CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

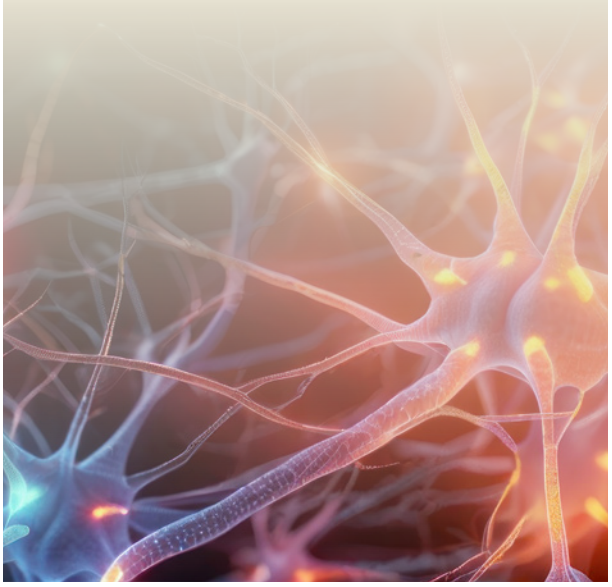
Epilepsy Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. The CDMRP manages each research program with a formal strategic plan that identifies program-specific research priorities, short- and long-term goals, investment strategies, and criteria to identify and evaluate achievements with respect to the priorities.

The Strategic Plan aims to provide clarity about the intent of the CDMRP's Epilepsy Research Program. The ERP identifies and explains the high-impact research goals that are most important to its stakeholders and creates a framework that adapts to changes in the medical research environment. The ERP annually reviews the Strategic Plan at the Vision Setting meeting and makes adjustments as necessary. Congress annually appropriates funds to the ERP and future funding is not guaranteed.



ERP BACKGROUND AND OVERVIEW

Congress initiated the ERP in 2015 in response to concerns about the long-term consequences of traumatic brain injuries that many Service Members experienced. Congress requested longitudinal epidemiological research to improve patient outcomes and understand the magnitude of post-traumatic epilepsy. Additionally, Congress requested the ERP to expand research into the mechanisms by which TBI produces epilepsy and to support research to ultimately prevent PTE and its concomitant comorbidities. Common comorbidities of PTE include depression, cognitive difficulties, and post-traumatic stress disorder, all of which may be interconnected.

Based on recommendations from the ERP Programmatic Panel, the ERP developed the following vision and mission in response to Congress' intent for the program:

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

FUNDING HISTORY AND NUMBER OF AWARDS

Between FY15 and FY19, Congress appropriated $7.5 million annually to the ERP. In FY20, Congress increased the annual appropriation to $12.0M (Figure 1). Total funding for the program through FY24 is $97.5M. During this period, the ERP funded 87 projects that address issues across the continuum of care, with the largest investment in foundational research (Figure 2).

