PROJECT SUMMARY/ABSTRACT – PROJECT 1 - BIOMARKERS OF EPILEPTOGENESIS AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY

Development of anti-epileptogenic (AEG) therapies for patients with the highest risk of epilepsy is seriously impeded by the lack of biomarkers for epileptogenesis. One critical obstacle in biomarker development is the heterogeneity of patient populations with acquired causes of epilepsy like TBI. Our objective is to discover plasma molecular, electrophysiological, and imaging markers which will diagnose epileptogenesis in a clinically relevant model of TBI. We will model the temporal lobe endophenotype of TBI, the most common injury location in humans with post-traumatic epilepsy, by inducing TBI in the lateral temporal cortex in rats using fluid-percussion injury (FPI), which results in epilepsy in about 50% of rats in a one-year follow-up. We will apply common data elements and multicenter study designs to obtain standardized data for a statistically powered study. Specific Aim 1 will investigate whether the distribution, spatial extent, and temporal evolution of changes in electroencephalogram (EEG) during up to 12-months follow-up will provide biomarkers of post-traumatic epileptogenesis. We will perfuse the animals for ex vivo MRI analysis, and save the brains in biobank for histological analysis. In Specific Aim 2 we will assess microstructural changes in hippocampal and thalamocortical pathways using magnetization transfer, phase contrast/susceptibility weighted imaging, diffusion tensor, and diffusion tractography magnetic resonance imaging (MRI) during a 6-month follow-up after TBI. We will assess whether specific temporal pathologies can be used as biomarkers for post-traumatic epileptogenesis, and whether their sensitivity and specificity will be increased by extra-temporal pathologies. In Specific Aim 3 we will collect blood samples from the same rats at different time points for analysis of molecular biomarkers. Our hypothesis-driven approach will investigate 15 plasma proteins which signal about neurodegeneration, neuroinflammation, axonal/dendritic injury, and metabolic disturbances. In our unbiased approach, we will perform plasma microRNA-seq to discover microRNAs which predict epileptogenesis. We will analyze the dataset further using bioinformatics tools to discover novel candidate biomarkers and mechanisms of epileptogenesis. Data analysis will be conducted using existing methods available on-site and methods available and developed in the *Informatics and Analytics Core (IAC).* We will combine results from blood tests, EEG, and structural MRI, and assess the biomarker value of different parameters alone and in combination using logistic regression analysis, principal component analysis, and receiver observed curves, in addition to novel computational and graphing techniques developed by the *IAC*. We will validate the best biomarkers discovered in *Project 1* in an independent animal cohort in *Project 2* and in human TBI cohort in *Project 3*. Our study will generate extensive molecular, electrophysiological, and imaging datasets which will be available for use in the *IAC*. As deliverables, our study will provide the first biomarker(s) for epileptogenesis which can be used for therapy development to combat epileptogenesis after experimental and human TBI.