CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

Epilepsy Research Program

Leading the Way to Understanding Post-Traumatic Epilepsy

For more information, please visit
cdmrp.health.mil/erp

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

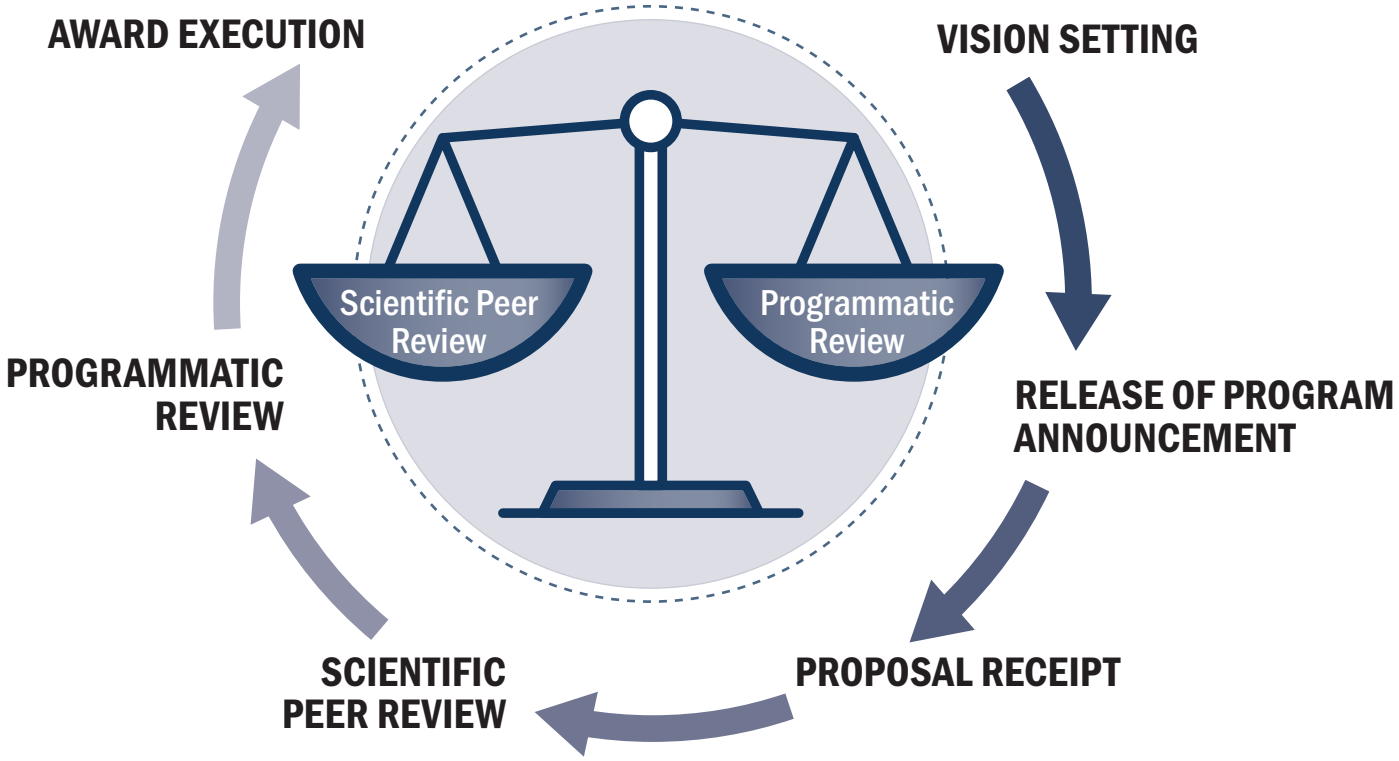
HISTORY

The Congressionally Directed Medical Research Programs were created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. Since then, the CDMRP grew to encompass over 35 targeted programs managing over $19.3 billion since its inception through FY24.

TWO-TIER REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications. Both tiers involve dynamic interaction between scientists and consumers with lived experience with the injury, disease, or disorder. The first evaluation tier is a scientific peer review of the applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of stakeholders from the field including leading scientists, clinicians, and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit and strategic programmatic considerations such as potential impact and relevance to program goals.

CDMRP AWARD EXECUTION PROCESS



EPILEPSY RESEARCH PROGRAM

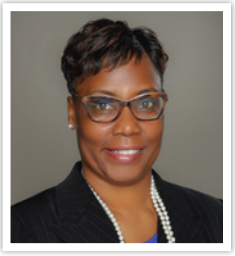
ABOUT THE PROGRAM

Congress initiated the ERP in 2015 to support longitudinal epidemiological research to better understand the incidence of post-traumatic epilepsy following a traumatic brain injury and to improve patient care and outcomes. The ERP is committed to funding research projects that investigate topics related to epileptogenesis for the identification of mechanisms by which brain injury produces epilepsy, study the prevention of PTE and concomitant comorbidities, and develop innovative research tools or biomarkers to better detect, diagnose, or predict the development of PTE. To this end, the ERP utilizes focus areas that applications should address to drive investment into specific program priority areas.