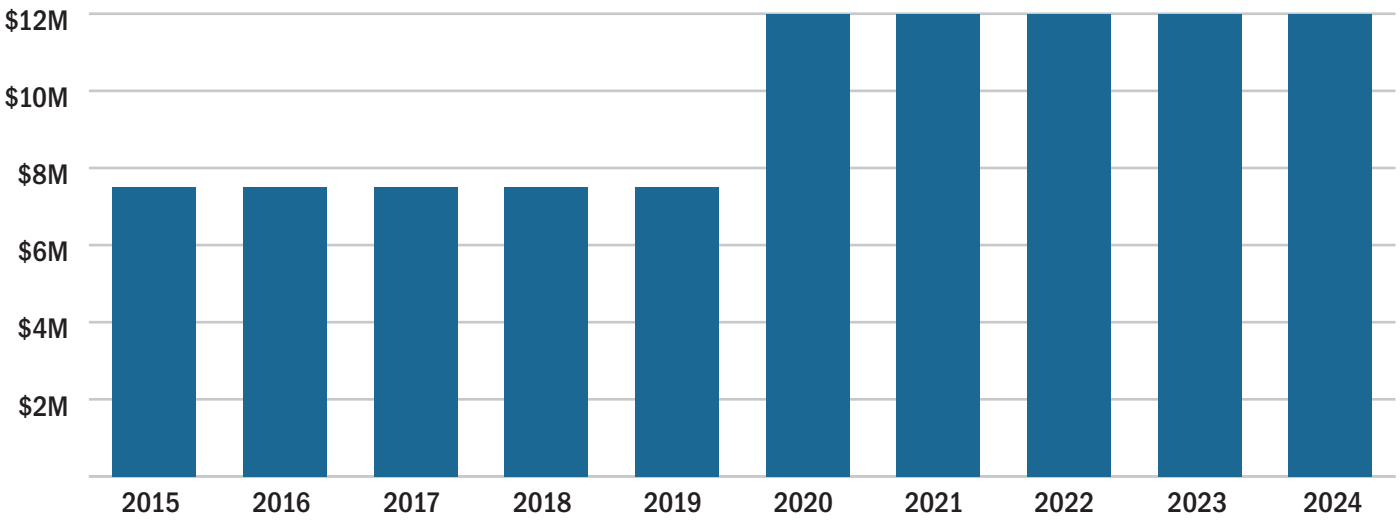


Figure 1: ERP Appropriations by Fiscal Year

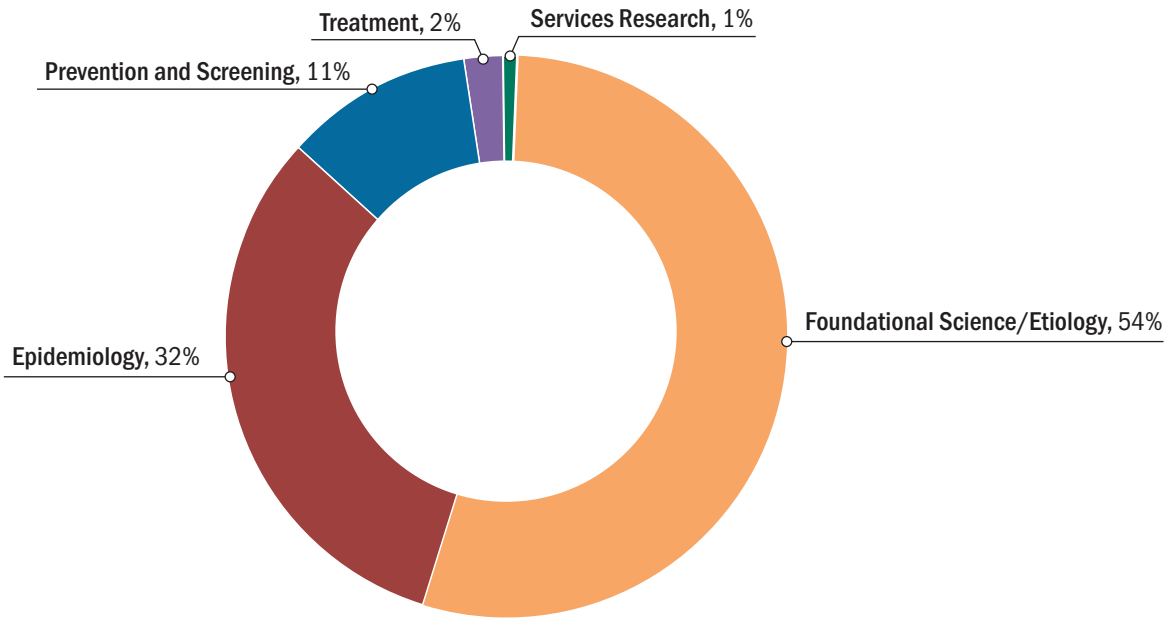


Figure 2: ERP Investment Across Care Continuum FY19-FY23 ($48.8M)

RESEARCH AND FUNDING ENVIRONMENT

RESEARCH FUNDING LANDSCAPE

Given the spectrum of neurological and behavioral symptoms associated with epilepsy and the breadth of what is needed to improve care, multiple partners are involved in funding epilepsy research. These include federal partners (e.g., the NIH, VA, CDC and CDMRP), as well as nonfederal entities (e.g., CURE Epilepsy, the Epilepsy Foundation and the American Epilepsy Society).

