MULTIPLE PI LEADERSHIP PLAN – EPIBIOS4RX OVERALL

The research proposed for the EpiBioS4Rx CWOW represents a multi-disciplinary, multi-institutional, and multinational program, relying on a combination of expertise in TBI and epileptogenesis, data collection in humans and animals, imaging, electrophysiology, experimental design, statistics, data analyses and modeling, informatics as well as the mobilization of consumer and consumer advocates and professional societies to plan and promote participatory clinical trials. A project of this magnitude and, with this number of participants, requires leadership that embodies exceptional depth and breadth of knowledge, large-scale research leadership experience, and diverse resources. Such a project also requires a clear organizational system to ensure that each component meshes cleanly and effectively with the others. A rigorous system of leadership, organization, and oversight is absolutely necessary to ensure that the project does not become unwieldy or lose focus. Building a multiple Principal Investigator (PI) leadership was, in our view, essential for the scientific and administrative goals of this project with multiple institutions involved.
Thus, EpiBioS4Rx will have seven PIs who are all leaders in complementary overlapping fields essential to the successful completion of the Specific Aims and long-term objectives of this CWOW. We realize that it is unusual to have seven PIs; however, the complex, multicenter, international nature of EpiBioS4Rx makes it essential that we have leadership expertise for all of the diverse areas of effort. The Co-PIs of EpiBioS4Rx have agreed to have a single Director, who will have overall responsibility for meeting the EpiBioS4Rx goals and objectives, with defined roles for each of the other six PIs allowing for broad participation and distributed governance. Each of the co-PIs of EpiBioS4Rx is a leading and highly experienced researcher, with outstanding support staff and resources, to enable them to accomplish the mission of this project effectively. Their proposed time and percentage effort are compatible with the responsibilities imposed by other obligations. Each of the PIs has available the time needed for commitment to this project. Together they form a strong leadership team, with strong existing collaborative relationship ties among them and excellent rapport with the other key members of the team.

The Co-PIs

Jerome Engel, Jr., MD, PhD (Overall Director), is the Director of the UCLA Seizure Disorder Center. He will be the Project Lead (PL) of the Administrative Core. He will also be co-PL of Project 3 and a co-investigator on Project 1. He is a clinical epileptologist and basic neuroscientist with over 50 years of extensive experience in research on epileptogenesis in patients and experimental models of human epilepsy including TBI/PTE. He is also an international authority in the field of epilepsy biomarkers. Dr. Engel is highly regarded nationally, and internationally, for his leadership abilities.
Arthur Toga, PhD (Contact-PI), is Director of the Laboratory of Neuro Imaging (LONI), which developed the bioinformatics platform to identify biomarkers for the Alzheimer's Disease Neuroimaging Initiative (ADNI), as well as several other multicenter projects on Parkinson's disease, Huntington's disease, and other brain disorders. He will also be co-PL of the Administrative Core. LONI has a very comprehensive administrative team with extensive experience managing very large, complex projects. LONI has been the lead on many multi-center U-type projects and has the necessary infrastructure and personal to insure a smooth and efficient operation from finances to science. Dr. Toga will also be PL of the Informatics Analytics Core. LONI is currently the most sophisticated bioinformatics program in the world for biomarker studies; its focus has been primarily on neuroimaging and it now also includes EEG. This open, multimodality, epilepsy-specific bioinformatics resource will provide powerful tools for finding, downloading and/or analyzing data, leading to the identification of antiepileptogenic agents.
Asla Pitkänen, MD, PhD, is a basic scientist at the University of Eastern Finland and a pioneer in the development and study of animal models of TBI and PTE. She is currently acknowledged as the preeminent investigator in this field. Dr. Pitkänen has pioneered the large scale molecular analyses of epileptogenesis. She has been the PI and Workpackage-leader in several European consortia. Dr. Pitkanen will be the PL of Project 1 on animal biomarkers, and a co-PL in Project 2 on preclinical trials.
Aristea Galanopoulou, MD, PhD, is a clinical epileptologist and basic scientist, the Director of the Laboratory of Developmental Epilepsy at Albert Einstein College of Medicine and an expert in epileptogenesis in animals. She is a co-chair of the AES/ILAE Translational Task Force of the ILAE, which aims to develop standardized methods for performing and interpreting video-EEG studies, common data elements and infrastructure for preclinical multicenter epilepsy therapy studies. She has expertise in developing rigorous and standardized preclinical protocols for trials of potential antiseizure and antiepileptogenic compounds, and will be PL on

Project 2 on preclinical trials.