- Appropriations for the ERP from FY15 through FY23 totaled $85.5 million. The FY24 appropriation is $12.0 M.

VISION: A time when post-traumatic epilepsy is prevented or optimally managed

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



"Having the opportunity to be a part of the of Epilepsy Research Panel as a Consumer Reviewer has allowed me to see the work that is being done for the epilepsy community. It has allowed me to see how funds are used as well as giving input towards decisions that will help impact the outcomes of Veterans and their caregivers. I look at this as an amazing way to give back to our Veterans who have held the fence to protect our soil."

Tanisha Tyler Graves,
FY22 ERP Peer Review Consumer Reviewer, Danny Did Foundation

SCOPE OF THE PROBLEM

An estimated 50 million individuals live with epilepsy worldwide.[1] This neurological disorder is characterized by repeated seizures caused by sudden changes in electrical functioning of the brain leading to involuntary movement of the body.

TBI is a known risk factor for acquired epilepsy.

- Of those 15 years or older hospitalized for TBI, it is estimated that 1 in 10 will develop epilepsy within 3 years.[2]
- TBI severity correlates with increased risk of developing PTE, with incidence rates of PTE at 2% for mild TBI, 4% for moderate TBI, and 15% for severe TBI.[3]

Over 450,000 Service Members from 2000-2022 reported cases of TBI and are at increased risk for developing PTE.[4]

- Among Service Members hospitalized for TBI, the incidence rate of PTE rises to up to 53% when including penetrating injuries.[5]
- Additionally, PTE is associated with a higher risk of death and affects an estimated 2,187 Iraq and Afghanistan War Veterans.[6]

Treatments for epilepsy have improved, but side effects from medicine, like headaches and memory loss, remain an issue. The efficaciousness of PTE treatments remains unclear, particularly in military populations.[7] Additionally, clinical trials are often not designed to capture long-term, rare adverse effects from treatments.[7]

[1] World Health Organization. *Epilepsy*. 2023. https://www.who.int/news-room/fact-sheets/detail/epilepsy

[2] Ferguson PL, et al. 2010. A Population-Based Study of Risk of Epilepsy After Hospitalization for Traumatic Brain Injury. *Epilepsia* 51(5):891–898. doi: 10.1111/j.1528-1167.2009.02384.

[3] Yuan, WH and Wang, SJ. 2020. Posttraumatic Epilepsy After Traumatic Brain Injury and Prophylactic Administration of Antiepileptic Drugs. *Journal of the Chinese Medical Association* Oct; 83(10):885-886. doi: 10.1097/JCMA.0000000000000395.

[4] Traumatic Brain Injury Center of Excellence. 2022. "Annual Report Traumatic Brain Injury Center of Excellence 2022." Retrieved from https://www.health.mil/Reference-Center/Reports/2023/03/21/2022-TBICoE-Annual-Report

[5] Ding K, et al. 2016. Epilepsy After Traumatic Brain Injury. In: Laskowitz D, Grant G, editors. 2016. *Translational Research in Traumatic Brain Injury,* Chapter 14. CRC Press/Taylor and Francis Group, Available from: https://www.ncbi.nlm.nih.gov/books/NBK326716/

[6] Pugh MJ, et al. 2016. Epilepsy Among Iraq and Afghanistan War Veterans – United States, 2002-2015. *Morbidity and Mortality Weekly Report* 65(44):1224-1227. doi: 10.15585/mmwr.mm6544a5. PMID: 27832054.

[7] Löscher W, Schmidt D. 2011. Modern Antiepileptic Drug Development Has Failed to Deliver: Ways Out of the Current Dilemma. *Epilepsia* 52(4):657-78. Doi: 10.1111/j.1528-1167.2011.03024.x.

PROGRAM PRIORITIES

The ERP asks investigators to address specific focus areas to drive investment into critical program priority areas.

