD), to prevent epilepsy using vigabatrin in infants with Tuberous Sclerosis Complex (PREVeNT), and to test dietary treatment of Glucose Transporter Type 1 Deficiency (G1D). And in recent years, NINDS has supported clinical trials testing new surgical approaches, best medical treatment of childhood absence epilepsy, best treatment of neurocysticercosis (a parasitic infection of

the brain that causes epilepsy), and best treatment of status epilepticus by emergency medical services personnel, and to determine the best anticonvulsant for individuals with status epilepticus who have failed first line therapy. Additional information about clinical research networks and to help guide investigators to the appropriate funding opportunities can be found on the NINDS DCR homepage here: https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research

Research Support:

- NINDS supports investigator-initiated projects in basic, translational, and clinical research related to epilepsy. The Institute also supports individual career development awards, training programs, conference grants, and small business awards related to epilepsy. See the NINDS Epilepsy Research Web for additional information: https://www.ninds.nih.gov/Current-Research/Focus-Disorders/Epilepsy

- The NINDS is committed to the development of a biomedical research workforce that is representative of the diversity in American society. NINDS supports diverse individuals through general training programs as well as with targeted efforts to increase the number of scientists from diverse population groups.

Examples of Recent Activities:

- BPN projects: NINDS is supporting 3 Blueprint Neurotherapeutics projects to develop new medications for epilepsy.

- Epilepsy Center Without Walls (CWoW) program:

  The Epilepsy 4000 (Epi4K) gene discovery in epilepsy
  Center for SUDEP Research (CSR)
  The Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBiosS4Rx)
  The Channelopathy-Associated Epilepsy Research Center (CAERC)
  The Epilepsy Multiplatform Variant Prediction Center (EpiMVP)

- Sudden Death in the Young Registry (SDY) - http://www.nih.gov/news/health/oct2013/nhlbi-24.htm

Resources Available:

- NINDS Common Data Elements for Epilepsy Research
  http://www.commondataelements.ninds.nih.gov/#page=Default

- NINDS Epilepsy Therapy Screening Program (ETSP)

- NIH Blueprint resources (animal models, gene expression, research reagents, cell/tissue/DNA, clinical resources, translational resources) http://neuroscienceblueprint.nih.gov/index.htm

- International Epilepsy Electrophysiology Portal https://www.ieeg.org/

- Neurological Emergencies Treatment Trials (NETT) network

- NIH Stroke Trials Network:
  http://www.ninds.nih.gov/research/clinical_research/NINDS_stroke_trials_network.htm

- NeuroNEXT Phase II/Biomarker network: http://www.neuronext.org/
- The Strategies to Innovate Emergency Care Clinical Trials Network (SIREN)
- Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR)
- NINDS Division of Clinical Research website resources: https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research
- NINDS Division of Translational Research website resources: https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research
- NINDS Office of Programs to Enhance Neuroscience Workforce Diversity resources: https://www.ninds.nih.gov/About-NINDS/Workforce-Diversity/Enhancing-Diversity

Priorities and/or Plans for Future Activities:

In general, the NINDS looks to the Epilepsy Research Benchmarks for priorities identified by the epilepsy community. Plans for future epilepsy research specific activities are currently being considered by follow up workshops and webinars on the research priorities identified at the recent 2021 Curing the Epilepsies conference.

National Institute on Aging (NIA), NIH

Primary Representative: Bradley C. Wise, Ph.D. Chief, Neurobiology of Aging and Neurodegeneration Branch, Division of Neuroscience, NIA

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Mission: NIA leads a broad scientific effort to understand the nature of aging and to extend the healthy, active years of life. Mission is to:

- Support and conduct genetic, biological, clinical, behavioral, social, and economic research related to the aging process, diseases and conditions associated with aging, and other special problems and needs of older Americans.
- Foster the development of research and clinician scientists in aging.
- Disseminate information about aging and advances in research to the public, health care professionals, and the scientific community.

The Institute is designated as the lead within NIH for research on Alzheimer's disease and related forms of dementia (AD/ADRD).

Major Topics of Interest:

Neurobiology of Aging and Neurodegeneration: Research on genetic, molecular, cellular, and neural mechanisms underlying changes in the structure and function of the nervous system, and its interaction with other physiological systems, that occur during normal as well as pathological aging, such as Alzheimer's disease.

Behavioral and Systems Neuroscience of Aging: Research on the neurobiological mechanisms underlying age-related changes in cognitive, affective, sensory, and motor processes.

Population Studies and Genetics Research: Understanding the contributions of population and genetics studies in brain aging, neurodegeneration and Alzheimer's disease and related dementias.

Translational Research: Full spectrum of drug discovery and preclinical drug development from target discovery and validation through securing Investigational New Drug (IND) status for small molecules and biologics aimed at prevention, treatment, and management of individuals with or at-risk for cognitive decline, Alzheimer's disease or a related dementia.

Clinical Interventions and Diagnostics: Research on the prevention, treatment, and management of individuals with or at-risk for cognitive decline, Alzheimer's disease, or a related dementia.

Research Support:

NIA support a variety of research project grant mechanisms appropriate for individuals with different levels of experience and who conduct different types of research. See:

https://www.nia.nih.gov/research/grants-funding

Examples of Recent Activities:

NOT-AG-18-051: Understanding Alzheimer's Disease in the Context of the Aging Brain (R01) (**Related announcement:** PAR-19-070)

- Define the age-related aberrant or compensatory neural activities in epileptogenic, sensory, motor, emotional or cognitive systems that contribute to AD.
- Characterize the molecular, cellular, synaptic and neural circuitry mechanisms underlying brain plasticity (e.g. neurogenesis or adaptive cell stress response pathways) in aging and AD.
- Employ a lifespan approach to study the genetic, epigenomic, molecular and metabolic changes during vulnerable periods/physiological transition states to understand the mechanisms of protective and risk factors.

NOT-AG-19-033: Selective Cell and Network Vulnerability in Aging and Alzheimer's Disease (R01 or R21) (**Related announcements:** PAR-19-070 and PAR-19-071)

- Identification of neural cell populations, brain regions, neural circuits, and/or large-scale networks (connectomes) that contribute to vulnerability in brain aging and AD.
- Role of cell-intrinsic versus cell non-autonomous and/or environmental factors in selective vulnerability or adaptive responses to cell or network stressors or neurodegenerative events.
- Role of differential activity and connectivity properties of neuronal populations, circuits, and networks in vulnerability (or resiliency) to aging and AD.

Resources Available:

NIA Resources: https://www.nia.nih.gov/research/resources

- Human and Disease Connectome https://www.humanconnectome.org/
- Accelerating Medicines Partnerships-Alzheimer's Disease www.nia.nih.gov/alzheimers/amp-ad
- Alzheimer's Clinical Trials Consortium www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc
- Alzheimer's Disease Research Centers www.nia.nih.gov/research/adc
- Alzheimer's Disease Neuroimaging Initiative http://adni.loni.usc.edu
- National Alzheimer's Coordinating Center https://naccdata.org
- National Centralized Repository for Alzheimer's Disease and Related Dementias http://ncrad.iu.edu
- Alzheimer's Disease Sequencing Project www.nia.nih.gov/research/ad-genetics
- Alzheimer's Disease Pre-Clinical Efficacy Database https://alzped.nia.nih.gov
- Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease https://www.model-ad.org
- International Alzheimer's Disease and Related Dementias Research Portfolio https://iadrp.nia.nih.gov
- AgingResearchBiobank
- Health and Retirement Study (HRS)
- Aged Rodent Colonies

National Institute on Alcohol Abuse and Alcoholism (NIAAA), NIH

Primary Representative: Qi-Ying Liu, M.D., MSc., Program Director, Division of Neuroscience and Behavior
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Mission: The mission of the National Institute on Alcohol Abuse and Alcoholism is to generate and disseminate fundamental knowledge about the effects of alcohol on health and well-being, and apply that knowledge to improve diagnosis, prevention, and treatment of alcohol-related problems, including alcohol use disorder, across the lifespan. NIAAA provides leadership in the national effort to reduce alcohol-related problems by: Conducting and supporting alcohol-related research in a wide range of scientific areas including genetics, neuroscience, epidemiology, prevention, and treatment; Coordinating and collaborating with other research institutes and Federal Programs on alcohol-related issues; Collaborating with international, national, state, and local institutions, organizations, agencies, and programs engaged in alcohol-related work; and Translating and disseminating research findings to health care providers, researchers, policymakers, and the public.

Major Topics of Interest:

- Both Alcohol Use Disorder (AUD) and epilepsy affect large numbers of Americans. According to the 2019 National Survey on Drug Use and Health (NSDUH), 14.5 million people ages 12 and older (5.3 percent of this age group) had AUD. This number includes 9.0 million men (6.8 percent of men in this age group) and 5.5 million women (3.9 percent of women in this age group). AUD costs the United States $249 billion in 2010. Epilepsy affects nearly 3 million Americans and 50 million people worldwide.

- Chronic alcohol exposure induces complex adaptive changes in the central nervous system, allowing the brain to function in an allostatic state in the presence of alcohol. Quick withdrawal from or reduction of alcohol consumption produces a hyper-excitable state and causes an alcohol withdrawal syndrome. Severe and life-threatening symptoms associated with alcohol withdrawal, including seizures, often make it difficult for an individual to quit drinking because of these negative aspects of withdrawal.

- Epileptic seizures and alcohol withdrawal seizures may share similar neurobiological mechanisms and respond to similar therapeutic treatments.

- Studies suggest that alcohol abuse, dependence and withdrawal may decrease seizure threshold and increase the frequency and severity of seizures in epilepsy patients. Alcohol consumption may also impair seizure control due to neurobiological, nutritional and/or pharmacokinetic mechanisms.

- A recent meta-analysis found that a strong and consistent association between alcohol consumption and epilepsy/unprovoked seizures exists, and that the probability of the onset of epilepsy increases with the amount of alcohol consumed daily in a dose-dependent manner. Further studies are necessary to make any conclusions.

