

Epilepsy Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) 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.

In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,¹ the committee recommended that each CDMRP program "... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Epilepsy Research Program (ERP). The ERP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the ERP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The ERP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

ERP BACKGROUND AND OVERVIEW

The ERP was initiated in 2015 per a request and funding from Congress. This was in response to concerns about the long-term consequences of traumatic brain injuries (TBIs), given the large number of Service members returning from the wars in the Persian Gulf and Afghanistan who had sustained such injuries. The Congressional request detailed the need for longitudinal epidemiological research to improve patient outcomes and understand the magnitude of post-traumatic epilepsy (PTE) within the military. Additionally, the ERP was urged to expand research into the mechanisms by which TBI produces epilepsy and to support research to ultimately prevent PTE and its concomitant comorbidities. Based on recommendations from the ERP Programmatic Panel, the ERP developed the following vision and mission in response to Congressional intent:

VISION: The ERP envisions a time when the causative links between TBI and epilepsy are understood and PTE is both preventable and treatable.

MISSION: The ERP's mission is to advance research to understand the mechanisms underlying the genesis and progression of PTE, especially in Service members and Veterans.

FUNDING HISTORY AND NUMBER OF AWARDS

The ERP has received Congressional appropriations of \$7.5 million (M) each year since fiscal year 2015 (FY15), for a total of \$22.5M in funding between FY15-FY17. During this period, 24 projects were funded by the ERP. Awards (13) for FY17 will be made no later than September 30, 2018. The FY18 ERP appropriation is \$7.5M.



RESEARCH PORTFOLIO AND ACCOMPLISHMENTS

The ERP is currently supporting a large number of animal studies pertaining to the basic mechanisms of PTE, research into the role of psychogenic non-epileptic seizures (PNES) related to PTE, and epidemiological research into the nature of PTE. The initially funded projects have yet to produce outcomes, given that time is needed to complete the ongoing efforts. Two key studies are underway that are based on human data. One is examining the nature of PNES in order to better understand differences between PNES and PTE using state-of-the-art imaging strategies. The other is evaluating the epidemiology of epilepsy and TBI in terms of severity, mechanism, and outcomes in Post-9/11 Veterans. Overall, these projects will improve our understanding of PTE so that better diagnostics and the most vulnerable populations can be identified. **Table 1** provides a snapshot of the ERP Focus Areas and investments between FY15 and FY16.

Focus Area	Fiscal Years Active	Investment through FY16 (Number of Projects)
Epidemiology	FY15-18	\$2.2M (1)
Markers and Mechanisms	FY15-18	\$3.6M (5)
Models of PTE	FY15-17	\$3.0M (2)
Psychogenic Non-Epileptic Seizures	FY16-17	\$5.0M (3)
Longitudinal Studies	FY18	N/A

Table 1: FY15-FY18 ERP Focus Areas and FY15-FY16 Investments

RESEARCH AND FUNDING ENVIRONMENT

STATE OF THE SCIENCE

The funding landscape for epilepsy research is complex. A 2012 report² cited multiple cross-cutting themes in epilepsy. These include disease complexity, quality of life for those living with epilepsy and their caregivers, the need to consider the “whole patient,” timely access to medications, better population-based data, improved information for healthcare professionals, better education for caregivers and those living with epilepsy, and removing the stigma of the disease.

Great strides have been made in the development of pharmacological interventions for epilepsy; however, the bulk of current research funding remains focused on basic research. Currently available medications require trial and error because they do not work for all individuals, and their side effects can vary greatly. A better understanding of post-traumatic epileptogenesis is needed. This will require advanced tools in genetics, animal models, and connectomics in order to develop better clinical endpoints to drive the drug discovery pipeline.

While research into PTE dates back as far as World War II,³ little is actually known about the magnitude of PTE in individuals who have sustained closed-head injuries in the current conflicts. There are also confounders such as psychogenic seizures that need research in order to better understand PTE. Care for individuals who have suffered PTE subsequent to TBI in the current conflicts have benefited from pharmacological interventions; however, the side effects of such medications are problematic.

RESEARCH FUNDING LANDSCAPE

Given the number of neurological disorders 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, Centers for Disease Control and Prevention, and CDMRP), as well as non-federal entities (e.g., Citizens United for Research in Epilepsy, the Epilepsy Foundation, the American Epilepsy Society, and the Patient Centered Outcomes Research Institute).

Epilepsy research activities are nationally coordinated by the NIH through the Interagency Collaborative to Advance Research in Epilepsy (ICARE) (<http://icarerp.nih.gov>). ICARE meetings are used as a forum for sharing information about epilepsy research activities, advances, and collaboration. The ERP also partners with the NIH by centralizing relevant data from human prospective studies into the Federal Interagency Traumatic Brain Injury Registry (FITBIR). The FITBIR is a central repository for phenotypic, genomic, and imaging data from TBI studies that is accessible as a web-based application to securely contribute and access data.