Terrence O'Brien, MD, is head of the Department of Medicine and the Epilepsy and Neuropharmacology Research Group at the Royal Melbourne Hospital, University of Melbourne. He is an expert on all aspects of experimental TBI and PTE, including molecular biology and experimental and clinical pharmacology, and also a highly regarded clinical epileptologist who is actively involved in clinical trials. He has a track record in successfully taking novel therapies from preclinical to clinical trials. He will play a leadership role when Projects 1 and 2 combine efforts to begin preclinical trials, and also will be involved in Project 3.
Paul Vespa, MD, Director of the UCLA NeuroICU, is a neurologist and neurointensivist with a background in clinical neurophysiology and epilepsy, who has focused his research on clinical TBI, including seizures and epilepsy in this condition, and is a recognized leader in the TBI and neurointensivist community. Dr. Vespa will be the PL of Project 3 on human studies.
Solomon Moshé, MD, Director of Child Neurology and Clinical Neurophysiology at Albert Einstein College of Medicine, is a neurologist who is highly regarded for translational animal and clinical research, and is well connected with patient advocacy groups through his leadership role in national and international epilepsy organizations. He will be PL of the Public Engagement Core and a co-investigator in Project 2.

Governance and Organizational Structure

The Co-PIs will be involved in all aspects of the project, scientific and administrative. Together, the co-PIs will have joint administrative responsibilities, as outlined in the RFA, for:

- Determining and coordinating research approaches and procedures, conducting experiments, and analyzing and interpreting research data
- Working closely with the project manager to ensure progress towards achieving all goals within 5 years
- Interacting with the External Advisory Board
- Participating in annual meetings with the Data Safety Monitoring Board for the review of procedures, progress, and strategy plans.
- Meeting annual milestones for progress, and otherwise making satisfactory progress, toward accomplishing the EpiBioS4Rx goals
- Overseeing the release of data, software and models according to the awardee's data sharing and software release plan and specific procedures to be developed by the awardee and consistent with NIH Resource Sharing Policy
- Releasing to the research community results, publications, data, models, and tools as soon as they have undergone basic quality control and quality assurance procedures in a time-delimited manner
- Providing information on progress of the project to the program officer in a standard format on an annual basis, and as needed
- Planning for, facilitating, and participating in pre-arranged site visits by NIH staff members
- Participating in governance meetings and providing summary information of those meetings to the Program Officer

The co-PIs, in combination, represent the forefront of research in every discipline needed to accomplish the immediate Specific Aims and long-term objectives of EpiBioS4Rx. All co-PIs share responsibility and authority for leading and directing the work within their components, as well as the overall center. The Overall Director is responsible for coordination among the NINDS and Co -PIs and other investigators within the components. The Overall Director will have day-to-day support from a Management Committee, consisting also of the contact PI, the NINDS Program Officer, and a fourth member rotated every year among the other five co-PIs. The contact PI will work in close coordination with the Overall Director. The leadership of EpiBioS4Rx can be changed according to the wishes of the component leadership, with the advice and consent of the Executive Committee consisting of all co-PIs and the NINDS Project Officer, and the Steering Committee, consisting of the Executive Committee and coPLs, as specified in the EpiBioS4Rx Charter.
The co-PIs will interact directly with an External Advisory Board, composed of leading scientific experts, as well as with the NIH Program Officer. The External Advisory Board will review project activities, adjudicate disputes, and contribute to the production of an annual review of the project for submission to NIH.

A more detailed description about the proposed administrative and organizational structure of EpiBioS4Rx can be found in the Administrative Core.