Scientific Summary: New onset seizures are common after acute brain injury and trauma, anoxia, and stroke-related seizures are major risk factors for epilepsy. Unfortunately, seizures after these events might become prolonged and hard to treat, i.e. status epilepticus, therefore deciding what medications to use and assessing if medications are actually working is challenging. Near 50% of patients with a cardiac arrest develop seizures or seizure-like activity due to poor brain oxygenation, but, differently from other injuries, continuous brain monitoring with EEG is started upon arrival to the intensive care unit (ICU) and before seizures start in cardiac arrest. This creates a unique opportunity to study how acute brain injury triggers seizure physiology and how seizures respond to treatment before they become refractory.
Project Goals: I am proposing to identify specific types of epileptiform brain wave changes that predict the likelihood of treatment response to antiseizure drugs in a cohort of >1,500 patients with acute brain injury after cardiac arrest (data already available). We will use innovative signal processing and machine learning techniques to analyze continuous scalp EEG data (+10TB) from patients admitted to the ICU. Specifically, we will utilize dynamic time warping and convolutional neural networks to characterize and model the morphological changes in spike activity before and after treatment is initiated. We will utilize a nonlinear mixed effects model for seizure control prediction. In addition to EEG, brain imaging, and pharmacological data, we have long-term patient-centered outcomes recorded for all subjects (functional neurological recovery). Our main overall hypothesis is that specific types of spike morphology modulation by specific anti-seizure drugs predict seizure treatment response.
Aims: 1) Determine the EEG characteristics predictive of status epilepticus development after acute brain injury and 2) Determine the specific EEG signal changes predictive of seizure control during treatment with antiseizure drugs.
Deliverables: 1) Definition of EEG biomarkers of seizure risk after acute brain injury, 2) Define specific EEG changes caused by specific antiseizure, and 3) design a context-sensitive framework to personalize feedback for antiseizure drug choice and titration.
Impact: A treatment response biomarker for status epilepticus would have a transformative effect in seizure management and patient-centered outcomes. I am determined to foster the growth of non-invasive point-of-care brain monitoring technologies that will enhance our

understanding about mechanisms of epilepsy development after acute brain injury and guide personalized care to these patients. Insights from this project will support my long-term goal of accelerating discovery of therapeutic targets for status epilepticus treatment.

Future Directions:

The mission of the critical care epilepsy research program I am developing is to improve quality and efficiency of seizure care delivery for patients, families, and providers through biomedical technology innovation. By leveraging the interpretability of traditional EEG processing techniques and the performance of Artificial Intelligence methods for personalized predictions, I am poised to impact seizure care for more than 100,000 Americans who every year develop status epilepticus or epilepsy after acute brain injury. The preliminary data generated by this award will inform a future NIH R01 grant application for an adaptive clinical trial validating whether personalized seizure management improves recovery after hypoxicischemic brain injury.

My mentor jointly with my scientific advisory board have been critical partners in designing and launching the critical care epilepsy research program I envision for UCSF. My mentor has expertise in human neurophysiology and prolonged invasive EEG recordings whose research is primarily focused on the neural mechanisms of speech. The cross-disciplinary mentorship and training opportunities afforded to me by the CURE Taking Flight Award will be instrumental to my short- and long-term career goals and to starting an independent laboratory focused on applying non-invasive neurophysiology to support data-driven clinician decision-making and personalize therapeutic interventions for patients with seizures secondary to acute brain injury.

Award Relevance:

Every year in the U.S. 500,000 adults and 16,000 children have a cardiac arrest. Most patients surviving to intensive care unit admission will have significant brain injury and half will develop seizures or other types of epileptiform activity. Hypoxic-ischemic encephalopathy is the most common cause of infantile spasms in children and it is associated with significant long-term neurological disability in adults. Current seizure and status epilepticus management

after acute brain injury is reactive and generic, and it has failed to incorporate objective markers of the brain's response to treatment. To improve seizure risk prediction accuracy and facilitate translation of seizure therapeutics, future clinical trials for seizures secondary to acute brain injury must rely on early biomarkers of treatment response that can differentiate responders from non-responders and minimize side-effects.

This tool-driven proposal is novel and applicable to a large number of patients as it aims to 1) determine seizure risk after hypoxic-ischemic brain injury and 2) identify signs of early treatment response to anti-seizure drugs that precede neurological exam improvement. This approach to seizure care has the potential to increase the likelihood of rapid and effective seizure treatment after acute brain injury and prevent permanent brain injury from poorly controlled seizures and status epilepticus – this approach directly supports CURE's mission to find a cure for epilepsy by promoting and funding patient-focused research.

The support from the CURE Taking Flight Award will allow me to foster a critical care epilepsy research program that will have a broad positive impact in status epilepticus, posttraumatic epilepsy, and infantile spasms care.