- A remarkably high prevalence of epilepsy and seizure was found in patients with fetal alcohol spectrum disorders. Animal studies reveal a possible role of genetic background in such perinatal effects of alcohol. Conflicting results were reported in this area and additional studies are required.

Research Support:

NIAAA supports basic, translational and clinical research and training in the area of alcohol misuse-related seizures. NIAAA also sponsors meetings and workshops in the areas of alcohol-related neural plasticity, adaptation, excitability and modulation that are relevant to seizures and epilepsy.

Examples of Recent Activities:

NIAAA has no active grants studying epilepsy. However, NIAAA is funding training and research grants investigating mechanisms and management of alcohol misuse-related (particularly alcohol withdrawal-induced) seizures. These include, but not limited to the following:

- Hippocamppal neurotoxicity induced by ethanol withdrawal
- Mechanisms of Alcohol Withdrawal
- Neurosteroid Modulation of Ethanol Withdrawal Severity
- Mechanisms of Alcohol Withdrawal Seizures
- Role of L-type Ca^{2+} Channels
- Alcohol withdrawal and tonic inhibition in the thalamus
- Optogenetic investigation of CNS sensitization following alcohol withdrawal.

Priorities and/or Plans for Future Activities:

NIAAA will continue to support research and training on the molecular, cellular, neurocircuit and genetic mechanisms of alcohol misuse-related seizures and epileptogenesis. NIAAA will sign on to appropriate epilepsy research initiatives of other NIH institutes and centers if they are relevant to NIAAA mission.

***Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIH**

Primary Representative: Tracy M. King, MD, MPH, Medical Officer, Intellectual and Developmental Disabilities Branch

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Mission: NICHD's mission is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all. (https://www.nichd.nih.gov/about)

Major Topics of Interest:

NICHD's interest in epilepsy research is centered primarily around the occurrence of seizures and epilepsy as comorbid conditions among individuals with intellectual and developmental disabilities (IDDs), including genetic, mitochondrial, and other inborn errors of metabolism and autism, as well as rare diseases that impact intellectual function and may include epilepsy as a co-morbidity. Studies of risk and protective factors for the occurrence of epilepsy among persons with IDD, and congenital brain malformations and other structural birth defects that impact intellectual function are also supported.

NICHD supports research for the development of treatments for new and existing newborn screening disorders, many of which have intellectual disability and/or seizures as a symptom, and validation of assays for conditions that could be added to newborn screening panels. NICHD also supports research to understand the mechanism of disease and treatment for neonatal and birth injury with hypoxic-ischemic encephalopathy and/or seizures, as well as research related to head injury, concussion, and trauma, including rehabilitation research. NICHD has also supported research aimed at understanding issues surrounding the use of antiepileptic drugs in children, and research in pregnant women with epilepsy to understand maternal and fetal outcomes.

Research Support:

NICHD supports basic, translational, and clinical research and research grants, including training awards, meetings, networks, infrastructure, and other resources. These include individual grants to identify genetic causes of structural brain malformations, many of which are associated with seizures, and research for the early detection, treatment, and disease mechanism for epilepsy and neonatal seizures. Training and career development grants examining the etiology of epilepsy and the mechanism of epilepsy following trauma are also being supported.

NICHD supports a variety of research networks, centers, programs, and initiatives, which can be found at https://www.nichd.nih.gov/research/supported/Pages/index.aspx. NICHD's Intellectual and Developmental Disabilities Branch (IDDB) supports 15 Intellectual and Developmental Disabilities Research Centers (IDDRCs) across the country by providing resources and infrastructure to support a wide array of projects pertaining to neurodevelopmental diseases that include epilepsy-based research. These include the Autism Centers of Excellence (ACE) Program and the Centers for Collaborative Research in Fragile X and FMR1-related Conditions (Fragile X Centers). For example, studies at the Fragile X Centers have included the identification of possible additional genes associated with likelihood of developing epilepsy.

Through the Best Pharmaceuticals for Children Act (BPCA), NICHD along with other NIH Institutes and the FDA aim to improve pediatric therapeutics through preclinical and clinical research that

improves knowledge of pediatric medications, which can include the use of anti-seizure drugs in children. NICHD's Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB) aims to assure that there are safe and effective therapeutics for children and pregnant and lactating women and that these medications are used optimally according to individual needs. In FY2019 the OPPTB and BPCA program co-sponsored "Pharmacotherapy of Epilepsy in Children", which focused on the current approach to treating pediatric epilepsy in children, with specific attention to the key clinical pharmacology issues of antiepileptic medication selection and management in children.

Examples of Recent Activities:

Structural and functional sequelae of neonatal anticonvulsant exposure: drug-seizure interactions (R01HD091994): Treating epilepsy in newborns is challenging because both the seizures and the drugs used to treat seizures may adversely influence brain development. To identify the therapies that minimize damage to the developing brain, NICHD-supported investigators will examine how several common anti-seizure medications modify the acute and long-term outcomes of early life seizures at the cellular and behavioral level.

The Hippocampus and Brainstem in the Sudden Infant Death Syndrome (R01HD090064): Sudden infant death syndrome (SIDS) remains the leading cause of post-neonatal infant mortality in the United States. Previous studies have shown that defects in the serotonergic (5-HT) network in the medulla (lower brainstem), including decreased levels of 5-HT, have been identified in SIDS cases compared to age-adjusted controls. A separate study reported about 40% of SIDS cases feature an abnormality in the dentate gyrus (DG) of the hippocampus characterized prominently by bilamination of the granule cells (GCs), so-called dentate bilamination (DB). DB and associated GC abnormalities in the SIDS cases had almost exclusively been reported previously in patients with temporal lobe epilepsy (TLE), some of whom died from sudden unexplained death in epilepsy (SUDEP). NICHD-supported researchers will test the overall hypothesis that the DG and medullary 5-HT network are both abnormal in the same SIDS cases, and that SIDS cases with DB share molecular, cellular, and genetic features in common with TLE and/or SUDEP.

The KMT2E Gene Plays a Role in Brain Development (PMID 31079897): Research had previously identified symptoms of brain disorders in three patients with changes in the KMT2E gene. To better understand the effects of these changes, researchers examined 38 patients, from 36 families, with various changes in the KMT2E gene. These changes led the patients' bodies to produce nonfunctional or altered KMT2E proteins, and most of the changes were not inherited from their parents. In general, the patients had similar facial features, larger- or smaller-than-average head size, muscle weakness, digestion problems, and mostly mild developmental delays. Male patients—who made up 70 percent of the group—were more likely to have autism; female patients were more likely to have epilepsy. The findings can help scientists better understand the genes that control brain development and help develop new treatments for brain disorders.

Better Ways to Predict Seizures in Newborns (PMID 30882530): Critically ill babies in pediatric intensive care units (ICUs) are at high risk for seizures, which can cause brain damage or death. A technique called continuous video electroencephalogram (cvEEG) can detect seizures, but monitoring patients with cvEEG is expensive, requires expertise and resources that some ICUs may not have, and there are no newborn-specific prediction methods. Scientists studied the medical records of 210 newborns who underwent cvEEG for more than 3 hours (73 had seizures) and developed three ways to predict seizures. One method used only clinical variables, such as sex, age, and the patient's disorder. Another used only EEG features, such as normal EEG readings or the length of time between activity bursts. The third method combined the first two. The method using only EEG features predicted

seizures better than the clinical variable method, but the combined method was best at predicting seizures.

Resources Available:

NICHD is committed to sharing data from its research and supports a variety of resources and tools for researchers. These resources include tissue banks and repositories, datasets and databases, model organisms, genome and DNA sequences, and resource libraries, and can be found at https://www.nichd.nih.gov/research/resources/index.

The NICHD-supported Newborn Screening Translational Research Network (NBSTRN) is a resource for investigators engaged in newborn screening related research. Its purpose is to improve the health outcomes of newborns with genetic or congenital disorders by means of an infrastructure that allows investigators access to robust resources for newborn screening research, including a virtual repository of dried blood.

NICHD welcomes collaborations that align with the priority areas outlined in the 2020 NICHD Strategic Plan: https://www.nichd.nih.gov/about/org/strategicplan. NICHD currently participates in several collaborations across NIH Institutes, as well as HHS and other Federal agencies, related to the study of brain development and health outcomes of newborns and children with genetic or congenital disorders.

- NICHD collaborates on several programs within the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which aims to revolutionize our understanding of the human brain by accelerating the development and application of innovative technologies to produce a new, dynamic picture of the brain showing how individual cells and complex neural circuits interact in both time and space.

- NICHD participates in the NIH Blueprint for Neuroscience Research, which is a cooperative effort that pools resources and expertise, and includes the NIH Office of the Director and 14 NIH Institutes and Centers supporting research on the nervous system. The Blueprint supports the development of new tools, training opportunities, and other resources to assist neuroscientists in both basic and clinical research, enables daily collaboration in how NIH conducts neuroscience research, and provides a framework for planning and implementing NIH's neuroscience research efforts.

- Led by NICHD, the NIH Pediatric Research Consortium (N-PeRC) is a trans-NIH initiative to capitalize on pediatric research expertise and resources across NIH's institutes and centers through increased collaboration. N-PeRC aims to harmonize pediatric activities across institutes, explore gaps in the overall pediatric research portfolio, and share best practices to advance science.

- NICHD collaborates with AHRQ, CDC, FDA, and HRSA on the Interagency Coordinating Committee for Newborn Screening, which makes recommendations for screening certain disorders, developing a system to adjudicate newborn screening expansion and assist states in implementing programs to test for the recommended conditions. NICHD and other NIH Institutes and HHS agencies collaborate on the HRSA-led Advisory Committee on Heritable Disorders in Newborns and Children (link), which advises the Secretary, US Department of Health and Human Services on the most appropriate application of universal newborn screening tests, technologies, policies, guidelines, and standards.

- NICHD serves on the American Academy of Pediatrics (AAP) Council on Injury, Violence and Poison Prevention (COIVPP), which addresses all facets of injury prevention policy, programs, advocacy, and education of general pediatricians, pediatric subspecialists, and families as a unified group. This may include research on traumatic brain injuries and other head traumas that can give rise to seizures.

