COSORTIUM/CONTRACTUAL ARRANGEMENTS – PROJECT 1 – BIOMARKERS OF EPILEPTOGENESIS AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY

The University of Southern California, in Los Angeles, is the submitting site for this work. The performance sites for the proposed EpiBios4Rx Project 1 experiments and analyses are:

1. University of Eastern Finland, Kuopio, Finland (Project Lead, Asla Pitkänen, MD, PhD)
2. University of Melbourne, Melbourne, Australia (Subaward Site PI, Terrence O'Brien, MD, PhD)
3. University of California, Los Angeles, CA, USA (Subaward Site PI, Richard Staba, PhD)

Justification for subcontract:

The objective of **Project 1** is to identify sensitive and specific plasma molecular, electrophysiological, and MRI biomarkers for post-traumatic epileptogenesis in a clinically relevant animal model within a three-year study period. To conduct a statistically powered study, we need large animal numbers, which are not practical to undertake in any single laboratory in the world (long-term video-EEG and its analysis is the major throughput limitation). Therefore, we need to run the experiments in a coordinated multicenter study design, which is new in preclinical research. Moreover, experiments will need to be done cost-effectively, appreciating 3R animal experimentation principles, and using rigorous experimental designs for robust and unbiased results. To achieve all these prerequisites, Project 1 needs to be undertaken in laboratories which (a) have experience in using TBI/PTE animal models, (b) have a facility and experience in using state-of-the art magnetic resonance imaging in rodents, (c) have facility and experience in conducting long-term video-EEG monitoring, and (d) have experience in molecular studies. Importantly, each of these needs to be available in the same study site as the same animal undergoes multiple tests. UCLA has an R01 (NS33310) that includes studies of rat TBI and has recently completely two electrophysiological studies in TBI animals. The first found cortical pHFOs and a new paroxysmal event consisting of repetitive pHFOs and EEG spikes or "rHFOSs" that only occurred in TBI rats that later developed seizures. The manuscript of these results was accepted by Epilepsia and described in preliminary studies section of this project. The other study quantified the progressive electrophysiological abnormalities after TBI in rats that later developed seizures and those rats that did not. This study is currently under review at the time this application was submitted. In addition, there are two other sites in the world which have proven track records, including published papers, in such studies: University of Eastern Finland (Kuopio, Finland) and University of Melbourne (Melbourne, Australia).

The investigators in Project 1 have complementary expertise, spanning the various aspects of the project: Pitkänen (Kuopio) – animal modeling, functional neuroanatomy, molecular analysis; Staba (UCLA) – electrophysiology; O'Brien, Jones, Shultz (Melbourne) – animal modeling for epilepsy and TBI, electrophysiology, molecular analysis, imaging; Gröhn (Kuopio), Harris (UCLA) – imaging. O'Brien (Melbourne) and Staba (UCLA) also work with patients, ensuring the experiments in this project have a direct translational perspective.

Project 1 will generate extensive molecular, electrophysiological, and imaging datasets, which will be available for use in the EpiBios4Rx ***Informatics and Analysis Core***. We will also use the analysis methods available in the Epibios4Rx ***Informatics and Analytics Core***.

Consortium Budget Arrangements:

As the submitting site, USC will be responsible for all consortium-related fiscal management. Changes in Budgets directed toward each institution will be separated on the Notice of Grant Award to reflect the agreed budget in the proposal. In this way, the consortium is specifically designed to meet the needs of the project Aims, employs a checks-and-balances mechanism to ensure proper fund expenditures, and ensures a close coordination between the consortium partners.