SPECIFIC AIMS – PROJECT 3 – BIOMARKERS OF HUMAN EPILEPTOGENESIS AFTER TRAUMATIC BRAIN INJURY

The mechanisms underlying human acquired epileptogenesis remain poorly understood and a novel multimodal approach to study the process from inception to manifest clinical epilepsy is needed. We have selected Post-Traumatic Epilepsy (PTE) as a model to pursue this understanding because the timing of the potential epileptogenic insult is known and the period of epileptogenesis can be determined. PTE is an important public health problem, accounting for 5% of all epilepsy[2, 3, 37, 44]. In this project, we outline our human studies which are highly integrated with *Projects 1 and 2*. Epileptogenesis is common after moderate-to-severe traumatic brain injury (TBI)[2] and begins early, offering a window of opportunity to test the efficacy of potential antiepileptogenic (AEG) drugs[36, 54, 57]. In order to design economically feasible antiepileptogenic clinical trials, however, it will be necessary to identify reliable biomarkers that: 1) predict later PTE, to enrich the subject population; 2) stage the epileptogenic process, to determine the timing of intervention; and 3) diagnose epilepsy, to provide biomarkers. To date, we have identified promising electrical, imaging, and blood biomarkers of epileptogenesis after TBI in our animal models, including pathological high frequency oscillations (pHFO) and recently a new electrophysiological disturbance termed "repetitive HFOs and spikes" (rFHOSs)[7-13]. In addition, our human studies of continuous EEG (cEEG) monitoring[52-58, 62] and MRI[37, 38, 39, 43,66] after TBI have revealed early post-traumatic seizures on surface and depth EEG which have metabolic and long-term negative anatomical[66] and cognitive effects[64]. In this project, we propose a prospective bioinformatics approach in the acute setting after moderate-to-severe TBI to identify and validate reliable electroencephalographic (EEG), blood and MRI biomarkers of epileptogenesis. We have derived our observational time points based on careful consideration of the animal studies in *Projects 1 and 2,* while building in flexibility based on discoveries to be made in those projects during the course of the proposed study. We hypothesize that the conduct of a future clinical trial will require a personalized medicine approach, including patient selection, timing of the antiepileptogenic drug, and outcome determination, based on acute EEG, structural, and metabolic biomarkers.

The EpiBioS4Rx Scientific Premise is Epileptogenesis after TBI can be prevented with specific treatments; the identification of relevant biomarkers and performance or rigorous preclinical trials will permit the future design and performance of economically feasible full-scale clinical trials of antiepileptogenic therapies.

Specific Aim 1: To perform prospective multicenter combined scalp and depth cEEG monitoring in moderate-severe TBI patients to determine if the occurrence of specific EEG changes, such as seizures, pHFOs and rHFOSs, predict later PTE.

Hypothesis 1: Early post-traumatic epileptic EEG activity (seizures, pHFOs, rHFOSs) indicates the presence of an epileptogenic process in patients after moderate-severe TBI.

Specific Aim 2: To determine if acute multimodal MRI can reveal structural and functional biomarkers (based on connectivity analyses) of local and global pathology within disconnections of hippocampal and thalamo-cortical networks that predict the development of PTE.

Hypothesis 2: Acute structural/functional disconnections abnormalities within hippocampal or thalamo -cortical networks circuits are associated with epileptogenesis after severe TBI.

Specific Aim 3: To determine if candidate treatment-specific serum biomarkers informed by animal models of PTE can be validated in blood from humans after TBI.

Hypothesis 3: Specific epileptogenic pathways amenable to therapeutic interventions will generate biomarkers that can be monitored in the post-traumatic patient.

Specific Aim 4: To establish a highly qualified ICU EEG TBI clinical trials network that would enable planning for a personalized medicine human intervention trial.

Hypothesis 4: Prospective implementation of high resolution advanced EEG methods among our TBI-ICU-EEG-study sites will enable the selection of an enriched population of patients at high risk based of developing PTE that can be targeted in a future interventional trial.

Deliverables: 1) Validation of a translational EEG biomarker that may be used in a future interventional trial. 2) Validation of a translational MRI biomarker or patterns of biomarkers that indicate high risk of or early development of PTE. 3) Temporal sequence of a translational soluble biomarker or biomarkers that indicate the temporal course of epileptogenesis. 4) A highly trained clinical trials network, meta-data biorepository, DSMB, and Public Engagement Core including centers from TRACK TBI, CENTER, and ADAPT.