National Institute of Nursing Research (NINR), NIH

Primary Representative: Martha Matocha, PhD, Chief, Office of Symptom Science, Genetics and Self-Management, Division of Extramural Science Programs

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Mission: NINR supports research that can build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, and enhance end-of-life and palliative care. In the context of this NOSI, research areas of relevance include, but are not limited to: interventions that consider social ecological models that influence adherent behaviors; studies to understand gaps in adherence to national guidelines that promote healthy lifestyles and preventive behaviors; and secondary data analysis to identify moderators of evidence-based intervention strategies and that can inform new approaches to adherence research. Studies that focus on health disparity populations are of particular interest.

Major Topics of Interest:

- Characterizing socioeconomic disparities associated with lower adherence
- Identifying community predictors of adherence, such as neighborhood, peer and school support systems
- Targeting adherence interventions to high-risk populations
- Testing multicomponent (behavioral, educational, economic) strategies to improve adherence
- Understanding barriers to sustainability of adherence behaviors
- Optimizing caregiver support tools that can reduce non-adherence
- Studying how best to implement effective adherence strategies into clinical and community settings

Research Support:

NINR supports individual training and career development programs (F and K grant awards) and support of research program grants (R series awards)

Examples of Recent Activities:

- R21NR017633, PI Modi, Avani, title "Improving Drug Adherence Using mHealth and Behavioral Economics in Adolescents with Epilepsy"
- R01NR017794, PI Modi, Avani, title "Fostering medication adherence in children with epilepsy using mHealth technology"

National Center for Advancing Translational Sciences (NCATS), NIH

Primary Representative: Anne Pariser, MD., Director, Office ofRare Diseases Research

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Mission: NCATS' mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

Major Topics of Interest:

NCATS is distinct in many ways; it focuses not on specific diseases, but on what is common among them and the translational science process. The Center emphasizes innovation and deliverables, relying on the power of data and new technologies to develop, demonstrate and disseminate improvements in translational science. In these ways, NCATS is serving as an adaptor to enable other parts of the research system to work more effectively. NCATS complements other NIH ICs, the private sector and the nonprofit community.

NCATS 3Ds:

- **Developing** new approaches, technologies, resources and models
- **Demonstrating** their usefulness
- **Disseminating** the data, analysis and methodologies to the community

Collaborations among government, academia, industry and nonprofit patient organizations are crucial for successful translation; no one organization can succeed alone. To this end, NCATS leads innovative and collaborative approaches in translational science that are cross-cutting and applicable to the broad scientific community. This could include epilepsy research where relevant to NCATS' translational research focus.

Research Support:

NCATS' organization of divisions and offices spans the entire spectrum of translational science. Through programs in the Division of Preclinical Innovation (DPI), the NCATS drives advances in early stages of the translational process, from target validation to first-in-human studies. Through its Division of Clinical Innovation (DCI), NCATS supports clinical and translational research, creating and sharing the expertise, tools and training needed to develop and deploy effective treatments in people. Through ORDR, NCATS supports clinical and translational research specifically focused on rare diseases. Our cross-cutting programs in rare diseases, translational technologies, strategic alliances and other emerging areas address common scientific and organizational barriers to enable faster and more effective interventions that tangibly improve human health.

Examples of Recent Activities:

NCATS, through its Tissue Chip Program and in coordination with other NIH Institutes and Centers and the Food and Drug Administration (FDA), is supporting 3-D platforms engineered to support living human tissues and cells, called tissue chips or organs-on-chips. Tissue chip devices are designed as accurate models of the structure and function of human organs, such as the lungs, liver and heart. Once developed and integrated, researchers can use these models to predict whether a candidate drug, vaccine or biologic agent is safe or toxic in humans in a faster and more effective way than current methods.

NCATS Tissue Chips for Disease Modeling and Efficacy Testing initiative supports development of tissue chip models of human disease that mimic the pathology in major human organs and tissues. The goals of this initiative are to (1) support studies to develop in vitro disease models using primary tissue or induced pluripotent stem cell (iPSC)-derived patient cell sources on tissue-/organ-on-chip platforms, (2) determine the disease relevance of these models by preliminary testing of key experimental features and (3) test the effectiveness of candidate drugs. Below are tissue chip projects that are exploring models of epilepsy:

- Integrated Microphysiological System of Cerebral Organoid and Blood Vessel for Disease Modeling and Neuropsychiatric Drug screening: This project proposes to use two well-defined genetic lesions, the 22q11.2 deletion syndrome (22q11.2DS or DiGeorge syndrome) and the Proteus syndrome, that affect both the CNS and vascular systems for the development and validation of form a cerebral microphysiological system (CMPS). The proposed CMPS, if successful, will offer a powerful platform to screen neuropsychiatric drugs as well as to develop novel neuropsychiatric treatment strategies that target the shared mechanisms between the CNS and the vascular system.
- Drug development for tuberous sclerosis complex and other pediatric epileptogenic diseases using neurovascular and cardiac microphysiological models: The goal of this proposal is to establish in vitro tissue chip models of the closely related neurological disorders tuberous sclerosis complex (TSC) epilepsy, DEPDC5-associated epilepsy, and their associated cardiac dysfunction. The proposed research leverages emerging bioengineering technology for microphysiological systems developed at the Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE) with human induced pluripotent stem cell tools in regular use at Vanderbilt University Medical Center to ask probing questions about genetic disorders that afflict the heart and brain and about the drugs to treat them.

Resources Available:

The Programs and Initiatives that provide opportunities to work with NCATS can be found at https://ncats.nih.gov/programs

Congressionally Directed Medical Research Programs (CDMRP), Epilepsy Research Program (ERP)

Primary Representative: Anthony Pacifico, Ph.D.
Email: Anthony.M.Pacifico.civ@mail.mil

Mission: To understand the mechanisms of post-traumatic epilepsy and associated comorbidities to improve quality of life, especially in Service members, Veterans, and caregivers.

Activities and Topics of Interest:

- **Innovative Research:** Tools intended to better inform or improve upon how PTE research can be performed
- **Markers and Mechanisms:** Identifying markers or mechanisms via preclinical models that address PTE
- **Epidemiology:** Epidemiological characterization of PTE following TBI
- **Longitudinal Studies:** Studies of the evolution of PTE
- **Quality of Life:** Understanding and improving the quality of life of individuals with PTE, their families, and their caregivers

Research Support:

https://cdmrp.army.mil/erp/

Award Mechanism	Eligibility	Key Mechanism Elements
Idea Development Award **Grants.gov Funding Opportunity Number:** W81XWH-21-ERP-IDA	**Level I:** Investigators **at or above** the level of postdoctoral fellow. • Mentor(s) required. **Level II:** The Principal Investigator (PI) must be an independent investigator **at or above** the level of Assistant Professor.	**Intent:** To solicit novel, innovative research to understand the magnitude and underlying mechanisms of post-traumaticepilepsy (PTE). **Applicants should select one of the FocusAreas below:** • Innovative Research • Markers and Mechanisms • Epidemiology • Longitudinal Studies
Quality of Life Award **Grants.gov Funding Opportunity Number:** W81XWH-21-ERP-QOL	**Level I:** Investigators **at or above** the level of postdoctoral fellow **Level II:** The PI must be an independent investigator **at or above** the level of Assistant Professor	**Intent:** To support research that better understands or improves the quality of life and care for individuals living with the symptoms of PTE, as related to the ERP's mission. **The following Focus Area must be addressed as part of the application:** • Quality of Life
Research Partnership Award: **Grants.gov Funding Opportunity Number:** W81XWH-21-ERP-RPA	The initiating PI must be an independent investigator **at or above** the level of Assistant Professor Each named Co-PI must be **ator above** the level of assistant professor	**Intent:** To create an avenue for collaborative research partnerships between/among investigators to address aresearch problem or question in a mannerthat would be unachievable through separate efforts. **Applicants should select one of the FocusAreas below:** • Markers and Mechanisms (FundingLevel I only) • Epidemiology (Funding Level I only) • Longitudinal Studies (Funding Level IIonly)

Priorities and/or Plans for Future Activities:

CDMRP 2020 Strategic Plan

Health Resources and Services Administration (HRSA), Maternal Child Health Bureau (MCHB), Division of Services for Children with Special Health Needs (DSCSHN)

Primary Representative: Yasmin Mazloomdoost, MPH, MSW, Public Health Analyst

E-mail: ymazloomdoost@hrsa.gov

Mission: HRSA's mission is to improve health and achieve health equity through access to quality services, a skilled health workforce and innovative programs. HRSA is the primary federal agency for improving health care to people who are geographically isolated, economically or medically vulnerable.

The mission of the Maternal Child Health Bureau is to improve the health and well-being of America's mothers, children, and families.

Major Topics of Interest:

HRSA's Epilepsy Program focuses on increasing access to coordinated, quality health care in a patient/family-centered medical home for children and youth with epilepsy (CYE) residing in rural and/or medically underserved areas. This is accomplished by supporting quality improvement (QI) networks to address four content areas:

- increasing access to specialists through telehealth and telemedicine strategies;
- increasing family engagement at various levels across the health care system;
- improving the transition from pediatric to adult health care; and
- increasing communication, collaboration, and co-management between primary care providers and epilepsy specialty providers.

Research Support:

HRSA funds seven demonstration grants that are supported with monthly trainings and ongoing technical assistance from the HRSA-funded National Coordinating Center for Epilepsy at the American Academy of Pediatrics.

Examples of Recent Activities:

The National Coordinating Center is currently conducting a national needs assessment of stakeholders critical to improving access to care for CYEs, including but not limited to CYE, families, and health care professionals. Stakeholders will be engaged in focus groups, interviews, and surveys. Findings will be published and will guide future efforts for CYE and their families in rural and/or medically underserved areas.

