CONSORTIUM/CONTRACTUAL ARRANGEMENTS - PROJECT 2 – PRECLINICAL MODEL FOR ANTIEPILEPTOGENIC THERAPY SCREENING IN POST-TRAUMATIC EPILEPSY

The University of Southern California, in Los Angeles, is the submitting site for this work. The performance sites for the proposed EpiBioS4Rx Project 2 experiments and analyses are:

1. Albert Einstein College of Medicine, Bronx, NY, USA (Project and site leadership Aristea S. Galanopoulou MD PhD)
2. University of Melbourne, Melbourne, Australia (site leadership Terence O'Brien, MD, PhD)
3. University of California, Los Angeles, CA, USA (site leadership Rick Staba, PhD)
4. University of Eastern Finland (UEF), Kuopio, Finland (site leadership Asla Pitkänen, MD, PhD)
5. University of Minnesota, Minneapolis, Minnesota, USA (site leadership James Cloyd III PharmD
6. University of British Columbia (UBC), (site leadership Terrance Snutch, PhD)

Justification for subcontract:
The Project 2 of EpiBioS4Rx proposes to perform a multicenter preclinical trial to identify treatments with antiepileptogenic potential in an animal model of posttraumatic epilepsy. Because of the high demands for specialized expertise (survival surgery, long-term wide band video-EEG, MRI, plasma proteomics and miRNA, pharmacokinetics, neurotherapeutics) and the decision to implement a multicenter preclinical trial with the intent to screen the candidate therapies more robustly and rigorously, it was important to invite centers with investigators and research labs with complementary expertise as follows.

Einstein: Galanopoulou / Moshé / Mowrey have been collaborating in NINDS/ Department of Defense / CURE funded grants on preclinical trials for therapy discovery in rodents. They have expertise in design and implementation of rigorous preclinical therapy trials (including antiepileptogenesis (AEG) trials) using animal models of epilepsy and seizures, survival surgeries, behavioral studies, long-term video-EEG studies across the lifespan of a rodent, seizure monitoring across al age groups. The Einstein group has had experience with drugs targeting the neuroinflammatory pathways (e.g., Kineret / VX-765) which will be used in this study. Einstein has been conducting pharmacokinetic studies in collaboration with the University of Minnesota (Drs. Cloyd, Coles). Einstein also has expertise in MRI imaging of rodents through Dr. Branch (Director of Gruss MRI Center) who is co-I in this grant. Drs. Galanopoulou and Moshé are also clinical epileptologists and EEGers who will add to the translational and clinical relevance of this project and the interpretation of the seizure phenotype and patterns recorded in this study. Dr. Galanopoulou is the co-chair of the AES/ILAE Translational Task Force of the ILAE, a group that has advocated and pioneered adopting standards of rigor and clinical relevance in preclinical epilepsy therapy. Dr. Galanopoulou is also the co-leader of the TASK1 groups of the AES/ILAE Translational Research Task Force that are currently working towards proposing a terminology and classification system for the video-EEG patterns in rodents. This expertise will be necessary for the interpretation of the AEG effects in this project. Dr. Moshé is also a member of the TASK4 group of this Task Force that is proposing to improve infrastructure for implementation of multicenter preclinical phase II trials. The Einstein group also has expertise in all aspects of histology, Western blots, qRT-PCR studies that will be used here.

U. Melbourne: O'Brien / Jones / Shultz have extensively utilized the lateral fluid percussion model in rodents for characterization of behavioral, MRI, epilepsy outcomes and have expertise in the induction and survival surgeries, behavioral and MRI studies, seizure scoring, and therapy testing in the models. The Melbourne group and their collaborators (Ashley Bush/ Chris Hovens / Snutch) has had preliminary data on some of the compounds proposed for testing in this proposal (selenate, deferiprone, Z944), which will be important in fine tuning doses and protocols. Dr. O'Brien is also the co-chair of the AES/ILAE Translational Task Force of the ILAE, a group that has advocated and pioneered adopting standards of rigor and clinical relevance in preclinical epilepsy therapy. Dr. O'Brien is also the co-leader of the TASK4 group of this Task Force that is proposing to improve infrastructure for implementation of multicenter preclinical phase II trials and has been collaborating with multi-PART, a consortium that has done this in stroke research. The Melbourne group also has expertise in all aspects of histology, Western blots, qRT-PCR studies that will be used here.

UCLA: Staba / Engel have expertise on the electrophysiological patterns and EEG biomarker search for epileptogenesis and have identified pHFOs and rHFOSs as candidate biomarkers of epileptogenesis in the lateral fluid percussion model. This is one of the candidate biomarkers selected for studying here and their expertise will be invaluable in this aspect. The UCLA group has expertise in the lateral fluid percussion model

of posttraumatic epilepsy including survival surgeries, EEG characterization of the phenotype and MRI studies included here. Dr. Harris has expertise in MRI imaging and will be supervising the MRI studies at UCLA.

UEF: Pitkänen / Grohn have expertise in models of traumatic brain injury, including the lateral fluid percussion used here. They have extensively characterized this model in regards to epilepsy and behavioral phenotype, progression of MRI pathologies, and response to different treatments. Dr. Pitkänen has special interest and expertise in epileptogenesis and antiepileptogenesis treatment and was the first author of the related report of the AES/ILAE Translational Research Task Force (Epilepsia 2013) stemming from the proceedings of the London Workshop in 2012. Dr. Grohn has expertise in MRI studies in rodents and has worked with the other sites (Einstein, Melbourne, UCLA) and the Analytics Core facility to harmonize procedures across groups. UEF also has expertise in miRNA studies which will be used here.

U. Minnesota: Cloyd / Coles have expertise in pharmacokinetic and pharmacodynamics (PK/PD) modeling of drugs and formulation optimization and have collaborated with the Einstein investigators in multiple funded studies for preclinical therapy development to optimize the treatment protocols. They will be responsible for the PK/PD studies in this proposal.

UBC: Dr. Snutch has developed the Z944 compound and collaborated with the Melbourne group for testing this compound in other models of epileptogenesis. He will be providing this compound to us for testing in our models.

In summary, the experimental work involved in Project 2 will be done at 4 sites (Einstein, Melbourne, UCLA, UEF) which are also equipped to perform survival surgeries, video-EEG studies, MRI studies. The Eisntein and Melbourne groups will also be involved in the histology, Western blots, qRT-PCR studies that will be used here. The Minnesota group will be collecting and analyzing the PK/PD data from samples provided to them by the Einstein group and drug levels from blood samples collected by the Einstein, Melbourne, UCLA, and UEF groups. UBC will be providing Z944 to Einstein, Melbourne, UCLA, and UEF groups, and will therefore be responsible for synthesis, quality control issues related to this compound.

We also include the following consultants**:** Dr. Anatol Brain (UCLA) will be a consultant on the methods of EEG analysis for the detection of pHFOs and rHFOSs. Dr. Istvan Mody (UCLA) will be a consultant the characterization and study of epileptogenesis related biomarkers and electrophysiological patterns. Dr. Ashley Bush (Melbourne) will be a consultant on the use and monitoring of efficacy of deferiprone. Dr. Chris Hovens will act as consultant on the use and monitoring of efficacy of sodium selenate.

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 specific aims, employs a checks-and-balances mechanism to ensure proper fund expenditures, and ensures a close coordination between the consortium partners.