Markers and Mechanisms: Identifying biomarkers or mechanisms of PTE	**Epidemiology:** Epidemiological characterization of PTE following TBI	**Longitudinal Studies:** Studies of the evolution of PTE	**Innovative Research:** Tools intended to better inform or improve upon PTE research and care

PROGRAM PORTFOLIO EVALUATION

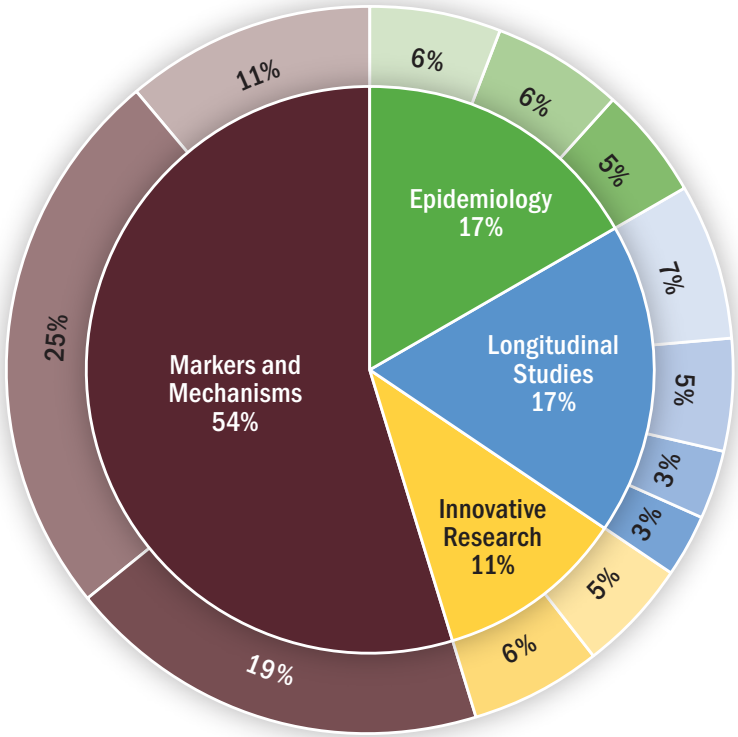
Figure 1: FY18 – FY22 ERP Funding Across Focus Areas Totaling $42.6M

Markers and Mechanisms

- Seizure prevention
- Epilepsy prevention
- Predictive biomarkers of acute and chronic epileptogenesis

Longitudinal Studies

- Understanding and improving the quality of life of individuals with PTE, their families, and/or their care partners
- Treatment and healthcare outcomes research, including quality of care
- Natural history of PTE and prognosis
- Comorbidities (e.g., depression, functional deficits, sleep disorders, major illness)



Epidemiology

- Understanding and improving the quality of life of individuals with PTE, their families, and/or their care partners
- Predictors of the development of epilepsy
- Outcomes, including latency to and prevention of epilepsy, comorbidities, and mortality

Innovative Research

- Strategies that will improve seizure detection, characterization, visualization, or diagnosis
- Development of new models or better characterization of existing etiologically relevant models for PTE