Resources Available:

Resources, including a compilation of resources for providing care to children and youth with epilepsy, can be found at: https://www.aap.org/pedsepilepsy

Priorities and/or Plans for Future Activities:

Priorities for future activities will include applying a framework to help youth successfully transition from the pediatric to adult system of health care, increasing family engagement and provider collaboration/communication/co-management at various levels across the health care system, and supporting other strategies to increase access to coordinated, quality health care for children and youth with epilepsy.

Department of Veterans Affairs (VA), Office of Research and Development (ORD)

Primary Representative: Amanda Hunt, PhD, Program Manager for biomedical and clinical Epilepsy Research

Email: Amanda.hunt@va.gov

Mission: For more than 95 years, the Veterans Affairs (VA) Research and Development program has been improving the lives of Veterans and all Americans through health care discovery and innovation.

The mission of VA Research is fourfold:

- to improve Veterans' health and well-being via basic, translational, clinical, health services, and rehabilitative research;
- to apply scientific knowledge to develop effective individualized care solutions for Veterans;
- to attract, train, and retain the highest-caliber investigators, and nurture their development as leaders in their fields; and
- to assure a culture of professionalism, collaboration, accountability, and the highest regard for research volunteers' safety and privacy.

VA Research is unique because of its focus on health issues that affect Veterans. It is part of an integrated health care system with a state-of-the-art electronic health record and has come to be viewed as a model for superior bench-to-bedside research.

Today, VA Research has five overarching strategic priorities: increasing Veterans' access to high-quality clinical trials; increasing the real-world impact of VA research; putting VA data to work for Veterans; actively promoting diversity, equity, and inclusion; and building community through VA research.

Major Topics of Interest:

- Post-traumatic epilepsy,
- Mechanisms of epileptogenesis,
- Clinical studies of cognitive, behavioral, and emotional impairments that accompany epilepsy.

Research Support:

VA ORD provides intramural research funding, PIs must be employees of a VA medical center to receive awards. Types of research include basic science, clinical, translational and outcomes research studies.

Funding Mechanisms include but are not limited to:

- Career Development Programs
- Merit Awards

- Pilot projects
- Collaborative Merits
- Development Awards
- Clinical Trials
- Centers of Excellence
- Research Career Scientist Programs
- Shared Equipment Programs
- Field-based meetings and workshops

The VA Epilepsy Centers of Excellence are clinically funded by VA Central Office and include 16 centers within four administrative regions. The ECoE has workgroups that focus on both basic science research and clinical research, allowing for collaboration and information sharing among the ECoE sites. These workgroups help to organize national efforts and provide guidance on potential collaborative studies.

Examples of Recent Activities:

All epilepsy-related studies funded by VA ORD can be found by searching the NIH RePORTER database at http://projectreporter.nih.gov/reporter.cfm.

Resources Available:

The mission of the Epilepsy Centers of Excellence (ECoE) is to improve the health and well-being of Veteran patients with epilepsy and other seizure disorders through the integration of clinical care, outreach, research, and education. Resources, training, and information for epilepsy in Veterans can be found at: Epilepsy Centers of Excellence (ECoE) Home (va.gov)

Priorities and/or Plans for Future Activities:

VA will continue to support investigator-initiated research and training on the molecular, cellular, neurocircuitry and genetic mechanisms of seizures and epileptogenesis; as well as finding treatments for development of seizures in Veterans.

American Epilepsy Society (AES)

Primary Representative: Douglas Coulter, PhD, AES President and Eileen Murray, MM, CAE, AES Executive Director

Email: coulterd@email.chop.edu, emurray@aesnet.org

Mission: The American Epilepsy Society is a community of physicians, scientists, advanced practice providers, nurses, psychiatrists, psychologists, engineers, pharmacists, advocates, and other professionals engaged in the understanding, diagnosis, study, prevention, treatment, and cure of epilepsy.

Values:

- We are dedicated to improving the lives of people with epilepsy.
- We embrace innovation as a foundation for a better future.
- We prioritize inclusivity, diversity, and equity as an interprofessional community.
- We value collaborating with other organizations that are aligned with our mission to achieve greater results.
- We operate with fairness, transparency, and integrity, and strive for excellence in everything we do.

Mission: To advance research, education, and practice for all professionals engaged in the understanding, diagnosis, prevention, treatment, and cure of epilepsy.

Topics of Interest:

AES grant programs fund basic and clinical projects that identify and deliver answers to understanding, treating and curing epilepsy and improving the lives of people living with epilepsy.

Research Support:

- Annual grant cycles providing more than $1-million toward
    - Early career investigators (Predoctoral Research Fellowships, Postdoctoral Research Fellowships, Junior Investigator Research Awards, Susan Spencer Clinical Research Fellowship, Sergievsky Award for Epilepsy Health Equity and Diversity)
    - AES Infrastructure Grants, Research and Training Workshop Grants, and Seed Grants

- Basic Science Research Award and Clinical Science Research Award, given annually to active scientists and clinicians working in all aspects of epilepsy research. The awards recognize professional excellence reflected in a distinguished history of research of important promise for the improved understanding and treatment of epilepsy.

- The AES Sergievsky Fund is dedicated to advancing the careers of doctors from underrepresented groups, preferably Black and African American, with an interest in medically underserved people with epilepsy. The fund was created through a gift from the estate of Kira Sergievsky, daughter of Gertrude H. and Boris Sergievsky. The first application cycle will begin in late 2021 with first awards expected to be announced in spring 2022.

- The AES Fellows Program is the Society's flagship career development program for early career researchers, clinicians, and advanced practice providers. Its goal is to engage promising epilepsy professionals in AES activities, education, and mentoring—and to connect them with AES leaders, members, and each other. Fellows receive support to attend the AES Annual Meeting for several

days of intensive exposure to epilepsy science, medicine, career skills and paths, networking, top-notch education, and social events.

- The Epilepsy Research Benchmarks Stewards Committee is charged with tracking and promoting progress related to the Benchmarks for Epilepsy Research. In January 2020, the Stewards published research progress reviews for the Benchmarks:
    - Editorial: The Benchmarks: Progress and Emerging Priorities in Epilepsy Research
    - Epilepsy Benchmarks Area I: Understanding the Causes of the Epilepsies and Epilepsy-Related Neurologic, Psychiatric, and Somatic Conditions
    - Epilepsy Benchmarks Area II: Prevent Epilepsy and Its Progression
    - Epilepsy Benchmarks Area III: Improved Treatment Options for Controlling Seizures and Epilepsy-Related Conditions Without Side Effects
    - Epilepsy Benchmarks Area IV: Limit or Prevent Adverse Consequence of Seizures and Their Treatment Across the Life Span

- The Epilepsy Research Benchmarks Stewards Committee is also discussing options for year-round activity following up on some of the ideas shared during the January 2021 NINDS Curing the Epilepsies meeting.

- As the largest educational and scientific event for professionals working in epilepsy, an average of 1,200 scientific abstracts are presented each year at the AES Annual Meeting.
    - Top rated abstract submitters are eligible for travel awards: Grass Foundation Young Investigator Awards, Jack M. Pellock Pediatric Travel Awards, Kimford J. Meador Research in Women with Epilepsy Award, Nurse and Advanced Practice Provider Awards, Suzanne and Peter Berry International Travel Award, and Young Investigator Awards.
    - The AES hosts a poster session, "Better Patient Outcomes Through Diversity," to celebrate the value of diversity in the professional community and research addressing the health equity in the diverse epilepsy patient community. New in 2021, there will be a poster session of cutting edge and innovative abstracts featuring basic science discoveries, emerging technologies, and paradigm challenging results. All selected abstracts will have high relevance to understanding and treating the mechanisms of epilepsy.

- Basic scientists and clinical researchers also present research throughout the Annual Meeting's education program:
    - Investigator Workshops highlight exciting developments in basic, translational, and clinical epilepsy research in a format promoting interactive discussion. The AES2020 event included 20 IWs focusing on a range of topics such as functional mapping in invasive brain recording, investigations in neuromodulation, and genetics.
    - Basic Science Skills Workshops at AES2020 looked at in vivo imaging approaches to visualize cells and networks during seizures and genome editing technologies and their implications for epilepsy research.
    - The Scientific Symposium, Merritt Putnam Symposium and Hot Topics Symposium present the latest in research each year, and the translational research symposium occurs every other year.
    - The Dialogues to Transform Epilepsy session focuses on the use of cutting-edge technology in neuroscience, including excitation/inhibition imbalance and machine learning, to evaluate patients with epilepsy. The AES2020 dialogue focused on how excitation/inhibition balance is being reinterpreted in the context of cortical networks.

Examples of Recent Activities:

Please refer to previous section.

Resources Available:

AES is one of the largest non-government organizations funding epilepsy research, awarding over $1 million a year through two annual grant cycles supporting early career investigators (Predoctoral Research Fellowships, Postdoctoral Research Fellowships, Junior Investigator Research Awards, Susan Spencer Clinical Research Fellowship) and AES Infrastructure Grants, Research and Training Workshops, and Seed Grants.

- AES is proud to partner with other nonprofit organizations to make dollars go further to support scientists. This partnership allows organizations to fund research in their area of interest utilizing a high quality, established review process and grant operations. Some partners will support a proposal in full, with money earmarked for a quality proposal that aligns with their priorities. Other partners will help to support a proposal that aligns with their priorities if it competes successfully for AES co-funding.

The EpiPORT program for clinical research training provides online, on-demand introductory training to key principles and concepts in epilepsy clinical research. EpiPORT was created to complement the NIH's Introduction to the Principles and Practice of Clinical Research covering topics such as grant writing, grading medical evidence, ethics of epilepsy research, and writing and publishing.

Priorities and/or Plans for Future Activities:

AES will continue supporting the activities described above. Additional activities to support research in epilepsy are intertwined throughout the goals in the new AES strategic plan, with a special emphasis continuing on early career investigators, and added assessment of mid-career professional needs, interdisciplinary and cross disciplinary collaboration, and addressing diversity, equity and inclusion in the profession and in addressing issues of health care equity for people with epilepsy.