The ERP is one of the largest administrators of federal funding for PTE research and has been since its inception, with the NIH investing a similar amount into PTE research annually (Figure 3).

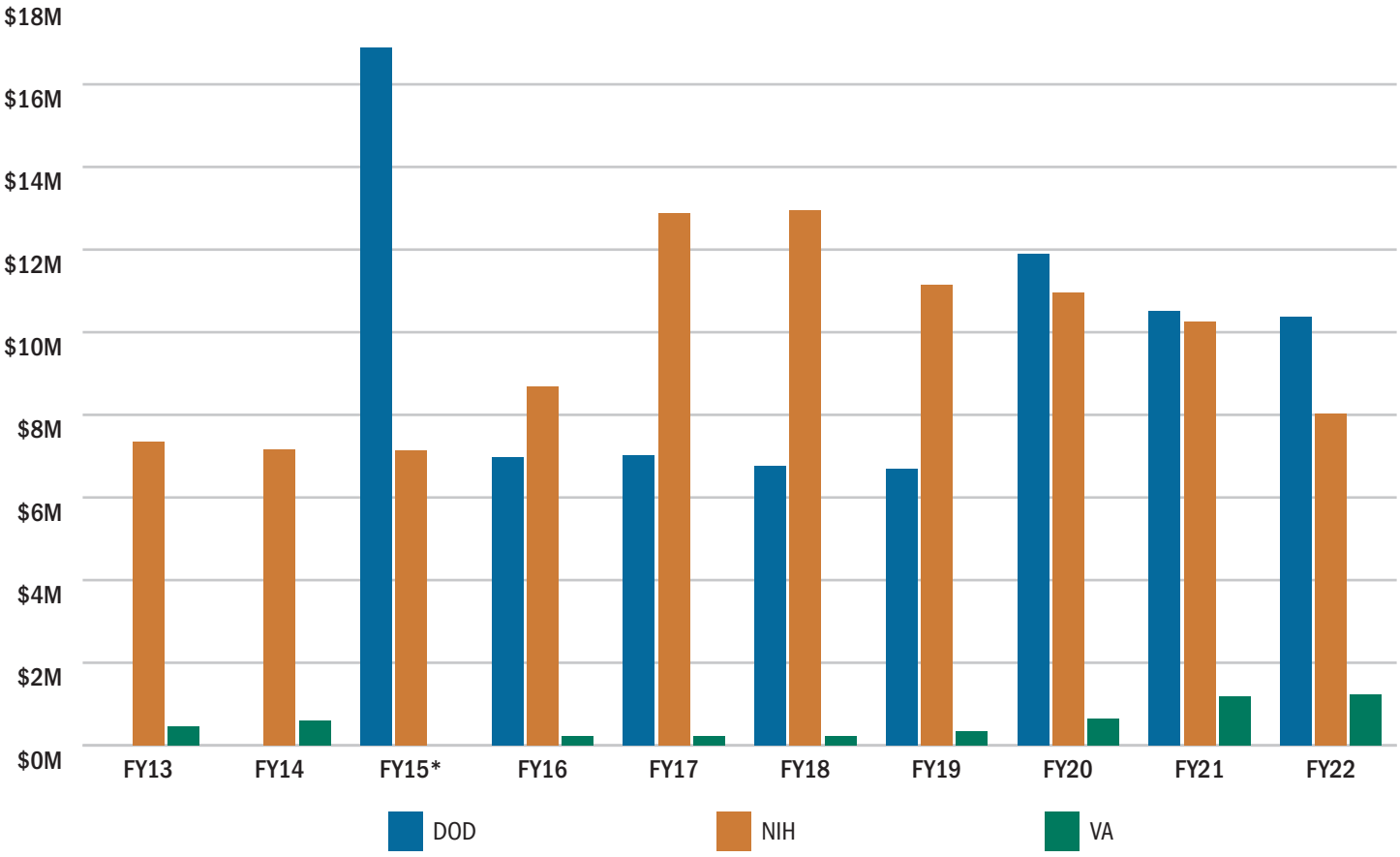


Figure 3: PTE Funding Landscape, 2013-2022.

