



REQUEST FOR APPLICATIONS
Post-Traumatic Epilepsy

Program Goal: To support collaborative, milestone-driven efforts that advance the understanding of epilepsy as a result of traumatic brain injury.

CURE’s mission is to cure epilepsy, transforming and saving millions of lives. We identify and fund cutting-edge research, challenging scientists worldwide to collaborate and innovate in pursuit of this goal. Our commitment is unrelenting.

For this initiative, CURE seeks to fund investigators focused on advancing the understanding of epilepsy as a result of traumatic brain injury (TBI) in order to build a body of knowledge that primes the community for more effective target identification and prevention strategies. The mechanisms underlying the development of epilepsy following injury are complex and not fully understood. Additionally, post-traumatic epilepsy (PTE) frequently does not respond to available treatments, imposing significant ill effects on quality of life and rehabilitation. Despite the risk to both civilian and non-civilian populations, prior attempts to intervene and prevent epilepsy after injury have yet to succeed. While many efforts have been made to study TBI, there is a paucity of research directed towards the chronic, life-long, often debilitating epilepsy that often follows. The goal of the initiative is to establish a multi-center, multi-investigator research team focused on post-traumatic epilepsy that will rapidly translate patient-relevant findings at the molecular, cellular and systems level into novel therapies to prevent the development of epilepsy from traumatic brain injury. Both basic scientists and clinicians are encouraged to apply.

Release date:	June 2016
Webinar/conference call*:	June 9, 2016 at 12pm ET June 22, 2016 at 4pm ET
Letter of Intent deadline:	Wednesday, July 20, 2016 at 8:00pm, ET
Full applications invited:	Friday, August 12, 2016
Full application deadline:	Thursday, November 3, 2016 at 8:00pm, ET
Anticipated funding:	January 2017

*CURE will hold two 1-hour teleconferences to clarify the goals of this RFA and answer questions. Interested investigators are requested to RSVP by email to Liz@CUREepilepsy.org. Please specify which date you plan to participate.

BACKGROUND

This new, targeted program was created in collaboration with the Department of Defense, Psychological Health and Traumatic Brain Injury Research Program, under award number W81XWH-15-2-0069. The program will support a team approach to advancing a greater understanding of the factors that may lead to Post-Traumatic Epilepsy (PTE).

PURPOSE

CURE issues this directed Request for Applications (RFA) to accelerate the understanding of epilepsy as a result of traumatic brain injury in order to build a body of knowledge that primes the community for

more effective target identification and prevention strategies. This program will fund milestone-driven proposals for up to 3 years.

There are two primary areas of research addressed in this RFA:

- Clinical phenotyping of patients who have developed epilepsy as a result of a brain injury.
- Thorough characterization of animal models used to study epilepsy as a result of brain injury, including repetitive TBI, and their potential utility for early identification of novel therapies for the prevention and treatment of TBI-induced epilepsy and attendant comorbidities.

Clinical phenotyping applications:

There is a significant lack of knowledge surrounding what types of brain injury lead to epilepsy. Deep phenotyping of patients with epilepsy as a result of brain injury is sought with this RFA. For such an application, please clearly describe the outcome measures that will be assessed (imaging, genetics, EEG, etc) to define the patient population. Retrospective or prospective cohorts can be included. While an established collaboration with an ongoing large human TBI study would be seen as a benefit, this is not a requirement for application.

Animal model applications:

It has been noted that there is similarly a lack of thorough knowledge surrounding animal models used to study epilepsy as a result of TBI. Applications are sought to work as members of a team in which multiple models will be evaluated in a prospective and parallel approach. In the application, please describe the model proposed, what type of injury it seeks to represent (severity, human relevance, single vs repetitive hit, etc.), and the outcomes that would be measured to conduct a thorough assessment of the model as it relates to human TBI and therapy discovery. Access to chronic video/EEG monitoring is required. A plan to assess and document the time between injury and first seizure must be described. Models studying the impact of a single hit or that which might occur as a result of repetitive injury are encouraged. If the application is centered on repeated trauma, describe how these injuries will be assessed, characterized, and documented. **Note: Any model proposed must exhibit spontaneous seizures, either behavioral or subclinical. Models that evaluate epilepsy solely by modification of threshold to induced seizures are not considered applicable and will not be considered.**

Outcome measures for both clinical and animal model applications should be designed to be used for both initial descriptive studies and biomarker discovery efforts to aid in the potential identification of which patients/animals are at highest risk for developing epilepsy following injury. Additionally, it is anticipated that any proposed investigation will provide important new information that can be used to guide therapy development for the person at risk for developing PTE as a result of TBI.