** Data do not include two FY22 awards not required to address a program focus area.*

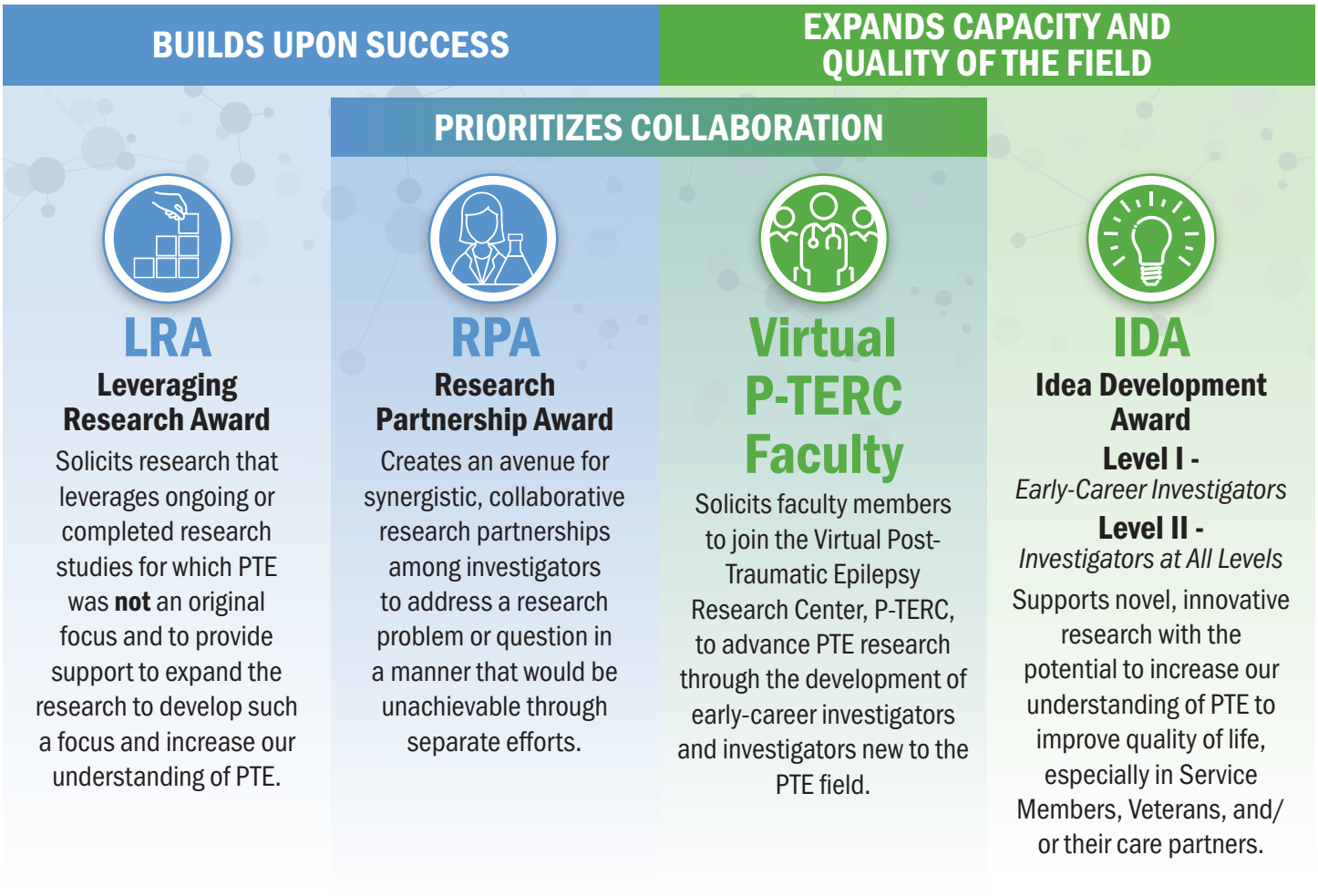
STRATEGIC PRIORITIES

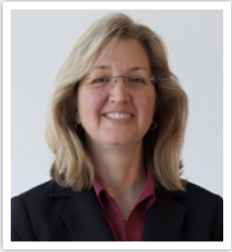
The ERP acknowledges the systemic challenges that exist within the field. The program identified three strategic challenges to address through the funding opportunities offered. The challenges include:

1. Small scientific community within the field
2. Competitive rather than collaborative research environment
3. Limited resources dedicated to the field that researchers may leverage

To address these challenges, the ERP offers funding opportunities that build capacity within the field, encourage collaboration, and build upon success inside and outside the field to advance understanding of PTE.

Figure 2: ERP Funding Opportunities





"The ERP funds high-risk, high-reward research that is providing insights on how TBI can result in PTE, as well as who may be most at risk for developing PTE. The ERP also funds critical research on other types of epilepsy that can have a profound impact on our Service Members, Veterans, and civilians. As an ERP Programmatic Review panel member, I am excited to see the advancements that have already been achieved by this research program and am eager to see how it will improve the quality of life of all those affected by epilepsy."

Laura Lubbers, Ph.D.,
Chief Scientific Officer,
CURE Epilepsy

EXPANDING CAPACITY

The ERP is committed to growing capacity within the PTE field. Named principal investigators on applications for ERP funding opportunities can be from any field or discipline. Furthermore, the ERP offers funding opportunities specifically for early-career investigators and those who are new to the PTE field. The following highlights feature initiatives supporting capacity-building efforts as well as exciting research led by emerging talents in the PTE field.

TRACKING ERP-SUPPORTED EARLY-CAREER INVESTIGATORS IMPACT ON THE FIELD

The ERP recognizes the importance of supporting early-career investigators who can foster innovation in the PTE field. The ERP has a long-standing commitment to funding early-career investigators, many of whom have grown within and continue to impact the PTE field.

FY15-FY19 The ERP invested $7.2 M in 13 investigators new to epilepsy research

- **54%** of investigators received follow-on funding from **19 grants**
- **77%** of investigators remain active in epilepsy research
- Investigators generated **244** publications post awards
- **69%** of investigators earned promotions or tenure

THE VIRTUAL POST-TRAUMATIC EPILEPSY RESEARCH CENTER

In FY22, the ERP initiated the Virtual P-TERC to develop successful, highly productive PTE researchers in a collaborative research and career development environment to enhance quality and expand quantity of the PTE research field. Ramon Diaz-Arrastia, M.D., and Mary Jo Pugh, Ph.D., two pioneers in the field of PTE research, lead this exciting effort. Through this, the ERP aims to expand capacity and foster mentorship and career development for researchers looking to break into the PTE field as well as those early in their careers.