Data obtained from the Interagency Collaborative to Advance Research in Epilepsy Research Portfolio, NIH Research Portfolio Online Reporting Tools Expenditures and Results, and Research.VA.gov.

*FY15 includes funding for ERP awards and the Team Approach to the Prevention and Treatment of PTE, which was awarded through the Psychological Health and Traumatic Brain Injury Research Program Broad Agency Announcement.

The NIH Interagency Collaborative to Advance Research in Epilepsy coordinates national epilepsy research (http://icarerp.nih.gov). ICARE meetings are used as a forum for sharing information about epilepsy research activities, advances and collaboration. The ERP partners with the NIH to centralize relevant data from human prospective studies into the Federal Interagency Traumatic Brain Injury Registry, a central repository for phenotypic, genomic and imaging data derived from TBI studies. The FITBIR is a web-based application that provides users secure access to use and contribute data. In addition, in 2021 the ERP worked closely with the NIH to develop a series of virtual workshops to optimize preclinical and clinical research to prevent epileptogenesis following TBI.[1] The goals of the workshops included improving communication and collaboration between TBI and epilepsy investigators to focus on the study of PTE, identify gaps in the research that require additional efforts, and identifying the next steps toward preclinical and clinical development of treatment paradigms to prevent PTE.

Nonfederal stakeholders are an important part of the PTE funding landscape. CURE Epilepsy's PTE Initiative, with support from the Army Psychological Health and Traumatic Brain Injury Program, is a multicenter, multi-investigator, and multinational research initiative focused on epilepsy that develops after TBI. The initiative aims to rapidly translate patient-relevant findings at the molecular, cellular, and systems levels into novel therapies to prevent the development of epilepsy from TBI. CURE Epilepsy manages six research teams of over 65 members with diverse expertise in PTE to validate and develop preclinical models, characterize pathophysiology and biological pathways, and identify risk factors. A number of publications, presentations, workshops and meetings have already resulted from this effort; furthermore, this team approach to biomedical research offers opportunities for brainstorming, troubleshooting, networking, and collaboration that isolated research is unable to provide.[2]

Representatives from federal and nonfederal funding entities serve on the ERP Programmatic Panel to provide strategic guidance and individual recommendations regarding funding, portfolio balance, scientific direction, and coordination activities that are relevant to the ERP vision and mission.

STATE OF THE SCIENCE

The landscape of epilepsy research is multifaceted and further complicated by PTE with the additional variables associated with TBI. In 2010, the U.S. Centers for Disease Control and Prevention estimated that 1 in 10 individuals 15 years or older hospitalized with TBI will develop PTE.[3] In 2000-2022, over 450,000 Service Members reported cases of TBI and are at increased risk for developing PTE, a correlation that has been evident since World War I.[4,5] Among Service Members hospitalized for TBI, the incidence rate of PTE is up to 53%, depending on the severity of the TBI. Treatments for epilepsy have improved, but side effects from medication (e.g., headaches and memory loss) remain an issue and the efficaciousness of treatments for PTE are unclear, especially in military populations.[6] Additionally, clinical trials are typically not designed to capture long-term, rare adverse effects from treatments.[6] Anti-seizure medications for PTE must be customized for each individual, depending on seizure control and side effects. Patient management and care in a population of individuals who have had a head injury and subsequently develop epilepsy still require systematic study. These gaps require advanced tools in neuroimaging, genetics, animal models, and connectomics in order to develop better clinical endpoints to drive the drug discovery pipeline. Unfortunately, literature specific to PTE is limited, with fewer than 100 publications submitted to PubMed between 2022-2023, likely due to a limited number of researchers within the field. Moreover, with the need to acquire expertise in both TBI and epilepsy, entering the PTE field is uniquely difficult. These complex challenges justify a need for additional PTE-targeted research to grow research capacity within the field.

STRATEGIC DIRECTION

KEY QUESTIONS

The ERP believes that the following key questions must be addressed if the field is to advance toward better understanding of PTE and improved care and outcomes for those living with the condition.

Who is most likely to be affected by PTE?

- What are the biomarkers of epileptogenesis?
- What factors (biological, clinical, socioeconomic, etc.) most contribute to the development of PTE?
- How can clinicians accurately identify the cause of seizure to improve accuracy and speed of definitive diagnosis of PTE?