FUNDS AVAILABLE

CURE will commit up to \$8.4 million over the next 3-4 years to fund proposals submitted for this initiative. CURE intends to fund multiple proposals as a part of this initiative. The number of awards will depend on the quality and the relevance of the proposed work to the RFA. Applicants may request project periods of up to 3 years for direct costs appropriate and justifiable for the work proposed. Each item and its cost must be clearly described in the budget. A maximum of \$1,000 (\$1,500 for international applicants) per year can be budgeted for travel to scientific meetings. CURE encourages all awardees to attend the annual American Epilepsy Society meeting. Multi-year support is not automatic for any award and is contingent upon meeting milestones and progress reports being favorably reviewed. **Per CURE's policy, indirect costs will not be supported.**

ELIGIBILITY CRITERIA

Applicants must be at or above the Assistant Professor level (or equivalent) and must be willing to work in a milestone-driven 'team' environment. **Applications are welcomed and encouraged from collaborative teams comprised of multiple investigators.** International applicants are welcome. Post-doctoral fellows are not eligible to apply as principal investigators. Researchers who serve on CURE's advisory councils are ineligible to apply for, or sponsor, a grant for the duration of their term. All materials must be submitted in English.

REVIEW PROCESS

There are two stages to the CURE review process: ***Letter of Intent*** and ***Full Proposal***.

Letter of Intent

All applicants must submit a Letter of Intent (LOI). The LOI should provide a brief description of the research plan that succinctly outlines the research plan and proposed milestones that will serve to measure progress. LOIs should specifically address the purpose of this RFA as outlined above. All LOIs will be subjected to a peer review process. Only a subset of applicants will be invited to submit full proposals.

LOIs will only be accepted through the proposalCENTRAL online application system (<https://proposalcentral.altum.com>). New users must register and fill out a professional profile before continuing on to the application process. Hard copies of LOIs will not be accepted. Please fill in all required fields in the online application form (instructions below).

Instructions for each section of the online application:

- 1) *Title Page*: Enter proposal title (maximum 150 characters, including spaces).
- 2) *Download Instructions*: Download additional copies of these guidelines, if needed.
- 3) *Enable Other Users to Access this Proposal*: Use this optional section to grant access to a collaborator or co-investigator.
- 4) *Applicant/PI*: This section should auto-populate from the applicant's professional profile. Double-check that the information is complete and correct. If it is not, click Edit Professional Profile to update the information.
- 5) *Institution & Contacts*: Information should auto-populate from the applicant's profile.
- 6) *Collaborators*: Please enter information for any co-investigators or collaborators, if applicable.
- 7) *Keywords*: Add at least 3 keywords that best describe the specific focus of your research proposal.
- 8) *Current and Pending Support*: List all current and pending support for you and any co-investigators.
- 9) *Attachments*: Once the LOI is finalized per the instructions below, attach by uploading the PDF into this section of proposalCENTRAL. Upload a current biosketch for each PI.

10) *Validate*: The system will check for required components that have not been completed. Applicants will not be able to submit until all required fields are completely filled out.

11) *Submit*: Make sure to hit *Submit* after your application has been validated!

Letter of Intent Instructions: In your uploaded letter of intent, please provide the following in a maximum of 2 pages:

- Clearly and succinctly describe the specific aims.
 - For human phenotyping/biomarker studies, describe the clinical network established or collaboration with an ongoing effort. Additionally, describe the outcomes anticipated to be collected on subjects.
 - For animal model studies, briefly describe the proposed model, its relevance to human post-traumatic epilepsy, and the outcomes/techniques that would be used to evaluate the severity, location, and other relevant features of the injury and subsequent epilepsy.
- Include any relevant preliminary data (optional).
- Provide a brief description of how the proposed research plan aligns with CURE's mission, as well as the goals of this specific initiative.
- References cited (up to 1 additional page), if necessary.

LOIs will be evaluated for the following criteria:

- Does the LOI meet the intent of the RFA?
- What are the merits of the scientific rationale for the study/model proposed as they pertain to the RFA?
- Are the qualifications of the PI and key personnel appropriate?
- Is the funding level appropriate for the research proposed?