The ERP also coordinates its activities with the international epilepsy research community. The International League Against Epilepsy has recently formed the Anti-epileptogenesis following TBI Task Force, with the goal of moving this topic forward from an international perspective. The task force will identify clear goals and steps that can be used to advance PTE science.

Representatives from federal and non-federal funding entities also serve as members on the ERP’s Programmatic Panel. As part of ERP Programmatic Panel membership, they provide individual recommendations regarding funding, portfolio balance, scientific direction, and coordination activities that are relevant to the ERP’s vision and mission.



The ERP has been one of the largest administrators of federal funding for epilepsy research since its inception. Between 2013 and 2016, funding has steadily increased for epilepsy research, from an estimated \$149M to \$209M. At the forefront of this research funding is the NIH, which funded an estimated \$180M for research across epilepsy in 2016, including 396 projects (**Table 2**). In its first year, the ERP administered \$6.81M in research funding, while the U.S. Army Medical Research and Materiel Command administered another \$10.08M in epilepsy research funding, bringing the Department of Defense's total FY15 investment to nearly \$17M for PTE.

	2013		2014		2015		2016	
Federal	425	\$141.00	460	\$172.01	445	\$183.23	440	\$195.82
Centers for Disease Control and Prevention	10	\$2.21	12	\$2.22	10	\$2.52	9	\$2.32
Department of Defense		\$0.00		\$0.00	6	\$16.89	12	\$6.98
Health Resources and Services Administration	8	\$3.37	8	\$3.47	8	\$3.74	8	\$3.54
National Institutes of Health	392	\$133.09	424	\$163.70	408	\$157.95	396	\$180.58
Department of Veterans Affairs	15	\$2.33	16	\$2.62	13	\$2.12	15	\$2.40
Nonprofit	93	\$8.30	112	\$6.61	131	\$9.33	156	\$13.95
American Epilepsy Society	19	\$0.59	23	\$0.69	26	\$0.70	30	\$0.92
Batten Disease Support and Research Association							2	\$0.07
Child Neurology Foundation							1	\$0.05
Citizens United for Research in Epilepsy	41	\$4.29	48	\$3.73	51	\$3.68	51	\$3.23
Dravet Syndrome Foundation	6	\$0.44	10	\$0.62	7	\$0.41	13	\$0.55
Dup15q Alliance							2	\$0.05
Epilepsy Foundation	15	\$0.73	16	\$0.81	23	\$0.49	27	\$1.30
Epilepsy Study Consortium					1	\$0.00	1	\$1.70
International Foundation for CDKL5 Research							2	\$0.06
LGS Foundation			2	\$0.05	2	\$0.06	2	\$0.06
PCDH19 Alliance	1	\$0.03	1	\$0.01				
Pediatric Epilepsy Research Foundation	2	\$0.32	2	\$0.09	5	\$1.14	7	\$0.47
Phelan-McDermid Syndrome Foundation	1	\$0.05	4	\$0.19	7	\$0.15		\$0.00
Ring14 USA							2	\$0.10
TESS Research Foundation							2	\$0.07
Tuberous Sclerosis Alliance	6	\$0.17	4	\$0.14	5	\$0.20	10	\$0.61
Wishes for Elliott					2	\$0.05	2	\$0.01
Patient Centered Outcomes Research Institute	2	\$1.68	2	\$0.27	2	\$2.45	2	\$4.70
Grand Total	518	\$149.30	572	\$178.62	576	\$192.55	596	\$209.76

Table 2: Federal Versus Nonprofit Funding for Epilepsy Research, 2013-2016.

Dup15q = Chromosome 15q11.2-13.1 Duplication; CDKL5 = Cyclin-Dependent Kinase-Like 5; LGS = Lennox-Gastaut Syndrome; PCDH19 = Protocadherin 19; TESS = Treatments for Epilepsy and Symptoms of Solute Carrier Family 13 Member 5 (SLC13A5).

STRATEGIC DIRECTION

STRATEGIC GOALS (NEAR TERM)

At the ERP inaugural Vision Setting meeting, the ERP Programmatic Panel of scientific experts used the charge from Congress⁴ to develop a course forward for research in PTE. The charge from Congress is discussed in the Program Background and Overview section of this strategic plan. The ERP Programmatic Panel used this charge to assess the state of the science, as well as available technologies, and identified capital research projects that would impact the ERP's vision and mission. Subsequently, the ERP Programmatic Panel developed FY15 ERP Focus Areas, which focused on Epidemiology, Markers and Mechanisms, and PTE Models (Table 1).

The ERP Programmatic Panel annually evaluates the research landscape and the balance of its research priorities, given the latest research outcomes in PTE. The ERP also considers the level of investment in each Focus Area as part of its selection process for future scientific planning.