Child Neurology Foundation (CNF)

Primary Representative: Amy Brin, MSN, MA, PCNS-BC, Executive Director/CEO

E-mail: abrin@childneurologyfoundation.org

Mission: To serve as a collaborative center of education and support for children and their families living with neurologic conditions.

Major Topics of Interest:

In partnership with the Pediatric Epilepsy Research Foundation (PERF) and the Child Neurology Society(CNS), CNF has provided research funding to child neurologists, medical students and researchers, supporting clinical, translational and basic science research for treatments and cures for pediatric neurologic diseases, including epilepsy. The following is a limited list of research topics supported via CNF research grants and scholarships:

- GABAA, NMDA and non-NMDA glutamate receptor subunit expression patterns and the relation to chemoconvulsive model of temporal lobe epilepsy and temporal lobe resections for refractory epilepsy
- Activity-dependent Ion Channel Regulation: A Candidate Mechanism in Developmental Epilepsy; Ion Channel Regulation of Excitability in Immature Brains
- Genetics of disorders of cerebral development
- Brain inflammation in childhood epilepsy
- Disorders that affect white matter development
- Roles of Nuclear Factor 1 (NF1) genes in glioma: Combining the principles of neuro-oncology and neuro-developmental biology to better develop glioma
- The impact of white matter injury on emerging functional motor connections in the developing brain
- Progenitor cell response to neonatal hypoxia ischemia
- Genetics of Infantile Spasms and Related Epilepsies
- Direct Health Care Costs of Non-febrile Seizures in the First Year of Life: Overall Trends and the Cost Impact of National Guidelines
- Neural networks in intractable epilepsy
- Quantification of neural progenitor cells in new onset pediatric seizures
- Neurophysiological and inflammatory biomarkers of seizures and brain injury in children
- Role of Interneurons in KCNT-1 associated epilepsy

Research Support:

Since 2001, CNF has awarded over $4.1 million dollars in research funding and scholarships to child neurologist, medical students and researchers who are working on treatments and cures for pediatric neurologic diseases. These grants support clinical, translational, and basic science research to young investigators early in their career. Annually, a minimum of $200,000 is distributed to support these research activities.

Examples of Recent Activities:

With support from the CNF PERF Elterman Research Grant, Juliet Knowles, MD, PhD of Stanford University is actively studying epileptogensis, "the process by which brain networks undergo maladaptive change(plasticity) and become predisposed to seizures." A newly discovered form of brain plasticity is activity-regulated myelination, which is known to play a critical role in multiple forms of learning and cognition. Dr. Knowles has found that absence seizures can induce aberrant myelination of the affected brain network in rodent models, which in turn worsens seizure severity. In her research entitled Targeting Aberrant Activity-Dependent Myelination in Absence Epilepsy, Dr. Knowles is "using MRI, neurophysiological and histological techniques to determine whether abnormal myelination induced by seizures is reversible and whether pharmacologically targeting abnormal myelination decreases seizure burden." The overarching goal for her studies is to better understand epileptogenesis to develop improved, disease-modifying therapies for pediatric epilepsy.

Resources Available:

The Child Neurology Foundation provides education and support to caregivers and providers for children living with neurologic conditions. Below is a list of program areas and resources:

- Back to School During COVID-19 Education – A hub of videos and education to help parents better understand sending their child to school in the era of COVID19

- Caregiver Education about Managing Harmful and Disruptive Behavior – Caregiver education focusing on a variety of topics to address harmful and disruptive behavior including: Age-Appropriate Behavior Management, Telehealth Best Practices for Children with Behavior Challenges, Communication Strategies to Improve and Prevent Challenging Behaviors for Minimally Verbal Children

- Peer Support – Virtual connection with other parents of children living with neurologic conditions to provide emotional support and assist in finding resources

- Respite Care Notebook – Comprehensive notebook for families to track information necessary to share with a respite care provider

- Epilepsy Education Hub – Educational videos for caregivers related to healthy epilepsy management. Topics focus on Controlling Seizures Through Diet, Responding To Seizures with Seizure Action Plans and Seizure Rescue Meds, Understanding The Risks (SUDEP), Palliative Care Decisions for Children with Epilepsy, Advocating For Alternative Therapies

- Transitions of Care Toolkit – Toolkit to assist caregivers and providers (specifically child neurologists) prepare child neurology patients for transition from pediatric to adult healthcare. CNF also hosts a Transitions Project Advisory Committee to oversee additional efforts around TOC such as reimbursement and federal advocacy. The committee consists of providers, patients, advocates,

and other partners.

- Genetic Testing Information – Education for caregivers about genetic testing and the importance of using it to get a diagnosis

- Infantile Spasms Action Network – Group of organizations including providers and advocates to raise awareness about infantile spasms through an annual awareness campaign.

- Surgery for Difficult-to-Treat Epilepsy: A Step-by-step Guide for Patients and Families – a booklet giving families information about epilepsy surgery

Priorities and/or Plans for Future Activities:

The Child Neurology Foundation, in partnership with the Child Neurology Society and PERF, provides research grant opportunities each year through the PERF Elterman Research Grant and the PERF Shields Research Grant both awarding $100,000 over two years for clinical or basic science research by a child neurologists or developmental pediatrician early in their academic career. These grants are open to researchers in the epilepsy field.

Citizens United for Research in Epilepsy (CURE)

Primary Representative: Laura S. Lubbers, PhD, Chief Scientific Officer
Email: Laura.Lubbers@cureepilepsy.org

Mission: The mission of the organization is to find a cure for epilepsy, by promoting and funding patient-focused research.

Major Topics of Interest:

- Transformative research to enhance the understanding of the cellular, molecular, genetic and systems-level mechanisms that lead to any of the epilepsies, facilitating the continued investigation of disease-modifying or preventative strategies
- Innovative approaches that can prevent, modify and/or arrest the development of acquired epilepsy. Examples include epilepsy that develops after stroke, tumor, traumatic brain injury or infection, including febrile infection-related epilepsy syndrome (FIRES) as well new-onset refractory status-epilepticus (NORSE)
- Research that will inform the development of novel therapies to prevent onset or halt the progression of the severe pediatric epilepsies
- Research focused on new, effective treatments for the >30% of the epilepsy population who are pharmacoresistant
- Novel research that furthers our understanding of the causes and ultimate elimination of SUDEP
- Translational, clinical, and clinically informed basic research that will facilitate understanding of the cellular-, molecular-, and systems-level mechanisms that underlie the relationships between sleep and epilepsy

Research Support:

- Research grants for basic, translational, and clinical research for established and young investigators. For a description of each grant mechanism: https://www.cureepilepsy.org/grants-program/#grant_opportunities
- Partnership with Department of Defense to support a team science initiative focused on post-traumatic epilepsy as a result of traumatic brain injury
- Epilepsy Genetics Initiative (EGI): Genetic database to house exomes and clinical data of people with epilepsy
- Conference and workshop sponsorships
- Sponsored research seminar series (virtual during pandemic)
- Communications that share research advancements
    - Daily research updates (email select audience)
    - Monthly research updates (email to general audience)
    - CURE Research highlights (email to general audience)

- Research-related webinars (video presentations to general audience)

Examples of Recent Activities:

- Current grant mechanisms: CURE Epilepsy Award, Taking Flight Award, Catalyst Award
- Strategic Partnerships: Epilepsy Canada Young Investigator Award (2021)
- Support for researchers experiencing COVID-19-related research challenges (2020)
- Epilepsy Genetics Initiative (EGI): EGI is an initiative created by CURE in 2015, in partnership with NINDS, to establish a database to hold the whole exome sequence data of people with epilepsy. The data have been re-analyzed on a routine basis to find the causes of epilepsy and results are then reported to treating physicians. These data have also been transferred to the NIH Database for Genotypes and Phenotypes (dbGaP) and are available for research. https://www.cureepilepsy.org/signature_programs/epilepsy-genetics-initiative/
- Partnership with Department of Defense: multi-year (2015-2022), $10M team science initiative focused on post-traumatic epilepsy https://www.cureepilepsy.org/signature_programs/post-traumaticepilepsy/
- Recent conference support committed (reduced number of requests due to COVID pandemic):
- 2020: 7th International residential course on Drug resistant epilepsies (Tagliacozzo (AQ), Italy); Phelan-McDermid Syndrome Foundation (Virtual meeting)
- 2021: 9th Eilat International Educational Course: Pharmacological Treatment of Epilepsy (Jerusalem, Israel); Lennox-Lombroso Pediatric Epilepsy Conference (Boston, MA)

Resources Available:

EGI (www.CUREepilepsy.org/EGI)

Priorities and/or Plans for Future Activities:

- Continuation of existing programs, with ongoing evaluation so CURE is poised to accelerate any program if an opportunity presents
- Assessing impact of the research program through various metrics in order to remain flexible and adjust where deemed necessary, with help from expanded internal research team and 5-member Scientific Advisory Council

Dravet Syndrome Foundation (DSF)

Primary Representative: Veronica Hood, Scientific Director
Email: veronica@dravetfoundation.org

Mission: The mission of Dravet Syndrome Foundation (DSF) is to aggressively raise funds for Dravet syndrome and related epilepsies; to support and fund research; increase awareness; and to provide support to affected individuals with epilepsy.

Major Topics of Interest:

DSF supports basic and clinical research with an emphasis on Dravet syndrome and related epilepsy disorders. Our research priorities include:

- Investigation of the genetic, molecular, and cellular mechanisms of epileptogenesis in Dravet syndrome;
- Development of new or improved preclinical models of Dravet syndrome;
- Investigation of comorbidities associated with Dravet syndrome, including sleep disturbances, motor impairments, cardiac disruptions, behavioral issues, and cognitive deficits;
- Studies that support the development of disease-modifying therapies targeting the cause of Dravet syndrome;
- Studies that lead to the development of effective methods of detection and intervention for seizures and comorbidities;
- Studies that expand our knowledge of the natural history of Dravet syndrome;
- Studies that help identify patient trends, characteristics, epidemiology, or other clinical aspects of Dravet syndrome

Research Support:

- **DSF Research Funding** provides funding to original research projects that investigate hypotheses and studies related to Dravet syndrome and the research interests of DSF.
    - **DSF Research Grants** support established, experienced, independent investigators affiliated with a research or academic institution. These grants are awarded for up to $150,000 over 2 years.
    - **DSF Postdoctoral Fellowships** are designed to support early-career postdoctoral researchers at an academic institution under the mentorship of an independent investigator. These fellowships are awarded for $50,000 to support a full-time research effort for one year.
    - **DSF Clinical Research Grants** are intended for established, experienced, independent investigators affiliated with a research or academic institution whose proposed research has a clinical focus. These grants are awarded for up to $150,000 over 2 years.