Full Proposal

Applicants will be notified as to whether they have been invited to submit a full proposal by July 27, 2016. CURE will work with invited applicants to discuss key issues and feedback received during the LOI review process to help develop a clear and focused proposal. Full proposals will be accepted through the proposalCENTRAL online application system.

Invited full proposals **must** be submitted through proposalCENTRAL (<https://proposalcentral.altum.com>) by **Thursday, November 3, 2016 at 8:00pm, ET**. Please fill in all required fields in the online application form.

To access your application, log in to proposalCENTRAL and go to your Manage Proposals tab. If you click on "edit" next to your approved LOI, you will be taken into the full proposal application. Below are instructions for each section on the online application:

- 1) *Title Page*: Enter proposal title (maximum 150 characters, including spaces).
- 2) *Download Templates & Instructions*: Access a copy of these guidelines and download a biosketch template if you do not already have one completed.

- 3) *Enable Other Users to Access this Proposal:* Use this optional section to grant access to co-investigators or collaborators so they may review or enter information into the application.
- 4) *Applicant/PI:* This section should auto-populate from your professional profile. Double-check that the information is complete and correct. If it is not, click Edit Professional Profile to update the information. Indicate whether you are an early career or established investigator.
- 5) *Institution & Contacts:* Information should auto-populate from your profile.
- 6) *Collaborators/Co-investigators:* Enter contact information for co-PIs and/or collaborators. Typically, co-investigators are co-funded by the grant, collaborators are not.
- 7) *Letters of Reference:* Submit up to 3 letters of recommendation from mentors, department heads, or collaborators. **Letters of support from mentors or department heads are only required for early career investigators.** Letters of support from collaborators can be requested here or uploaded in the attachments section.
- 8) *Abstract:* Please provide a scientific abstract for your project.
- 9) *Budget Period Detail:* Provide a detailed budget appropriate to the work proposed. Additionally, while stipend support can be provided for graduate students, tuition is not an allowable expense. All expenses must be converted to U.S. dollars (USD).

*Note that there is a travel cap of \$1,500 USD for international applicants and \$1,000 USD for U.S. applicants per year, which can be budgeted for a maximum of 2 investigators (the PI and Co-PI). If awarded funds, CURE encourages all grantees to attend the annual AES meeting. Additional funds outside of the award will not be given to attend this event.
- 10) *Budget Summary and Justification:* Review the budget summary. Provide budget justification that clearly states how the funds will be used and why these expenditures are critical to the success of the proposed research.
- 11) *Current and Pending Support:* Enter current and pending support for all PIs on the proposal. Please indicate if there is any overlap with the proposed work.
- 12) *Organization Assurances:* Answer the questions regarding use of human subjects, animals, recombinant DNA, and the possession of a Schedule 1 license.
- 13) *Proposal Narrative and Other Attachments:* Upload the following documents:
 - a. Proposal Narrative according to the instructions below.
 - b. PI Biosketch: Upload a biosketch for the submitting PI on the application (use NIH format).
 - c. Institutional Assurances: Provide a letter (or letters, if applicable), signed by the Department Chair or appropriate organization official, confirming the laboratory space, equipment, and other resources available for the project. Please submit institutional assurances for each PI.

- d. Facilities, Existing Equipment, and Other Resources: Describe the facilities and equipment available for performance of the proposed project and any additional facilities or equipment proposed for acquisition at no cost to the award.
- e. Co-Investigator Biosketch: Upload biosketch for each co-investigator, if applicable.
- f. Collaborator Letters of Support: Provide a signed letter from each collaborating individual or organization that will demonstrate that the PI has the support or resources necessary for the proposed work.
- g. Signed signature pages: Upload signed signature pages which are generated in Step 15 of the application.

14) *Validate*: The system will check for required components that have not been completed. You will not be able to submit until all required components are completed.

15) *Signature Pages*: Click “print signature page” to obtain a PDF of the document that needs to be signed by you (the submitting PI) and an institutional representative. After signatures have been collected, scan and upload to Section 13.

16) *Submit*: Please **make sure to hit submit** once your application has been validated by the system.