DIRECTOR AND DEPUTY DIRECTOR

Ramon Diaz-Arrastia, M.D., Ph.D., University of Pennsylvania

Mary Jo Pugh, Ph.D., R.N., University of Utah

FACULTY

Chad Frasier, Ph.D., East Tennessee University

Paul Koch, M.D., Virginia Commonwealth University

Oleksii Shandra Ph.D., Florida International University

Haneef Zulfi Ph.D., Baylor College of Medicine

CAREER GUIDES

Bret Smith, Ph.D., Colorado State University

Jerome Engel, M.D., Ph.D., University of California Los Angeles

Richard Staba Ph.D., University of California Los Angeles

Alan Towne Ph.D., Virginia Commonwealth University

HIGHLIGHTABLE RESEARCH FROM ERP-SUPPORTED EARLY-CAREER INVESTIGATORS:

The following highlights feature initiatives supporting capacity building efforts as well as exciting research led by emerging talents in the PTE field.

Phenotypes of Epilepsy Etiology and Drug Resistance, PEER

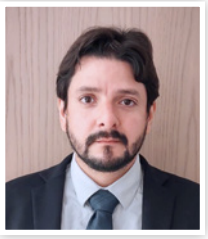
Eamonn Kennedy, Ph.D., University of Utah
FY22 Idea Development Award

Recent studies funded by the ERP found that PTE is associated with medication failures relating to seizure freedom and pain management. However, it is still not well-understood why PTE is associated with treatment-resistance and why these treatments are less effective for PTE and its co-occurring conditions. The PEER study will test a newly formed hypothesis that the magnitude and mechanisms of PTE, its comorbidities, and its treatments all act in concert where timing and directionality of care are critical for treatment success and better outcomes. People with PTE often experience co-morbid health conditions, making it difficult to disentangle the complex patterns of drug prescription from the health conditions they treat. Kennedy will use three existing DOD/Veterans Health Administration datasets containing detailed patient information to produce individualized "risk scores" for the development of epilepsy following head trauma. Findings from this work are anticipated to improve PTE diagnosis, understanding of available treatments, and outcomes and quality of life for those living with epilepsy.

Innovative Tools for Detection of Post-Traumatic Epilepsy

Anand Joshi, Ph.D., University of Southern California
FY17 Idea Development Award, FY22 Idea Development Award

Joshi evaluated patients with traumatic brain injuries to map changes in structure and detect functional differences in the brain from functional magnetic resonance imaging data with FY17 ERP funding. Joshi's team developed and publicly released a data analysis extension toolbox for open-source BrainSuite software that uses high-resolution anatomical and functional MRI images to define regions and abnormalities in the brain after a TBI. The tool can enable clinicians to map differences in a person's anatomic and neural connectivity and may be useful for the prediction of outcomes, including post-traumatic epilepsy. Now, with support from FY22 ERP funding, Joshi plans to enhance the BrainSuite software toolbox and improve PTE prediction by analyzing a larger dataset of TBI patients. Using deep learning, the team aims to predict the risk of PTE based on MRI data. Development and implementation of these innovative tools are crucial for accurately assessing the risk of developing epilepsy after a TBI.



Acute Pharmacological Augmentation of Kv7 K+ Ion Channel Prevents Post-Traumatic Epilepsy and Chronic Traumatic Encephalopathy

Fabio Borges-Vigil, Ph.D., University of Texas, Health Science Center at San Antonio
FY21 Idea Development Award – Funding Level 1

Borges-Vigil is a post-doctoral researcher evaluating the contribution of potassium channels, proteins that transport potassium ions in and out of cells, in the development of PTE. Preliminary data found that mice treated with retigabine, a U.S. Food and Drug Administration-approved potassium channel opener, shortly after receiving repetitive TBIs had shorter post-traumatic seizures and showed minimal other indicators of neurodegenerative disease. Retigabine also reduced the number of mice developing PTE. With FY21 ERP funding, Borges-Vigil will assess the effects of retigabine, as well as a newer, more-potent and specific potassium channel activator in the long-term prevention of epilepsy after TBI. Borges-Vigil hopes that this work will lead to clinical trials and offer a new treatment option to individuals experiencing TBI.

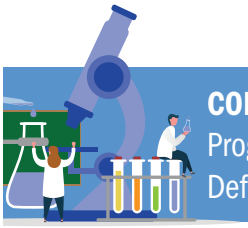
COLLABORATION

The ERP fosters collaboration among investigators by creating an avenue for synergistic and collaborative research partnerships to address knowledge gaps that would be unattainable through individual efforts alone. The following showcase the collective endeavors aimed at advancing the field of PTE.