While TBI severity has been shown to play a key role in development of PTE as indicated by incidence rates of 2% for mild TBI, 4% for moderate TBI, and 15% for severe TBI,[7] additional risk factors are not well understood. Accuracy of PTE diagnosis and the length of time necessary to obtain a diagnosis are identified as major barriers to care. Epidemiologic studies are needed to address this gap in knowledge to characterize PTE risk and identify alternative avenues to prevent PTE development.

How does PTE pathogenesis impact those living with PTE?

- Beyond seizures, what other comorbidities/conditions contribute to poor outcomes and how can they be addressed/treated?
- Examples of comorbidities for TBI and PTE include psychiatric disorders, cognitive/physical deficits, sleep disorders and fatigue.

The pathogenesis of PTE is not only the development of seizures but also includes the spectrum of comorbid health conditions which affect the health and quality of life for those living with PTE and those who care for them. Better characterization of this range of symptoms and their impact on day-to-day life is essential to inform the development of interventions to improve patient and caregiver outcomes.

What are the pathological mechanisms linking TBI to PTE?

- How does a lifetime load of head trauma contribute to the likelihood of developing PTE?
- Which subpopulation of TBI victims will develop PTE?

A better understanding of the underlying mechanisms linking TBI to PTE is needed to advance scientific knowledge and improve clinical outcomes. After TBI, the onset of PTE is often delayed, and there is a lack of understanding about how the downstream consequences of TBI correlate with epileptogenesis and PTE onset.[8]

How can we better model PTE development in animals?

- What are the necessary pathophysiological characteristics for modeling PTE in animals?
- What are the most appropriate methods for recording seizure in animal models?

To better simulate the human disease, improved animal models are necessary. Currently, rodents are the standard animals used for PTE preclinical research, with a number of options for TBI modeling, including fluid percussion injury, controlled cortical impact injury, weight-drop impact acceleration injury, and blast injury. Large animals with more human-like brains also show promise for modeling PTE.[9]

How can we more effectively manage PTE?

- What antiepileptogenic therapies can prevent PTE development?
- What factors preclude adequate treatment of PTE?
- What are the mechanisms underlying drug resistant epilepsy in PTE?

A recent observational study demonstrated that the prevalence of drug-resistant epilepsy was significantly higher for those with PTE than for those with nontraumatic epilepsies, with 43% of people with PTE reporting that multiple interventions were unable to provide freedom from seizures.[10] Currently, there is a lack of strong evidence for the effectiveness of PTE treatments, in part due to the poor understanding of its pathophysiology. There is some evidence that suggests more than one mechanism is involved in the development of PTE and therefore treatments targeting more than one mechanism may be needed. Additional research is necessary to assess multiple interventions targeting the various underlying mechanisms of PTE and understand the pathophysiology to better target these mechanisms and effectively prevent or manage PTE.

STRATEGIC GOALS (NEAR-TERM)

Program Research Priorities

The members of the ERP Programmatic Panel encompasses stakeholder communities within PTE, including scientists, clinicians, other funders, and persons living with PTE who contribute their invaluable perspective from lived experience. During the vision setting meeting, the panel members convene to discuss strategic programming and to consider congressional intent, the current research and funding landscapes, and research priorities of the lived-experience community for both short- and long-term program planning. From these conversations, the program developed three overarching challenges to address fundamental needs within the field: (1) investigate topics related to epileptogenesis for the identification of mechanisms by which brain injury produces epilepsy, (2) study the prevention of PTE and concomitant comorbidities, and (3) develop innovative research tools or biomarkers to better detect, diagnose, or predict the development of PTE.

To address these challenges and to drive the focus of research, the ERP has established the following key program priorities and near-term goals.