Proposal Narrative Instructions (10-page limit*):

Main body of proposal (not to exceed 10 pages) should contain the following sections:

- **Specific Aims**: Clearly state the aims of the proposed research.
- **Background**: Present the ideas and reasoning behind the proposed research; include relevant literature citations. Describe previous experience most pertinent to this application.
- **Preliminary Data**: Provide preliminary data (if available) to support the rationale and feasibility of the study. Preliminary data can come from PI’s published work, pilot data, or from peer-reviewed literature.
- **Research Strategy**: Detail the experiments that will be done to address each specific aim, details of research design and methods, the expected outcomes, potential pitfalls, and how you will interpret the results. If this is a collaborative proposal, briefly describe how this collaboration adds particular value to the application.
- **Project Milestones**: Concisely provide expected project milestones relevant to each of the project’s technical objectives and specific aims.
- **Statement of Relevance** to this specific initiative and to CURE’s mission: Include one paragraph detailing how the proposed research addresses CURE’s goal of transforming epilepsy research and ultimately transforming patient care, and specifically how the proposed research will lead to a greater understanding of epilepsy as a consequence of traumatic brain injury.
- **Data Sharing Plan**: Describe the plan for the provision of access to the data or resource generated from the proposed work to the public, and how the data or resource will be made available after the award expires. *Note: All genetic data generated with CURE funding is required to be deposited in CURE’s [Epilepsy Genetics Initiative \(EGI\)](#) database.*

* The 10-page limit of the Proposal Narrative is inclusive of any figures, tables, or graphs.

References: Please include all literature cited within the proposal (no page limit).

Formatting Requirements:

Font: Use an *Arial, Helvetica, Palatino Linotype* or *Georgia* typeface, a black font color, and a font size of 11 points or larger.

Figures, Tables, and Graphs: You may use a smaller type size but it must be in a black font color, readily legible, and follow the font typeface requirement. Color can be used in figures but all text must be in black font.

Spacing: Single-spaced between lines of text, no more than five lines of type within a vertical inch.

Margins: Minimum of 0.5-inch top, bottom, right and 1-inch left.

Full Applications will be evaluated for the following criteria:

Research Strategy and Feasibility

- How well the scientific rationale supports the project and its feasibility as demonstrated by a critical review and analysis of the literature, relevant preliminary data, and/or logical reasoning.
- How well the objectives, aims, experimental design, methods, and analyses, including statistical analyses, are developed.
- How well the PI acknowledges potential problems and addresses alternative approaches.
- How well the plan for addressing unanticipated delays is likely to lead to success in completing the proposed study within the performance period.
- How relevant the proposed work is to the intent of the Request for Applications.
- How reasonable/feasible are proposed project milestones.

Personnel

- How the PI shows potential for addressing the RFA's intent based on his/her background and experience.
- How the research team's background and related expertise are appropriate with respect to their ability to perform the proposed work.
- How the research team demonstrates expertise in both TBI and epilepsy.
- To what degree the levels of effort are appropriate for successful conduct of the proposed work.

Data Sharing Plan

- The quality of the proposed plan for data sharing to include (but not limited to):
 - The description of the type of data or resource to be made available.
 - Ease of access for other researchers to the data or resource.
 - The appropriateness of plans to ensure the data or resource is accessible after the period of performance expires.
 - The appropriateness of the milestones with respect to making the data or resource available.
 - The appropriateness of the FITBIR data sharing plan (if applicable).

Budget

- Whether the budget is appropriate for the proposed research and within the limitations of this Request for Applications.

Selection Process

To make funding recommendations and select the application(s) that, individually or collectively, will best achieve the program objectives, the following equally considered criteria are used:

- Ratings and evaluations of the peer reviewers
- Adherence to the intent of the award mechanism

EXPECTATIONS

Milestones

In consultation with CURE staff and an External Advisory Board, applicants will develop time-dependent milestones to ensure completion of study objectives. Investigators will be expected to interact with CURE staff and advisors regularly to discuss the project and progress toward milestones. Budgets should be structured and allocated in accordance with these milestones. Continuation of funding will be contingent upon meeting milestones.

Collaboration

One of the goals for this initiative is for all funded laboratories to function as part of a collaborative team focused on a common goal: building a comprehensive body of knowledge regarding epilepsy as a result of brain injury. As such, awardees will be expected to share data and progress with each other through regularly scheduled conference calls. Additionally, awardees will be expected to attend scheduled assessment meetings approximately twice per year. These meetings will function to report on progress, exchange information with other awardees, explore potential collaborations, and identify opportunities that would enhance the productivity of all grantees or the field-at-large.