TRACK-TBI Epileptogenesis Project

Ramon Diaz-Arrastia, M.D., Ph.D., University of Pennsylvania
FY18 Longitudinal Risk Factors Award

PTE is a common complication to TBI of any severity level and often has a delayed onset following injury that makes diagnosis and prevention difficult. To increase success in developing anti-epileptogenic therapies, Diaz-Arrastia is studying PTE in the ongoing Transforming Research and Clinical Knowledge in Traumatic Brain Injury, TRACK-TBI, initiative and engaging expert epileptologists in the research. By extending the follow-up period for participants to over five years, the TRACK-TBI team will be able to monitor participants longer and collect more clinical imaging and blood biomarker data to facilitate comprehensive PTE specific evaluations. To date, Diaz-Arrastia's team identified 225 TRACK-TBI patients living with PTE via phone interviews and successfully started in-person follow-up. The team will continue screening participants and conducting follow-up analyses to identify and validate predictive biomarkers for PTE for therapeutic development and prevention of PTE occurrence following TBI.



COLLABORATION: Epilepsy Research Program and other Department of Defense supported resources

Military Injuries: Understanding Post-Traumatic Epilepsy (MINUTE), Health, and Quality-of-Life Effects of Caregiving

Mary Jo Pugh, Ph.D., R.N., University of Utah
FY19 Research Partnership Award

Pugh's FY15 ERP Idea Development Award found that Veterans with PTE have a unique set of needs compared to fellow Service Members without PTE, that TBI severity alone could not explain.[8] While previous studies show caregivers improve the overall health and well-being of "children" with epilepsy, no current data exist to support this with post-9/11 Service Members or Veterans living with PTE.[9, 10] Additionally, there has been little research into the effects of long-term caregiving for those assisting someone living with PTE. With FY19 ERP funding, Pugh is leveraging her expertise in PTE and longitudinal neuroepidemiology along with U.S. Department of Veteran Affairs, DOD, and academic collaborators to assess this gap and identify unique issues of caregivers of Veterans with PTE. Pugh's team will also assess the quality of life and health trajectories of post-9/11 Veterans, Service Members, and their caregivers to expand understanding of the impacts PTE and comorbidities have on the experience and overall well-being of these affected populations.

COLLABORATION: Epilepsy Research Program, Department of Veterans Affairs, and other Department of Defense supported resources

[8] Pugh MJ, et al. 2021. The Military Injuries: Understanding Post-Traumatic Epilepsy Study: Understanding Relationships Among Lifetime Traumatic Brain Injury History, Epilepsy, and Quality of Life. *Journal of Neurotrauma* 38(20):2841-2850.

[9] Ferro MA, et al. 2013. Trajectories of Health-Related Quality of Life in Children with Epilepsy: A Cohort Study. *Epilepsia* 54(11):1889-1897.

[10] Maslow GR, et al. 2011. Young Adult Outcomes of Children Growing Up with Chronic Illness: an Analysis of the National Longitudinal Study of Adolescent Health. *Archives of Pediatrics & Adolescent Medicine* 165(3):256-261.

Epidemiological Characterization and Prognostic Models for PTE: A Collaborative TBI-MS and VHA Study

Amy Wagner, M.D., University of Pittsburgh
FY17 Epilepsy Risk Factors Award

Veterans who experienced a TBI have an increased risk of epilepsy, depending on the severity of the TBI.[11] Wagner, in collaboration with Mary Jo Pugh, Ph.D., and experts in TBI epidemiology and rehabilitation, is analyzing clinical demographic and genetic data in a series of studies to assess how these factors can impact PTE risk. The goal is to develop more accurate prognostic models. Additional work will evaluate how PTE influences mental health and cognitive comorbidities to impact multiple domains of function. Wagner's team is leveraging a large retrospective cohort of over 6,000 civilians from the TBI Model System National Database for prognostic model generation and assessing PTE effects on outcome. She and Pugh used the Veterans Health Administration database to prospectively screen and enroll post-9/11 Veterans to evaluate genetic influences on PTE risk. Progress to date includes completing the proposed civilian participant studies and submitting the findings for publication. Enrollment and data collection are complete for the Veteran samples and the proposed data analysis is being finalized.

COLLABORATION: Epilepsy Research Program, Department of Veterans Affairs, and the National Institute on Disability, Independent Living, and Rehabilitation Research

Figure 3: Collaborative Care Schema

Collaborative Care to Improve Quality of Life for Anxiety and Depression in Post-Traumatic Epilepsy

Heidi Munger Clary, M.D., M.P.H., Wake Forest University Health Sciences
FY21 Quality of Life Research Award

Munger Clary is conducting a clinical trial to assess how a collaborative care approach can impact neurological outcomes and quality of life for people living with PTE. In this study, the research team integrates neurological and psychological care together with a care management coach and a social worker to provide holistic and accessible care to participants, Figure 3. Munger Clary's remote intervention has the potential to increase patient access to care, including overcoming transportation barriers faced by people with PTE, while also improving overall quality of life.

