SPECIFIC AIMS – INFORMATICS AND ANALYTICS CORE

The overall goal of the Informatics and Analytics Core (IAC) is to provide an infrastructure for CWOW investigators, collaborators, and the broader epilepsy clinical and research community as well as methods for mining the complex, multi-modal data collected in *Projects 1-3* and ultimately to lead to models of epileptogenesis. In addition, the IAC will coordinate CWOW's resources to conduct a trial, which will collect data that will complement the existing data. Biomarkers that are discovered will be instrumental in our efforts in developing models aimed at predicting the probability of developing epilepsy in post-TBI subjects and identifying specific times, regions, and processes where intervention may be most beneficial. (1) The online interface will allow users to search across raw and processed data in a data mining way and enable visualization and analyses (Aims 2-3) to test hypotheses and validate results. By sharing access from this Core to the broader international epilepsy research community, we plan to encourage collaborations among different centers as well as to bring awareness to investigators about the data collected and analysis methods used by other teams. This infrastructure should help the advancement and development of research directed toward translational or clinical development of additional disease-modifying or preventative therapies. (2) This Core will extract features derived from neuroimaging, electrophysiologic, molecular, clinical, cognitive, and behavioral measures over time to identify candidate primary biomarkers of epileptogenesis. Novel statistical tools will be used to visualize complex associations among multiple variables as they evolve over time during epileptogenesis. This will reveal processes, regions, and stages in epileptogenesis correlated with specific anatomical changes in imaging. (3) Based on (2), we will then use innovative statistical techniques to try to build models of epileptogenesis to predict the probability of epilepsy, based on biomarker inputs. Results of the predictive models will be validated by testing the robustness of the results in the presence of uncertainty. Success in this project will be measured by our ability to predict the probability of subjects developing epilepsy post-TBI and using specific biomarkers to predict when a TBI patient with epilepsy will develop seizures. We anticipate that our search for biomarkers will reveal mechanisms that can be used as targets for pioneering antiepileptogenic treatments. The specific aims of the IAC core are:

Specific Aim 1: Centralized data repository and innovative standardization/co-registration references: We will develop capabilities for importing heterogeneous multi-modal data, automatically and manually linking data across modalities and sites, and searching content (metadata, data, annotations, and relationships). It will enable the community to access and analyze all stored data and ensure that every result can be validated and reproduced. Data collected in this CWOW will be mapped into a common spatio-temporal reference frame with key information including the generating laboratory, subject type, TBI, and epilepsy features. A spatial coordinate system will be implemented for humans and for animal models so that findings can be compared, and specimen information will be stored in the centralized IAC.

Specific Aim 2: Imaging and Electrophysiology: Apply novel image and electrophysiology processing methods to extract candidate biomarkers from brain images, EEG, and multi-modal data.

Hypothesis 1: Novel quantitative features extracted from brain images and EEG may be key biomarkers of epileptogenesis. For images, these features will include measures of structure, function, and connectivity between specific regions. For EEG, measures will quantify epileptiform discharges, bursts, frequency spectrum changes, HFOs, spike morphology, and changes found by unsupervised learning methods.

Hypothesis 2: Biomarkers derived from neuroimaging, electrophysiological recordings, blood, CSF, and tissue will change in reproducible ways during epileptogenesis.

Hypothesis 3: Explicit changes in the features in combination with other candidate biomarkers, or in particular, patterns over time will correlate with the probability of the onset of epilepsy.

Specific Aim 3: Models of Epileptogenesis: Build models of epileptogenesis based on heterogeneous biomarkers that track the probability of developing epilepsy over time.

This Core will lead data analysis for the projects and coordinate statistical analysis among the laboratories by a committee comprised of CWOW members and outside experts delegated with establishing common best practices, data standards, formats, and protocols for uploading and analyzing data. The investigators will communicate closely with the statisticians on the 3 projects, based on already established collaborations, by verifying and validating the analysis results. This committee will offer support for software, computing, investigator training for CWOW investigators, and will hold frequent meetings and calls.