REGULATORY AND REPORTING REQUIREMENTS

If selected for funding, PIs should be aware of the following requirements:

Research Involving Human Anatomical Substances, Human Subjects, or Human Cadavers:

All Department of Defense (DoD)-funded research involving new and ongoing research with human anatomical substances, human subjects, or human cadavers must be reviewed and approved by the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), in addition to the local Institutional Review Board (IRB) of record. Local IRB approval at the time of submission is **not** required. The HRPO is mandated to comply with specific laws and requirements governing all research involving human anatomical substances, human subjects, or human cadavers that is supported by the DoD. These laws and requirements will necessitate information in addition to that supplied to the IRB. **Allow a minimum of 2 to 3 months for HRPO regulatory review and approval processes.** Refer to the Human Subject Resource Document available on the eBRAP “Funding Opportunities & Forms” web page (<https://ebrap.org/eBRAP/public/Program.htm>) for additional information.

Research Involving Animals:

All DoD-funded research involving new and ongoing research with animals must be reviewed and approved by the USAMRMC ORP Animal Care and Use Review Office (ACURO), in addition to the local Institutional Animal Care and Use Committee (IACUC) of record. IACUC approval at the time of submission is not required. Specific documents relating to the use of animals in the proposed research will be requested if the application is selected for funding. The ACURO must review and approve all animal use prior to the start of working with animals. PIs must submit the institutional animal use protocol, IACUC approval of that protocol, and a version of the animal use appendix titled “Research Involving Animals.” **Allow at least 3 to 4 months for regulatory review and approval processes for animal studies.**

Use of TBI Common Data Elements:

Data elements must be reported using the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs) or entered into the Federal Interagency TBI Research (FITBIR) data dictionary as new, unique data elements. For the most current version of the NINDS TBI CDEs, go to <http://www.commondataelements.ninds.nih.gov>. Assistance will be available to help researchers map their study variables to specific CDEs and ensure the formats of the CDEs collected are compatible with the FITBIR Informatics System. If the proposed research data cannot be entered in CDE format, the investigators must supply a proposal for an alternative data submission or data sharing vehicle and justification for its use. Use of the TBI CDEs is required wherever possible in an effort to create standardized definitions and guidelines about the kinds of data to collect and the data collection methods that should be used in clinical studies of TBI.

Note: In addition to the TBI CDEs, applicants are also strongly encouraged to consider developing a plan to incorporate the NINDS CDEs for epilepsy found at the link above.

FITBIR Reporting Requirement for Projects Producing TBI Datasets:

The DoD requires that awardees make data generated via this award mechanism available to the TBI research community by depositing de-identified research data into the FITBIR Informatics System on a quarterly basis. The FITBIR Informatics System is a free resource to the TBI community designed to accelerate comparative effectiveness research on brain injury diagnosis and treatment. Data reporting to FITBIR is an opportunity for investigators to facilitate their own research and to collaborate with others doing similar research. While there is no direct charge to users of the FITBIR Informatics System, a project estimation tool (<https://fitbir.nih.gov/jsp/contribute/fitbir-costs.jsp>) is available to help estimate costs and manpower needs that may be associated with data submission. To contribute to FITBIR, researchers should contact the FITBIR Operations Center ahead of time to arrange for data entry support and to ensure all data have been made compatible with the system. FITBIR guidance and policies, as well as the considerable advantages of FITBIR use to the researcher, are detailed at FITBIR: Federal Interagency Traumatic Brain Injury Research Informatics System (<http://fitbir.nih.gov/>). FITBIR allows for de-identification and storage of data (medical imaging, clinical assessment, environmental and behavioral history, etc.) of various types (text, numeric, image, time series, etc.). Use of FITBIR's Global Unique Identifier (GUID) system facilitates repeated and multi-user access to data without the need to personally identify data sources. FITBIR encourages collaboration between laboratories, as well as interconnectivity with other informatics platforms. Such community-wide sharing requires common data definitions and standards.

INQUIRIES

Questions regarding this RFA are welcome. All inquiries should be directed to Julie Milder, Associate Research Director, at Julie@CUREepilepsy.org or (312) 255-1801.