FOREIGN JUSTIFICATION - PROJECT 2 – BIOMARKERS OF EPILEPTOGENESIS AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY

Why the two foreign sites (Kuopio, Finland; Melbourne, Australia) are necessary for the project success

The aim 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 3-y study period. To conduct a statistically powered study, we will 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 will 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 will need to be conducted 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, all these will need to be ***available in the same study site*** as the same animal undergoes multiple tests. There are few laboratories in the world with such capacity, expertise and track record. 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 (Epilepsia, in press). These data are included in the preliminary studies 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, and the study is under review as of the submission of this application. In addition, there are two other sites in the world which have proven track records, including multiple published papers and competitive grant funding, in such studies: University of Eastern Finland (Kuopio, Finland) and University of Melbourne (Melbourne, Australia). This is the reason why Project 1 has two foreign study sites, Finland and Australia.