- **DSF Clinician Researcher Grants** are intended for clinicians in early stages of establishing research efforts under the mentorship of a more senior clinician researcher for projects with a patient-oriented focus. These awards are for up to $75,000 over 1 year.

- **DSF Research Roundtable** is an annual meeting that brings together researchers, geneticists, neurologists, and other professionals with a strong interest in Dravet syndrome and related epilepsies. The roundtable allows the establishment of a "research roadmap" to guide DSF in funding research projects that address the critical challenges of this syndrome.

- **DSF Biennial Family & Professional Conference** is a 3-day event uniquely designed to unite all groups committed to improving the lives of those with Dravet syndrome- including families, caregivers, clinicians, researchers, and professionals in the pharmaceutical and biotechnology industry. Talks span overviews of the clinical presentations of Dravet syndrome across the lifespan, new treatments in the clinic and in development, ongoing clinical research, and basic science advancements contributing to our understanding of Dravet syndrome.

- **DSF Listen + Learn Series** is an on-demand webinar series for health care providers featuring experts from DSF's Medical Advisory Board providing guidance and sharing current treatment approaches for patients with Dravet syndrome and related epilepsies. Continuing Medical Education (CME) credits are available through partnership with the American Epilepsy Society until November 1, 2021.

Examples of Recent Activities:

2020 Grant Awards

- **Eric J. Kremer, PhD; Moran Rubinstein, PhD; Ethan Goldberg, MD, PhD -DSF Research Award ($150,000/ 2-year project)** ***Optimizing a novel SCN1A delivery approach for Dravet syndrome therapy.*** Dravet syndrome is generally caused by a haploinsufficiency of the SCN1A gene that encodes the Nav1.1 sodium channel. The large size of the SCN1A gene has created a challenge for traditional gene therapy approaches. An adenovirus vector may be able to overcome this challenge, and preliminary data suggests this gene therapy can ameliorate seizure and survival phenotypes in a mouse model of Dravet syndrome. This proposal seeks to optimize this delivery system.

- **Cameron S. Metcalf, PhD- DSF Research Award ($165,000/ 2-year project)** ***Brainstem glial control of respiration in a mouse model of Dravet syndrome.*** This proposal is an exploration of a novel mechanism of Sudden Unexpected Death in Epilepsy (SUDEP). They aim to address changes in respiratory neurocircuitry that affect breathing following seizures. They propose that in Dravet syndrome, changes in the brainstem may be driven by the responses of glial cells to seizures. They will additionally investigate interventions to reduce mortality and improve outcomes.

- **Ala Somarowthu, PhD- DSF Postdoctoral Fellowship ($50,000/ 1-year project)** ***Seizure prediction and detection in a mouse model of Dravet syndrome via machine learning***. Dravet syndrome is a chronic infantile myoclonic epilepsy that is not entirely curable with the available treatments in every patient. The current study proposed to design a seizure detection/prediction system by implementing advanced machine learning algorithm on extracted behavioral signatures in a mouse model of Dravet syndrome.

2019 Grant Awards

- **Danielle Andrade, MD – DSF Clinical Research Grant ($150,000/ 2-year project)** ***Multi-modal assessment of adults with Dravet syndrome.*** This study plans to better characterize the adult patient with Dravet syndrome by studying balance, gait, posture, memory, ability to perform day-to-day activities, and genome in a cohort of adults with Dravet syndrome. The study will test the hypothesis that there may be premature brain aging in adult patients. They also plan to explore whether previous use of contraindicated medications influences adult outcomes.

- **Jennifer A. Kearney, PhD – DSF Research Grant ($150,000/ 2-year project)** ***MicroRNA-mediated modification of Dravet syndrome.*** MicroRNAs are small RNA molecules that regulate expression of gene products and have the potential to modulate expression of Nav1.1 in the context of Dravet syndrome. The major goal of this proposal is to determine if severity of Dravet syndrome is influenced by microRNAs. They identified two microRNAs that are elevated following seizures and can target SCN1A to repress expression. The proposed study will evaluate the potential of these microRNAs to modulate Nav1.1 expression and determine whether a therapy based on this miRNA-SCN1A interaction holds promise.

- **Vania Broccoli, PhD – DSF Special Grant for Genetic Approaches ($75,000/ 1-year project seed funding)** ***Gene therapy for Dravet syndrome by CRISPR/dCas9 mediated activation of SCN1A.*** The haploinsufficiency of SCN1A in Dravet syndrome leads to a reduction in the Nav1.1 sodium channel and reduced activity of inhibitory interneurons. A possible cure for Dravet syndrome pathology would be the restoration of normal levels of the functional Nav1.1 protein through expression of the normal copy of the gene by a novel technology called 'activatory CRISPR/dCas9.' Preliminary work in cell lines suggests the SCN1A gene is responsive to dCas9 activator. This study will improve upon critical aspects of the dCas9 activator approach including efficient delivery methods to the correct neuronal populations.

Resources Available:

DSF is open to opportunities for collaboration with other rare epilepsy organizations, clinicians, researchers, or private companies with an interest in the Dravet patient community. We maintain an informal patient registry and active support groups that can aid in the distribution of information about a clinical study or survey opportunity.

Priorities and/or Plans for Future Activities:

- We will continue our yearly grant calls through regular announcements in May, with applications due in September, and decisions announced in December. Our 2021 grant applications (clinical research grants, postdoctoral fellowships, clinical research grants, and clinician-researcher grants) are due on September 10, 2021.

- Our Research Roundtable will be held on December 2, 2021; these meeting will continue to be held yearly in conjunction with the annual AES meeting

- Our next Biennial Family and Professional Conference was rescheduled from 2020, to be held virtually June 24-26, 2021. We hope to meet in person and back on schedule in June of 2022 in Fort Worth, Texas, and will continue to hold these meetings every 2 years thereafter.

- DSF will continue to consider special-focus RFAs to meet critical needs in our community, such as grants focused on gene-based therapies or working groups to address critical comorbid conditions. Special off-cycle RFAs are announced through our newsletter, email list, website, blog, and social media accounts.

Epilepsy Foundation of America (EF / EFA)

Primary Representative: Caitlin Grzeskowiak, PhD, Senior Director, Research and Innovation

E-mail: cgrzeskowiak@efa.org

Mission: The mission of the Epilepsy Foundation is to lead the fight to overcome the challenges of living with epilepsy and to accelerate therapies to stop seizures, find cures, and save lives.

Major Topics of Interest:

Our purpose is to develop an epilepsy research ecosystem that covers the entire spectrum of discovery from the idea to market. We foster the development of new scientists and support research that leads to better treatments and care. We strive for excellence, innovation, and radical thinking to find cures.

- SUDEP
- Social Determinants of Health
- Rare epilepsies
- Learning Healthcare Systems
- Epilepsy Pipeline
- Epilepsy Devices
- Epilepsy Registries

Research Support:

- Research grants for basic, translational, and clinical research with partners, AES, AAN, ABF
- SUDEP Biomarker Challenge
- My Seizure Gauge Grant - $3 million grant to an international team of scientists, researchers and interoperability experts to evaluate biosensors that can track an individual's physiology, behavior, and environment to improve seizure prediction.
- Travel awards to AEDD and Pipeline Conferences
- New Therapy Commercialization Grant
- Research Roundtable for Epilepsy
- Clinical Fellowships
- Epilepsy Venture Fund

Examples of Recent Activities:

- Research Roundtable for Epilepsy – held virtually April 8-9, 2021. Topic: Seizure types and epilepsy syndromes: opportunity or obstacle?
- Pipeline Conference – held virtually August 27-28, 2020.
- New Therapy Commercialization Grant awarded 2021. Project title: Pharmacokinetics study of oral 2-Deoxy-D-Glucose (2DC) in epilepsy
- Year 3: My Seizure Gauge

Resources Available:

www.epilepsy.com

Priorities and/or Plans for Future Activities:

- 2021 Shark Tank Competition to take place during the AEDD XVI Trials meeting on June 16-18, 2021 in Blue Bell, PA
- Research Roundtable to be held May 11-13, 2022 in Washington D.C.
- Pipeline Conference to be held March 3-5, 2022 in Santa Clara, CA.
- SUDEP Research – planning underway for a roundtable discussion with SUDEP Biomarker Challenge finalists to discuss barriers to realization of SUDEP biomarkers and potential opportunities for additional research based on previous work showcased in their challenge submissions.
- EDEN (Epilepsy Digital Experience Navigator) – a personalized digital services platform for people with epilepsy and caregivers. The platform will aggregate Real World Data for thousands of people with epilepsy to inform therapeutic outcomes while simultaneously giving insights personalized to individual patients.
- ELHS – Epilepsy Learning Healthcare System - implementing a system of co-production to improve outcomes for people with epilepsy and their families/caregivers through: (1) improving quality of life (2) improving seizure control and (3) improving seizure freedom.
- Startup Bootcamp – 5 week course for new founders in epilepsy space to provide tools, resources, and networking to accelerate new therapies and devices for PWE.

Patient-Centered Outcomes Research Institute (PCORI)

Primary Representative: Theresa Kim, PhD, MS. Program Officer, Science-Clinical Effectiveness & Decision Science
Email: tkim@pcori.org

Mission: PCORI helps healthcare stakeholders make informed healthcare decisions, and improves healthcare delivery and outcomes by producing and promoting high integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community.