Priority 1 – Markers and Mechanisms: Identify biomarkers or mechanisms of PTE

Goal 1: Identify predictive biomarkers of epileptogenesis (acute and chronic)

Goal 2: Identify markers of PTE that are informed by or correlate with clinical observation

Goal 3: Expand research into the prevention of epilepsy and/or seizures

Goal 4: Improve understanding of drug resistance and PTE

Priority 2 – Epidemiology: Epidemiological characterization of PTE following TBI

Goal 1: Improve understanding and quality of life of individuals with PTE, their families, and/or caregivers

Goal 2: Identification of epilepsy predictors after TBI

Goal 3: Improve outcomes for those at risk of developing PTE as well as those living with PTE, including latency to and prevention of epilepsy, comorbidities, and mortality

Priority 3 – Longitudinal Studies: Studies of the evolution of PTE

Goal 1: Improve understanding, characterization, and awareness of PTE and its comorbidities (e.g., psychiatric disorders, cognitive/physical deficits, sleep disorders and fatigue)

Goal 2: Expand treatment and health care outcomes research, including quality of care

Goal 3: Improve quality of life of individuals with PTE, their families and/or caregivers

Priority 4 – Innovative Research: Tools intended to better inform or improve upon PTE research and care

Goal 1: Develop strategies to improve seizure detection, characterization, visualization and diagnosis (e.g., artificial intelligence, bioinformatics, clinical databases, devices or tissue banks)

Goal 2: Develop new models or better characterization of existing etiologically relevant models for PTE

By funding projects in these focused areas of research, the ERP can build a pipeline of short-term success that lead to advances in the field that include improved prognosis/diagnosis/prediction and treatment methodologies; improved understanding, recognition, and acceptance of PTE and its comorbidities; and improved self-management tools for people living with PTE, their families and care partners.

Strategic Challenges

In addition to the need for research that tackles key scientific topics, the ERP acknowledges that there are additional systemic challenges that exist within the field. The program identified three strategic challenges that the funding opportunities will address. The challenges include: (1) the small scientific community within the field, (2) a competitive rather than collaborative research environment, and (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 our understanding of PTE (Figure 4).