COLLABORATION: Epilepsy Research Program, and Department of Veterans Affairs

[11] Pugh MJV, et al. 2015. The Prevalence Of Epilepsy and Association with Traumatic Brain Injury in Veterans of the Afghanistan and Iraq Wars. *Journal of Head Trauma Rehabilitation* 30(1):29-37. https://doi.org/10.1097/HTR.0000000000000045

BUILDING UPON SUCCESS

The ERP looks to advance our understanding of PTE by building upon successful research from inside and outside the PTE field. To do this, the program leverages funding mechanisms that require applicants to demonstrate how their research builds upon a successful foundation of previous investigation. Through these initiatives the program hopes to more rapidly advance research ideas to impact the PTE field, patient care, and/or those living with PTE.

FROM TARGET IDENTIFICATION TO LEAD VALIDATION

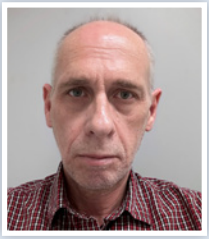
Prevention of Post-Traumatic Epilepsy by Inhibiting the Initiation of Innate Immune Reaction

Xiaoming Jin, Ph.D., Indiana University
FY22 Research Partnership Award

While the underlying mechanisms of PTE remain unknown, a TBI can initiate the body's innate immune response and neuroinflammation. Jin collaborates with Randy Brutkiewiczto, Ph.D., an immunologist, to investigate the role of inflammatory pathways in PTE development. CD1 is a surface protein on specific cells of the innate immune system that binds to natural killer T-cells, the activation of which may contribute to the development of PTE and be modified following a TBI. Jin will evaluate the role of CD1 following TBI by measuring markers and cells of inflammation in animal models and assess whether a novel use of statins, a type of widely-used lipid-lowering drug, to block CD1 signaling could be effective in preventing PTE development.

FROM LEAD IDENTIFICATION TO IN-VIVO TESTING

Leveraging Innate Immunity to Prevent Post-Traumatic Epilepsy



Andrey Mazarati, M.D., University of California Los Angeles
FY21 Research Partnership Award

A TBI can activate immune cells in the brain called microglia.[12] There are two types of microglia: M1, with a propensity for causing inflammation, which can lead to PTE, and M2, with anti-inflammatory effects that can protect against PTE.[13] Recent studies indicate that molecules expressed by bacteria called lipopolysaccharides, LPS, are effective in directing microglia to the M2 type and have protective effects for neurological disorders such as TBI[14] and Alzheimer's disease,[15] but has not been investigated in the context of PTE. In his earlier experiments,[16] Mazarati observed that low-dose LPS may be protective against PTE. He is currently conducting a study in a rat model of TBI-PTE to expand on this observation and to identify molecular mechanisms that afford such protection. If successful, this study could offer a preventative measure for PTE in those living with TBI.

[12] Ravizza T, et al. 2008. Innate and Adaptive Immunity During Epileptogenesis and Spontaneous Seizures: Evidence from Experimental Models and Human Temporal Lobe Epilepsy. *Neurobiology of Disease* 29:142-60.

[13] Chen Z, Trapp BD. 2016. Microglia and Neuroprotection. *Journal of Neurochemistry* 136 Suppl 1:10-7.

[14] Eslami M, et al. 2015. Lipopolysaccharide Preconditioning Prevents Acceleration of Kindling Epileptogenesis Induced by Traumatic Brain Injury. *Journal of Neurochemistry* 289:143-51.

[15] DiCarlo G, et. al. 2001. Intrahippocampal LPS Injections Reduce Abeta Load in APP+PS1 Transgenic Mice. *Neurobiology of Aging* 22:1007-12.

[16] Mazarati A, et al. 2021. Disruption of Intestinal Barrier and Endotoxemia After Traumatic Brain Injury: Implications for Post-Traumatic Epilepsy. *Epilepsia* 62:1472-81.

[17] Delorenzo RJ, 2005. Cellular Mechanisms Underlying Acquired Epilepsy: the Calcium Hypothesis of the Induction and Maintenance of Epilepsy. *Pharmacology & Therapeutics* 105(3):229-66.

[18] Yaari Y, Yue C, Su H. 2007. Recruitment of Apical Dendritic T-Type Ca2+ Channels by Backpropagating Spikes Underlies De Novo Intrinsic Bursting In Hippocampal Epileptogenesis. *Journal of Physiology* 15;580(Pt. 2):435-50.

[19] Casillas-Espinosa PM, et al. 2019. Disease-Modifying Effects of a Novel T-Type Calcium Channel Antagonist, Z944, in a Model of Temporal Lobe Epilepsy. *Progress in Neurobiology* 182:101677. Doi: 10.1016/j.pneurobio.2019.101677. Epub 2019 Aug 13. PMID: 31419467.