The FY18 ERP Focus Areas include the following:

Epidemiology: Epidemiological characterization of PTE following TBI, which may include the following:

- Risk factors such as demographics, genetic factors, organic head injury factors, or type of insult
- Differentiation of PTE and PNES
- Outcomes including latency to epilepsy, morbidities and comorbidities, and mortality
- Pre-existing conditions including psychological and psychiatric risk factors
- Treatment

Markers and Mechanisms: Identifying markers or mechanisms (via clinical prospective or preclinical models) that address PTE, which may include the following:

- Early detection
- Diagnosis
- Prognosis
- Morbidity
- Comorbidity
- Mortality
- Risk stratification

Note: Research considering the development of new models or better characterization of existing etiologically relevant models for PTE, including repetitive TBI, could be considered under this Focus Area.

Longitudinal Studies: Studies of the natural evolution of PTE, which may include the following:

- Seizure frequency and severity
- Comorbidities (e.g. depression, functional deficits, sleep disorders, major illness)
- Latency between injury and PTE
- Mortality
- Treatment
- Quality of life of individuals with PTE

STRATEGIC GOALS (MEDIUM TO LONG TERM)

The ultimate goal of the ERP is to improve patient care and outcomes by making PTE preventable and treatable. The challenges of epilepsy research are further compounded by the need for an enhanced understanding of TBI in military populations. Therefore, progress in PTE requires not only the resources and experience of the epilepsy research community, but also the research and experience of researchers in TBI. The ERP brings together researchers from these communities to achieve this goal.

Currently, the ERP research portfolio is targeted towards its near-term and medium-term goals. While the near-term goals are reflected in the FY18 Focus Areas, outcomes from research funded under these Focus Areas will undoubtedly lead to the achievement of medium- and long-term goals. In order to achieve the ERP's long-term goal of improving patient care and outcomes, the ERP has set out since its inception to understand who is most likely to be affected by PTE. This is accomplished by funding both longitudinal and epidemiological research that requires not only an understanding of PTE, but also of closely related medical conditions, such as PNES. Understanding the similarities and differences between PTE and PNES on an individual patient basis will positively affect medical decisions regarding medication and other forms of therapy by promoting better understanding of the "whole patient" and enabling personalized medicine treatment regimens.

Despite research dating as far back as World War II, many of the pathological mechanisms linking TBI to PTE remain a mystery. The program has devoted much of its funding to two Focus Areas that are designed to explore the physiological and molecular mechanisms of post-traumatic epileptogenesis. A considerable investment in new animal models was made over the first three FYs of funding. This was done with the intention of exploring whether advances in TBI research could be applied to PTE. New research in this space is needed; but this is an investment that must be watched over time to understand its long-term value. ERP-funded research in the mechanisms of PTE pathogenesis will reveal new and key pathways by which TBI produces PTE. It is deeply hoped that this will ultimately result in new biomarkers for PTE that could provide new endpoints for new interventions.

Through the combination of bringing together both patient-based and basic research, the ERP will achieve its ultimate goal of enhancing the standard of care for individuals living with PTE.



INVESTMENT STRATEGY

NEAR TERM

In order to achieve the ERP's vision, the investment strategy is to maintain a balance between person-centered and basic research. The ERP Idea Development Award, offered since the ERP's inception, offers two funding levels that are designed to fund either high-risk/high-gain research or a more mature project. Overall, this mechanism is intended to fund basic research that will be the basis of potentially larger studies if the funded studies are successful. The ERP also offers the Longitudinal Risk Factors Award, which is intended to facilitate high-impact, systematic, population-based research investigating the natural evolution of PTE from TBI. This award is intended to capture a cohort of individuals with PTE, follow them, and potentially identify new tools to understand the differences between the individuals participating in the cohort.

MEDIUM TO LONG TERM

Research examining the epidemiological and longitudinal nature of PTE, as well as the mechanisms involved, will inform the development of future investment strategies as appropriate. A number of options exist, including the formation of consortia or multi-partnered, research-focused award mechanisms. 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. With continued progress in research outcomes, the ERP's long-term investment strategy will ideally include research to improve the care of individuals living with PTE or to support early-phase clinical research for novel interventions.

MEASURING PROGRESS

NEAR TERM

The ERP will monitor the response and number of funded applications for each of its Focus Areas. It will monitor the progress of awardees according to their statements of work; track a broad range of research outcomes (e.g., publications, presentations, and patents); and share this information with the ERP Programmatic Panel. These outcomes will be used to adjust the ERP's portfolio direction on a yearly basis.

MEDIUM TO LONG TERM

The ERP will closely monitor the PTE research landscape, continue to capture key research accomplishments funded by the ERP (e.g., patents and publications), and use this data to measure progress toward addressing its strategic goals as well as its overall vision and mission. The ERP will also continue working to remain cognizant of other funded PTE and TBI research outcomes and initiatives that may drive its overall funding strategy.

REFERENCES

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4. Department of Defense Appropriations Bill. 2015. pp. 257-158.