# ABSTRACT– PROJECT 2 – PRECLINICAL MODEL FOR ANTIEPILEPTOGENIC THERAPY SCREENING IN POST-TRAUMATIC EPILEPSY

There is currently no validated antiepileptogenic therapy for acquired epilepsies, such as post-traumatic epilepsy. Despite the grave human cost of post-traumatic epilepsy, undertaking the effort to perform a clinical antiepileptogenesis trial is currently hugely difficult, due to the significant cost, time to follow up, and very high numbers of subjects needed to treat to eventually observe antiepileptogenic effect. The availability of a biomarker that predicts, at an early stage, who will develop epilepsy and who might benefit from the antiepileptogenic effect of a treatment would significantly accelerate and de-risk the process of identifying an antiepileptogenic therapy. Furthermore, the concern that animal studies report several promising discoveries that do not always translate into clinically relevant findings has discouraged efforts to sponsor rigorous antiepileptogenesis trials in humans, when there is a significant risk of failure. In this study, Project 2 of the EpiBioS4Rx Center Without Walls, we aim to create a rigorous and effective preclinical model to screen antiepileptogenic therapies for posttraumatic epilepsy by trying to fill two important gaps (a) identify and validate a biomarker of posttraumatic epileptogenesis that can predict the antiepileptogenic effect of a treatment and (b) enhance the reproducibility of the study by creating the first multicenter, double-blinded, vehicle controlled, randomized preclinical antiepileptogenesis study following the high standards of rigor advocated by NINDS, the AES/ILAE Translational Research Task Force and the ARRIVE guidelines. We have formed a collaborative group of four international preclinical testing centers (Albert Einstein College of Medicine, University of Melbourne, UCLA, University of Eastern Finland), supported by experts in pharmacokinetic modeling (University of Minnesota), and experts in peripheral electrophysiology and imaging biomarker discovery, as well as neurotherapeutics. A preclinical Data Safety Monitoring Board will be overseeing the progress and advise on strategies and the preparation of a clinical cohort for the future clinical trial. We have selected 5 novel treatments that target different mechanisms and using a multimodal screening process for target engagement and modification of candidate biomarkers of posttraumatic epileptogenesis, we aim to identify (a) at least one treatment to screen in this rigorous model for its antiepileptogenic potential, and (b) at least one biomarker of posttraumatic epileptogenesis that can predict early the antiepileptogenic effect. Our investigators work closely with *Project 1* (discovery of biomarkers of epileptogenesis in animals), *Project 3* (discovery of biomarkers of epileptogenesis in humans), the *Informatics and Analytics Core*, and the *Public Engagement Core.*