[20] Casillas-Espinosa PM, et al. 2015. Z944, a Novel Selective T-Type Calcium Channel Antagonist Delays the Progression of Seizures in the Amygdala Kindling Model. *PLoS One* Vol. 10, Issue 8, Pages e0130012. PMCID: PMC4537250 Doi: 10.1371/journal.pone.0130012.

[21] As of Feb 2024, Dmitry Esterov, D.O., is the principal investigator of this project.

[22] Pease M, et al. 2022. Risk Factors and Incidence of Epilepsy After Severe Traumatic Brain Injury. *Annals of Neurology* 94(4): 663-669.

FROM LEAD IDENTIFICATION TO IN-VIVO TESTING

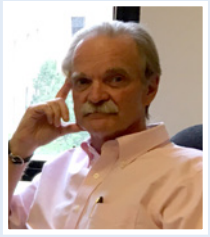
Calcium Channel Modulation to Prevent Post-Traumatic Epilepsy

Terence O'Brien, M.D., Monash University
FY22 Research Partnership Award

Channels located on the surface of neuronal cells, called T-type calcium, Ca2+, play a key role in synchronized neuronal network firing and can be disrupted after TBI. Such disruption can contribute to the development of epileptic seizures.[17] Recent research indicates that low-threshold T-type Ca2+ channels are promising targets as disease-modifying anti-epileptogenic therapies to prevent the development of epilepsy after a brain injury.[18,19] O'Brien, Pablo Casillas-Espinosa, M.D., Ph.D., of Monash University, and collaborators identified that an investigational new drug, Z944, prevents activation of these channels with promising evidence for a disease-modifying anti-epileptogenic effect.[19,20] In collaboration with Aristea Galanopoulou, M.D., Ph.D., of Albert Einstein College of Medicine, this team will assess the effects of Z944 to prevent the development of seizures and associated cognitive and psychiatric comorbidities in a rat model of PTE. O'Brien's research could lead to a better understanding of the impact of low-threshold T-type Ca2+ channel inhibition following TBI and the potential of this approach to prevent the development of dangerous and disabling PTE.

FROM PTE CHARACTERIZATION TO CLINICALLY RELEVANT MODEL DEVELOPMENT

The Role of Preinjury Stress in Development of Post-Traumatic Epilepsy



Daniel S. Barth, Ph.D., University of Colorado
FY21 Research Partnership Award

The most common rat model for studying PTE is the fluid percussion injury model of TBI. With an FY15 ERP-funded Idea Development Award, Barth and F. Edward Dudek, Ph.D., of the University of Utah, discovered that the FPI model in rats did not produce reliable spontaneous recurrent seizures, or SRS, in most animals. The inability to reproduce SRS, a hallmark characteristic for PTE diagnosis for patients, calls into question the reliability of the model to reproduce useful outcomes in humans. Continued work with the FPI model revealed that animals exposed to psychological stress prior to TBI could more reliably develop SRS compared to animals without psychological stress exposure. Barth continues to explore and validate these findings more thoroughly with this FY21 award. To date, the team collected data and developed artificial intelligence methods to evaluate pattern recognition for seizure analysis to assess the effect of psychological stress on the development of PTE. Findings from this study could be used to optimize the rat FPI model, making it more effective in replicating PTE characteristics observed in patients. These enhancements would address the TBI status and the stress that Service Members experience on the battlefield.

FROM ROUTINE CLINICAL DATA COLLECTION AND STORAGE TO PTE INCIDENCE CALCULATION

Post-Traumatic Epilepsy: A Longitudinal, Population-Based Medical Record Review Analysis of Incidence, Risk, and Prediction

Allen Brown, M.D., Mayo Clinic[21]
FY20 Research Partnership Award

The lack of accurate incidence data hinders the development of effective prevention and treatment methods for PTE.[22] Brown collaborated with Dmitry Esterov, M.D., to lead a research team at the Mayo Clinic to leverage the Rochester Epidemiology Project, a population-based record linkage system, to confirm cases of TBI from 1985-2014 and determine the incidence of PTE. The team will compare the incidence of PTE to the incidence of epilepsy among people without history of TBI. The research team will then identify cases of PTE and note clinical characteristics, neuroimaging and brain activity predictors. Using machine learning methods, the team will combine this data into an integrated model of PTE. Brown's model could expand the understanding about the associations between TBI and development of PTE.

For more information, please visit
https://cdmrp.health.mil
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@health.mil
(301) 619-7071

6/2024
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The Congressionally Directed Medical Research Programs is a part of the U.S. Army Medical Research and Development Command, U.S. Army Futures Command.