SPECIFIC AIMS – EPIBIOS4RX OVERALL

The **Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx)**, a CWOW proposal in response to RFA-NS-16-012, is designed to facilitate the development of antiepileptogenic (AEG) therapies by removing barriers and promoting large-scale collaborative research efforts by multidisciplinary teams of basic and clinical neuroscientists with access to extensive patient populations, well-defined and rigidly standardized animal models, and cutting-edge analytic methodology. We focus our proposal on antiepileptogenesis in post-traumatic epilepsy (PTE) following traumatic brain injury (TBI) as this condition offers the best opportunity to determine the onset of the epileptogenic process in patients.

The EpiBioS4Rx Scientific Premise is: Epileptogenesis after TBI can be prevented with specific treatments; the identification of relevant biomarkers and performance of rigorous preclinical trials will permit the future design and performance of economically feasible full-scale clinical trials of AEG therapies. Based on the work from a P20 planning grant, our program will consist of the following: (1) identify biomarkers of Epileptogenesis in our animal model and in patients, (2) Develop and utilize a standardized platform for preclinical trials of potential AEG drugs, (3) Identify 1 or more lead AEG drugs for a future interventional clinical trial, (4) Establish a network of advanced TBI centers capable of carrying out future clinical trials featuring our lead AEG drugs used in the context of a personalized medicine approach utilizing our panel of biomarkers, and (5) Develop and incorporate a public engagement program involving the mutual education and collaboration of consumers, consumer organizations, and professionals to design and execute future large-scale interventional clinical trials of AEG therapies.

Specific Aim 1: Carry out focused multicenter, collaborative, preclinical and clinical investigations to identify and validate biomarkers of Epileptogenesis following TBI and preclinical investigations to evaluate potential interventions that prevent the development of PTE as well as their effects on the identified biomarkers of epileptogenesis in a standardized animal model of TBI/PTE.

Research Project 1: Animal studies at 3 centers using a standardized lateral fluid percussion injury rat model of PTE to identify plasma, imaging, and electrophysiological biomarkers measured at different post-injury time points, alone or in combination, to diagnose with high sensitivity and specificity ongoing epileptogenesis independent of the severity of brain damage.

Research Project 2: Animal studies at 4 centers to identify targets and biomarkers for treatment implementation, which in combination with the biomarkers of epileptogenesis from *Project 1*, will guide rigorous randomized preclinical trials of potential AEG interventions to prevent PTE in the standardized animal model of TBI/PTE.

Research Project 3: Clinical/translational studies at 13 experienced TBI centers will identify biomarkers and validate in humans the biomarkers identified in *Projects 1 and 2.*

Specific Aim 2: Our multi-modal epilepsy-specific bioinformatics approaches will be applied to the results obtained in Projects 1, 2, and 3 to derive a combination of biomarkers that will reliably predict epileptogenesis following TBI in both animals and humans and identify specific AEG treatments to be used in future clinical trials. Following the completion of the aims, and in partnership with the consumer and scientific groups in the Public Engagement Core, our approach will permit the design and execution of a feasible, cost-effective, personalized medicine-focused, interventional, randomized, international clinical trial for AEG therapies in TBI.

Deliverables: At the end of the funding period for this CWOW, we will deliver for use by the entire epilepsy community: (1) A validated and rigorous operational platform to perform preclinical randomized multicenter trial protocols to assess the effectiveness of AEG interventions, (2) One or more candidate AEG drugs ready for an interventional clinical trial, (3) An epilepsy-specific bioinformatics platform with tools, resources, database, and biobank, (4) A profile of biomarkers of post-TBI epileptogenesis identified and validated in preclinical and clinical studies that would help prepare future transition to clinical testing of promising AEG interventions in TBI, (5) A network of TBI centers with facilities, expertise, and sufficient patients to carry out future clinical trials of AEG therapies, and (6) A fully operational public engagement program committed to support recruitment and retention of subjects effectively.