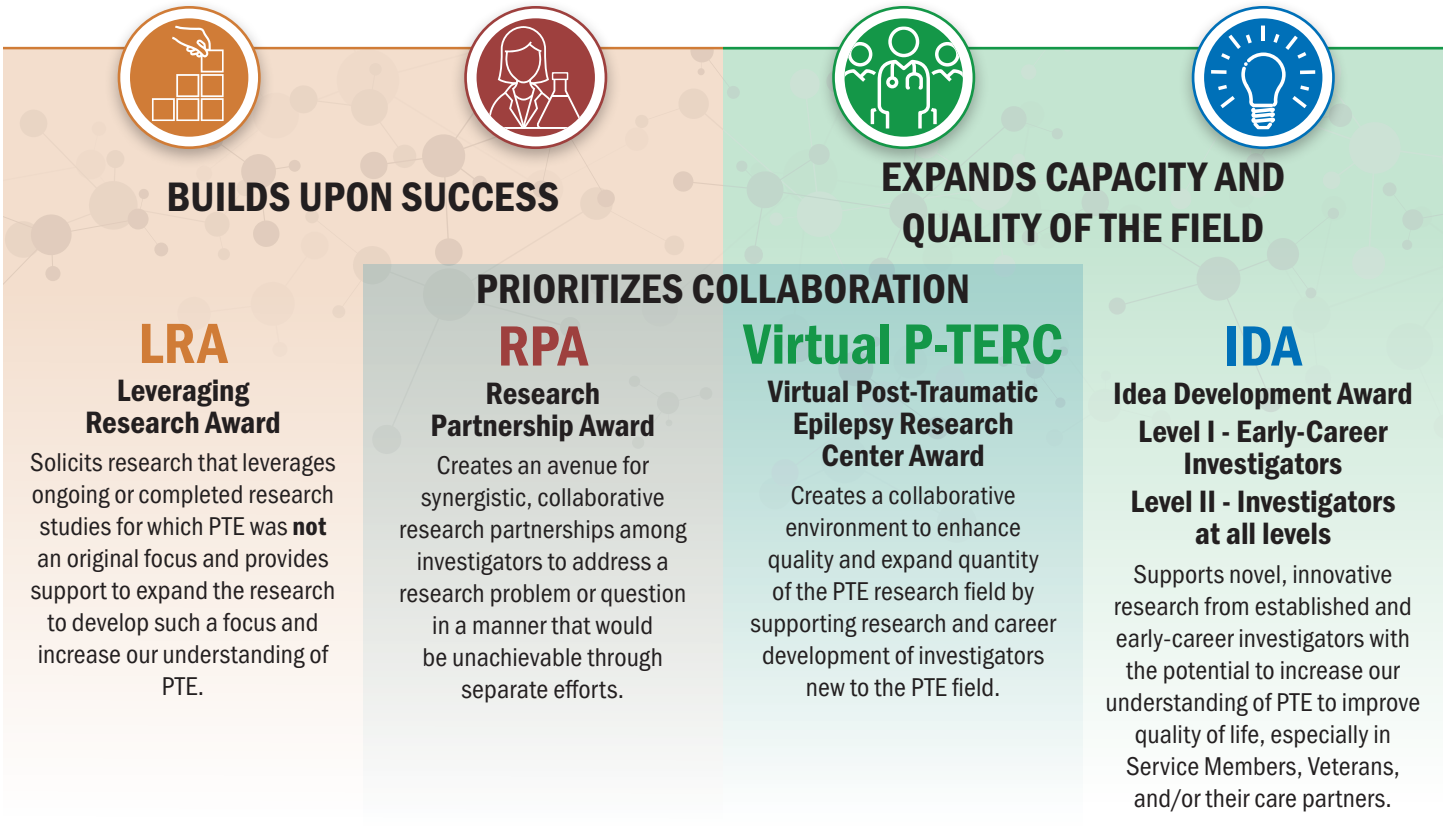


Figure 4: ERP Funding Opportunities

STRATEGIC GOALS (MEDIUM- TO LONG-TERM)

Research that examines the epidemiological and longitudinal nature of PTE, as well as the mechanisms involved, will inform the development of future investment strategies as appropriate. In the medium-term, these efforts will likely focus on supporting the translational aspects of basic research outcomes or the appropriate expansion of studies with human cohorts. Establishing requirements and expectations for future clinical trials will also be necessary before fielding future interventions. With continued progress in research outcomes, the ERP's long-term investment strategy focuses on improving our understanding of PTE to help inform research that may ultimately improve the care and outcomes of those living with PTE by making PTE preventable and treatable.

MEASURING PROGRESS

The ERP measures outcomes by assessing receipt and funding of high-quality submissions that contribute toward meeting the intent and strategic goals of the program. Program success, in the short term, is determined by reviewing and monitoring award technical and research progress, including publications, patents, and other outcomes, as well as the development of technology and knowledge products, on a quarterly reporting basis. Contributions to the scientific community and follow-on research that result from ERP-funded projects contribute to medium- and long-term program success. The ERP team provides the Programmatic Panel with information regarding the status and progress of funded awards for consideration while developing the program's investment strategy during Vision Setting.

SHORT-TERM OUTCOMES, 1-5 YEARS

- Increase investment in research leading to markers and mechanisms of PTE
- Increase investment in research leading to epidemiological characterization of PTE following TBI
- Increase investment in research leading to improved understanding of drug resistance and PTE
- Increase investment in research leading to prevention and treatment of epilepsy
- Expand contributions to the scientific community via publications, patents and other outcomes
- Expand identification of predictive biomarkers and targets for the prevention of epileptogenesis after TBI
- Improve characterization of epileptogenesis after TBI, comorbidities of PTE and TBI
- Improve understanding of the impact of PTE on people with PTE, their families, and caregivers
- Improve strategies for seizure detection, characterization, visualization, or diagnosis
- Develop new models or better characterization of existing etiologically relevant models for PTE

MEDIUM- TO LONG-TERM OUTCOMES, 6+ YEARS

- Increase follow-on research to expand on the knowledge gained from ERP-funded projects
- Increase FDA submissions, approvals, or indications for prevention strategies and treatments of PTE
- Expand clinical implementation of improved prognosis/diagnosis/prediction methodologies for PTE
- Expand clinical implementation of improved treatment options to prevent PTE development
- Expand clinical implementation of improved treatment options for PTE
- Improve understanding, recognition, and acceptance of PTE and its co-morbidities
- Improve support infrastructure for people living with PTE, their families and care partners

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