Major Topics of Interest:

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

Newborns who have seizures represent a vulnerable population for treatment related cognitive side effects because they are developing cognitively and socially. Furthermore, seizures in newborns can be a sign of brain injury. At least half of newborns with seizures will have long-term health problems such as epilepsy, cerebral palsy, or intellectual disability. Physicians treating seizures typically use phenobarbital. However, there are negative side effects that can harm children's brain development if used for a long time. Physicians do not know the shortest amount of time they can treat seizures safely while reducing the changes of side effects from phenobarbital. The project compares the health of newborns treated for seizures only while in the hospital with those are treated while in the hospital and for several months after going home. Results of this study will inform parents and physicians when considering approaches to treating newborns who have had a seizure.

Research Support:

PCORI has a sizeable and growing portfolio of projects designed to improve patient care and outcomes through patient-centered comparative effectiveness research (CER). The scientific programs track and evaluate the effectiveness of work under these priorities. PCORI also develops and improves the science and methods of CER because methods matter when it comes to producing valid, trustworthy, and useful information that will lead to better healthcare decisions and improved patient outcomes. PCORI's emphasis on engaging patients and the broader healthcare community is evident in the criteria we have developed for the research funded. PCORI also provides engagement awards that focuses on engaging patients and other stakeholders in CER.

Examples of Recent Activities:

The Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study has created a database of 300 newborns with seizures who were born in nine hospitals in the United States. The team has followed-up on the health of two groups of newborns with seizures: (1) newborns treated for seizures while in the hospital only and (2) newborns treated for seizures while in the hospital and after returning home until a follow-up visit between two and four months after birth. The research team followed up with the population at 12, 18, and 24 months to find out whether newborns developed any development problems or epilepsy. The project also asked parents about their quality of life, risk of anxiety, and risk of depression.

Resources Available:

PCORnet, the National Patient-Centered Clinical Research Network, is an innovative initiative of PCORI. It is designed to make it faster, easier, and less costly to conduct clinical research than is now possible by harnessing the power of large amounts of health data and patient partnerships. In the process, it is transforming the culture of clinical research from one directed by researchers to one driven by the needs of patients and those who care for them.

Priorities and/or Plans for Future Activities:

PCORI accepts studies that address seizure treatment options through our Broad funding announcement, which is released three times a year. PCORI continues to refine its national priorities for funding agendas. However, there is not specific guidance at this moment as PCORI has not yet finalized its national priorities for its next funding cycle.

Pediatric Epilepsy Research Foundation (PERF)

Primary Representative: Deborah Hirtz, MD

Email: Deborah.Hirtz@uvmhealth.org

Mission: The foundation's mission is to enhance the quality of life of children with epilepsy and other neurology disorders and, to support: efforts to improve treatment options for infants, children and adolescents with epilepsy; meritorious clinical and basic science research related to epileptic conditions in children; and encouragement of the recruitment of young physicians in the field of child neurology.

Major Topics of Interest:

The Pediatric Epilepsy Research Foundation provides grant funding to child neurologists in the US/Canada for meritorious clinical, translational, basic science, comparative-effectiveness, implementation research, etc. related to all neurologic conditions in infants, children and adolescents. Epilepsy projects are of particular interest.

PERF is also interested in supporting consortium groups focusing on specific neurological conditions such as:

- The Pediatric Epilepsy Research Consortium (PERC)
- The Cerebral Palsy Research Network (CPRN)
- International Stroke Organization (IPSO)
- And others.

Research Support:

Grant amounts range up to $200,000.00, awarded over two years. The two year grant is divided into two equal payments (10% of the award is held back with payment upon submission of a yearly scientific and financial report). Occasionally grants for larger funding amounts may be considered for multi-year (greater than two years) projects. Grants are competitive.

PERF offers two grant categories

PERF Career Development Grant

The PERF Career Development (Young Investigator) grant awards are administered through the Child Neurology Foundation. Please refer to their website for application deadlines and information. The two young investigator awards funded by PERF are the "Elterman Scientific Research Grant" and the "Shields Research Grant".

PERF Grant for Infrastructure/Registry Research

This competitive grant in child neurology is directed at developing new infrastructure, (registries and networks) or enhancing an existing infrastructure to enable advancement of patient based research. To that end, PERF offers the "PERF Grant for Infrastructure/Registry Research". We are interested in pediatric epilepsy and will also consider projects relevant to all areas of child neurology. Research projects providing opportunities for training and/or mentoring young investigators are of particular interest. We look forward to evaluating your exciting and innovative projects. To be eligible for this grant, the applicant should be a child neurologist at any stage in his or her career, or someone working

in an area relevant to child neurology, either M.D. or Ph.D. and must be a legal resident of the United States or Canada. Non-child neurologists and PhD's developing infrastructure/registry projects in child neurology may also apply.

Examples of Recent Activities:

Most recent funded grants (2019 & 2020):

Zachary Grinspan, MD/Weill Medical College of Cornell University
"A Learning Healthcare System for Pediatric Epilepsy
The long term goal is to change practice and improve outcomes for children with epilepsy by creating a learning healthcare system to support standardized collection of electronic clinical information and facilitate rapid analysis and dissemination of results. This approach has dramatically improved health outcomes for children with other pediatric diseases, notably cancer, inflammatory bowel disease and hypoplastic left heart syndrome. We have constructed a network called the Pediatric Epilepsy Healthcare Learning System (PELHS). The current grant supports the development of a charter for PELHS, an academic conduct guideline and a plan for sustainability. Expansion of data collection from 8-20 sites. Develop algorithms that allow a computer to automatically identify individuals with specific subtypes of epilepsy. Implement quality metrics for child neurology care and link the metrics to quality improvement initiatives at each site. Conduct a comparative effectiveness study examining different treatments for neonates with hypoxic ischemic encephalopathy, and how treatment affects the risk of developing infantile spasms.

Mirjana Maletic-Savatic, MD, PhD/Baylor College of Medicine
Ashura Williams-Buckley, MD/NIMH
"Sleep and Neurodevelopment: Establishing Infrastructure for Sleep Metrics Data Collection and Dissemination"
Sleep is essential for proper brain development, yet the complex processes that establish the sleep pattern and ultimately influence the formation of functional brain circuits from onward are barely known. A wide variety of conditions influence sleep, from day/night cycle to diet, and it has become clear that no single discipline working in isolation can put the sleep and neurodevelopment pieces together. The Sleep and Neurodevelopment Research Consortium was founded in 2017 by Dr. Ashura Williams-Beckley and is tasked with research on sleep characterization throughout early development with particular attention on the neural oscillatory patterns of the sleeping brain from birth to school-age and then beyond. This grant will establish the framework that will enable us to launch longitudinal, prospective studies designed to follow newborns over their first five years of live and characterize sleep in association to overall motor, cognitive, social, genetic, and metabolic maturational trajectories.

Elysa Widjaja, MD/Hospital for Sick Children Toronto
"Pediatric Epilepsy MR-guided Laser Interstitial Theramal Therapy (PEP-LITT) Registry"
Drug resistant (or poorly controlled) epilepsy can have devastating consequences on children's quality of life. We have shown that surgery resulted in higher seizure freedom and better QOL than medical therapy in children with drug resistant epilepsy. However, there are concerns about the risk of epilepsy surgery. Laser therapy has the advantage of faster recovery and shorter hospital stay. It is a promising treatment but we do not know how well it works, what the risks are and who would the most. This study will identify the predictors of good seizure outcome after laser surgery, the complications and outcomes of laser therapy. We hope to discovery how effective laser therapy is at controlling seizure and improving QOL compared with surgery and medication therapy and the risks associated with laser therapy. The database developed from this registry will lay the groundwork for assessing long-terms outcomes of laser therapy and a future cost-effectiveness study of laser therapy

compared with surgery and medical therapy.

Madison Berl, MD/Children's Research Institute, Washington DC
"A Multi-site Collaborative for Pediatric Epilepsy Surgery Outcomes Beyond Seizure Freedome"
Guidelines and consensus statements related to pediatric epilepsy surgery are uniformly lacking high quality published outcome data to support clinical decisions that impact likelihood of seizure freedom and optimizing outcomes beyond seizure control(neuropsychological functioning, QOL, improved sleep). Despite recognition of the need standardized collection of data on a multi-institutional basis, the efforts that exist are limited in scope. As new techniques such as laser ablation and brain stimulation are approved for pediatric patients, there is little information available to determine which children will benefit from which intervention. While seizure control is primary, functional outcomes are just as important and, when seizure control is similar, may be the critical factor in deciding on a treatment course. We will leverage current successful efforts to standardized data collection through commonly available online platforms and scale them for multi-institutional implementation. Our long-term goal is to create a pediatric surgical clinical data platform. Short-term goal: finalize the data and methods for collection; and test the capability of our collaborative by testing specific hypotheses.

The Epilepsy Study Consortium (TESC)

Primary Representative: Jacqueline French, MD; Professor of Neurology, NYU School of Medicine; President, TESC and Dennis Dlugos, MD; Professor of Neurology, Children's Hospital of Philadelphia; Vice President

Email: Jacqueline.french@nyumc.org; dlugos@email.chop.edu

Mission: The Epilepsy Study Consortium is a group of scientific investigators from academic medical research centers who are dedicated to accelerating the development of new therapies in epilepsy to improve patient care. The organization's goals include building a partnership between academics, industry and regulatory agencies and optimizing clinical trial methodology in order to responsibly speed new treatments to patients.

Major Topics of Interest:

- Clinical trials
- Clinical trial methodology
- Protocol development
- Novel Therapeutics

Research Support:

We have 32 academic medical centers in the US and 11 in Australia as members of the consortium. These centers have been screened to find the optimal sites for clinical trial research. Each site specializes in epilepsy and has a rather large patient population which enables careful patient selection, and good recruitment.

We have been involved in a number of early trials from industry, as well as trials funded by non-profits.

We have created diagnostic review forms and seizure classification forms that are now widely used in epilepsy studies, to ensure that patients enrolled in trials have been properly selected and classified.

The Consortium has also assisted sponsors with protocol development, CRF and source document design and assembled DSMBs.

We sponsor a biennial research conference focusing on issues related to antiepileptic drug (AED) development from preclinical discoveries through clinical evaluations. This symposium brings together representatives from academia, industry, the NIH, and the FDA to review what has been learned and to discuss strategies to enhance AED development. Website: www.aedtrials.com

Four grants of $1,500 were awarded to fellows and early career faculty interested in new therapies for epilepsy. The grants were used to cover expenses associated with attending the Antiepileptic Drug & Device Trials XV Symposium. The registration fee was also waived. In addition to the grants, the Epilepsy Consortium sponsored 'mentoring lunches' which were held throughout the meeting. This enabled the grant recipients to meet with faculty members with interests similar to their own. This will again be offered during the June 2021 meeting.

The Consortium organized an in person Coordinator Boot Camp in December 2019. This was made available to all Consortium Coordinators. There were 26 coordinators representing 15 Consortium sites who attended with a wide variety of experience from 4 months to over 15 years. There are plans to continue this in person annually. In addition, in the interim, we have been hosting Virtual Coordinator Boot Camps monthly over the past year.

In July 2019, the Study Consortium organized a monthly eDiary working Group comprised of representatives from ~15 pharmaceutical sponsors, experts in the field, patients and caregivers, to identify issues, establish eDiary specifications and develop an electronic seizure diary application for clinical trials that will work better for our unique population, while also collecting necessary trial data to meet regulatory requirements. In August 2020, we began a rigorous selection process, starting with 13 potential eDiary vendors, ultimately selecting 2 vendors who will build seizure e-diaries specifically for regulatory trials: Irody (of the patient mobile app, EpiDiary) and Signant Health. We have begun initial stages of building a "core" eDiary for epilepsy clinical trials. We recognize that every diary cannot be identical, and there should be common data elements so that trials can be compared, and study participants and site staff have greater continuity and improved ease of use.

The Epilepsy Study Consortium sponsored two mini-grants of $15,000, for epilepsy fellows to support research related to antiepileptic drug therapy. The goals of the program are to foster research on AEDs and to motivate epilepsy fellows to undertake research projects during their fellowship training.

Photosensitivity Studies – The photosensitivity proof of concept model has been used to evaluate potential antiseizure effects of new agents in relatively small groups of patients with photically induced generalized epileptiform responses on their EEG. The Epilepsy Consortium is performing central EEG review and on-site training to all of the sites involved.

Examples of Recent Activities:

HEP - The Human Epilepsy Project is a five-year, prospective, observational study whose primary goal is to identify clinical characteristics and biomarkers predictive of disease outcome and progression, and treatment response in participants with new onset or recently diagnosed focal epilepsy. The data to be collected on these participants include high-resolution clinical phenotyping (including comorbidities) and treatment response, neuroimaging, electrophysiology, and genomics and proteomics. A major objective of the project is to create an open data repository of clinical information and biologic samples for future studies.

Resources Available:

Additional information can be found on the TESC website:
www.epilepsyconsortium.org

Priorities and/or Plans for Future Activities:

We are available to assist for trials of new diagnostic ortherapeutic interventions performed by any non-profit or for-profit entity.

Tuberous Sclerosis Alliance (TS Alliance)

Primary Representative: Kari Luther Rosbeck, President and Chief Executive Officer
Email: krosbeck@tsalliance.org

Mission: The Tuberous Sclerosis Alliance is dedicated to finding a cure for tuberous sclerosis complex (TSC) while improving the lives of those affected.

Major Topics of Interest:

- Preventing epilepsy and developmental delay secondary to epilepsy
    - Identify biomarkers that accurately predict those with TSC at high risk of developing epilepsy
    - Develop approaches to prevent development of epilepsy in those with TSC at high risk
- Understand the range of signaling pathways that play a role in the development of epilepsy in TSC
- Understand the relationship of mTOR activity to epilepsy and epileptogenesis
- Development of novel therapeutics for the treatment of epilepsy
- Move toward personalized medicine for epilepsy
    - Further investigate the epilepsy-related genotype-phenotype correlations in TSC
    - Population stratification, understanding of different responses to specific anti-seizure medications
    - Individual risk-of-seizure assessment

Research Support:

- Annual research grant and postdoctoral fellowship awards supporting research focused on TSC, which may include the study of any aspect of epilepsy in TSC, such as molecular mechanisms, preclinical models, biomarker discovery, etc.
- The TSC Clinical Research Consortium provides infrastructure to conduct clinical studies in TSC, including epilepsy-related studies, at thirteen TSC Clinics around the country.
- The TSC Preclinical Consortium has established partnerships with CROs, academic advisors, and industry partners to examine candidate drugs for efficacy in mouse models of TSC using standardized, rigorous protocols.
- The TSC Natural History Database and Biosample Repository collect and share data and biospecimens as resources to stimulate research on TSC including epilepsy
- The TS Alliance hosts a biennial International TSC Research Conference. The next conference will be October 28-30, 2021, held virtually.

Examples of Recent Activities:

- Research grant and postdoctoral fellowship awards:
  - 2018-2020
    - Rosemary Ekong, PhD: "The TSC1 and TSC2 variation database." (University College London)
    - Angélique Bordey, PhD: "Non-cell autonomous effects in TSC brain malformations." (Yale University)
    - Christine Ochoa-Escamila, PhD: "Neural circuits underlying autism-related behaviors in tuberous sclerosis." (University of Texas Southwestern Medical Center)
  - 2019-2021
    - Mustafa Sahin, MD, PhD: "Non-cell autonomous mechanisms of epilepsy in TSC2." (Boston Children's Hospital)
    - Ilaria Barone, PhD: "Harnessing the circadian clock to modulate TSC-related neuronal phenotypes." (Boston Children's Hospital)
- Clinical research support
    - Darcy Krueger, MD, PhD: Stopping TSC Onset and Progression (STOP-2): Epilepsy prevention in TSC infants (NCT04595513)
    - Mustafa Sahin, MD, PhD: Rare Diseases Clinical Research Consortium
- Preclinical Consortium
  - Data generated by the Consortium have been used by companies and academic researchers to secure follow-on funding to support additional TSC research.
  - Two industry partners have planned clinical trails in TSC-related epilepsy based on research generated utilizing resources from the Preclinical Consortium and TSC Biosample Repository.

Resources Available:

- The TSC Biosample Repository, as of April 1, 2021 contains 1,715 biosamples. Samples are linked either to clinical study data from the Rare Disease Clinical Research Network, the TSC Natural History Database, and/or the TSC Autism Center of Excellence Research Network (TACERN) study. Biosamples may be collected at specific sites or via a mobile phlebotomy/walk-in phlebotomy program coordinated by the TS Alliance
- The TSC Natural History Database was launched in 2006 and contains 2,289 participants with medical data, as of April 1, 2021.
- The Preclinical Consortium runs studies nominated by investigators and makes these data available to members. As of 2021, the Preclinical Consortium has run 35 experiments in mouse models of epilepsy associated with TSC. Three of these studies have examined neuropsychiatric phenotypes associated with TSC-epilepsy.

Priorities and/or Plans for Future Activities:

- Ensuring, to the extent we can, the successful execution of clinical trials, including PREVeNT, STOP-2, and industry-sponsored trials in TSC-associated epilepsy.
- In 2021, releasing a hypothesis-driven funding opportunity announcement for research toward an assay relevant for use in newborn screening for TSC, with the eventual goal to develop a reliable and inexpensive screening test that can be used to detect TSC as soon as possible upon birth and allow for preventative treatment.
- Development of a patient-reported outcomes portal for individuals with TSC and/or caregivers to track individual TSC-Associated Neuropsychiatric Disorders (TAND) Checklist metrics, which would be linked to natural history data, Seizure Tracker data, and any previously donated biospecimens.
- The addition of a Tsc2-Syn-Cre mouse model that exhibits a TSC-relevant epilepsy phenotype to the TSC Preclinical Consortium.

Agenda

ICARE meeting May 21, 2021

11:00am –11:05am Welcome

11:05am-11:45am ICARE member introductions

11:45am-12:35pm ICARE member Research Updates

11:45am-12:00pm NIH/NINDS – Dr. Walter Koroshetz, MD; Director, NINDS

12:00pm- 12:15pm AES – Eileen Murray, MM, CAE; Executive Director, AES

12:15am-12:30pm ELC – Amy Brin, MSN, MA, PCNS-BC; Executive Director and CEO Child Neurology Foundation; Chair, ELC

12:30pm-1:00pm ICARE Portfolio Analysis Update - ICARE funding landscape – Miriam Leenders, PhD; Program Director, Division of Neuroscience, NINDS

1:00pm-1:30pm BREAK

1:30pm-2:00pm Curing the Epilepsies conference: 2021 Benchmarks and transformative research priorities – Eric Marsh, MD, PhD; CHOP; Chair, AES/NINDS Benchmark Stewards Committee

2:00pm-4:00pm Panel Discussion: Steps in moving the field forward in most impactful way to improve treatment and care of people with epilepsy

Moderator: Adam Hartman, MD; Program Director, Division of Clinical Research NINDS

Panel: Overview of translational research for the epilepsies: Gaps and Opportunities

- Funding for Translational Research on the Epilepsies
  Amir Tamiz, PhD; Director Division of Translational Research NINDS
- Perspective from Individual with Epilepsy or Patient Advocate
  Steve Roberds, PhD; Chief Scientific Officer, TS Alliance
- Perspective from Basic Scientist
  Doug Coulter, PhD; CHOP; President, AES
- Perspective from Translational Scientist
  Greg Worrell, MD; Mayo Clinic and Jim McNamara, MD, Duke University
- Perspective from Clinician Scientist
  Annapurna Poduri, MD, MPH; Boston Children's Hospital
- Perspective from Clinician
  Susan Herman, MD; Barrow Neurological Institute; President, NAEC
- Perspective from Industry
  Gene Liau, PhD; Chief Scientific Officer, Stoke Therapeutics.

Discussion