

## viii. Neuronal Hyper Excitability and Seizures in Alzheimer's Disease (NHESAD)

**Competition Objectives:** The Alzheimer's Association is launching a new initiative to stimulate the development of new pharmacological strategies to prevent or treat seizures and abnormal neural network activity in Alzheimer's disease (AD). The Association's Request for Applications (RFAs) is aimed at the identification, screening and development of therapeutic strategies to reduce seizures and other types of abnormal neural network activity and at the evaluation of drug safety and efficacy at the preclinical and clinical levels. The RFA is designed to enable preliminary pilot research or proof-of-principle studies that can provide data for further research support by other funding agencies.

**Background:** A number of drug targets have been identified in AD, including proteases that cleave the amyloid precursor protein (APP), aggregation of amyloid- $\beta$  ( $A\beta$ ) peptides, kinases that phosphorylate tau, tau aggregation, structural and biological properties of apolipoprotein E that differentiate it from more protective apoE isoforms, and inflammatory mediators. All of these targets are already being pursued in large, highly competitive drug development programs. Indeed, drugs aimed at some of these targets are in advanced clinical trials. However, the long-term efficacy and safety of these drugs will remain unknown for many years to come. Therefore, the Association aims to keep open the pipeline for new treatments with the potential to significantly improve the symptoms and progression of AD, either as monotherapy or in combination with drugs that are or soon will be available.

The comorbidity between epilepsy and AD raises opportunities for improving care and possibly even for the development of novel therapeutic approaches to AD. Up to 15 percent of patients with AD develop seizure disorders, with much higher rates in early-onset and familial cases. Notably, most of the FDA-approved antiepileptic drugs (AEDs) can have cognitive side effects, and it is unclear which of these drugs provide the best efficacy against AD-associated epilepsy and the least amount of cognitive impairment in this patient population. Indeed, there is a need to better understand the mechanisms underlying the development of epileptic seizures and other network dysrhythmias in AD and to identify novel treatment approaches. In several human amyloid precursor protein (hAPP) transgenic mouse models, high levels of  $A\beta$  in the brain induce epileptiform activity and seizures, compensatory hippocampal remodeling, and cognitive impairments. Genetic reductions in tau expression block this aberrant neuronal activity and prevent cognitive deficits, implicating  $A\beta$ -induced aberrant excitatory activity as a potentially reversible cause of cognitive dysfunction in AD.

**Potential themes:** Based on discussions with the Medical and Scientific Advisory Council, the Association has chosen several themes that may be particularly worthy of further research. For this application "epilepsy" is broadly defined as aberrant synchronization of neural network activity as evidenced by convulsive seizures, non-convulsive or subclinical seizures, or simply aberrant neural network activity recorded on EEG or by other methods. Grant proposals may address, but are not limited to, the following areas of study:

**1. Discovery of novel treatment approaches for network dysrhythmias in AD.**

Research projects in this category may focus on hypothesis-driven candidate approaches to identify novel treatments for AD-related epilepsy. Projects may include human subjects, human samples, animal models, or samples from such models.

**2. Validation of novel treatment approaches.** Research projects in this category should aim to validate novel treatment approaches for epilepsy or related network dysrhythmias in AD by demonstrating that the treatment affects an outcome measure that is clearly relevant to AD. Projects may include human subjects, human samples, animal models, or samples from such models.

**3. Identification of clinical tools to detect epilepsy in AD patients.** Research projects in this category may include the identification of biomarkers or clinical phenotypes that correlate with epilepsy or related network dysrhythmias in AD. Projects may also include development of clinical tools, besides routine EEGs, to detect epileptiform activity or aberrant neural network synchrony in people with AD.

**4. Evaluation of drugs for treating epilepsy or related network dysrhythmias in AD.** Research projects in this category may focus on the evaluation of drugs at the preclinical or clinical level. Projects may consist of drug trials in well established experimental models of AD that have spontaneous epileptiform activity and/or abnormally low seizure thresholds, or of small pilot trials in humans with AD or MCI and new-onset seizures or epileptiform activity.

**General considerations:** Any proposal must have a clear focus on epilepsy related to AD and on a therapeutic approach as defined above. Any study that uses animal models must clearly and explicitly outline potential methods of translating and relating findings to the human condition in the future. Ultimately, the goal is to translate the research into strategies to improve the treatment of people with AD.

Because the principle idea is to encourage studies into new approaches and translation of this novel technology to human studies, an interdisciplinary approach might be most fruitful. Therefore, the Association strongly encourages submissions from collaborative research teams (e.g., basic scientists and clinical researchers). In addition, while novel and creative ideas are sought, proposals also need to demonstrate feasibility.

The Alzheimer's Association recognizes the need to increase the number of scientists from underrepresented groups in the research enterprise. Researchers from these groups are encouraged to apply.

**Funding and award period:** The Association anticipates funding up to two (2) Neuronal Hyper Excitability and Seizures in AD awards. Each award is limited to \$400,000 (direct and indirect costs) for two to three years. Requests in any given year may not exceed \$200,000 (direct and indirect costs). Indirect costs are capped at 10 percent (rent for laboratory/office space is expected to be covered by indirect costs paid to the institution).

**Eligibility:** Researchers with full-time staff or faculty appointments are encouraged to apply. Applications from post-doctoral candidates will not be accepted.

**Deadlines and award dates:** Letters of Intent must be received by 5:00 PM EASTERN STANDARD TIME, December 20, 2011. Letters of Intent will not be accepted after this date. No exceptions will be made.

**Applications must be received by 5:00 PM EASTERN STANDARD TIME, February 7, 2012.** Scientific and technical review will be conducted from March through June 2012.

The second-level review by the Medical and Scientific Advisory Council will be conducted during June 2012. Funding will be awarded by late July/early August 2012.

**Mechanism of award, reporting requirements and allowable costs:** The mechanism of the award is the individual research grant. The maximum allowable duration is three years. Annual scientific progress and financial reports are required. Continuation of the grant over the awarded duration is contingent upon the timely receipt of scientific progress and financial reports.

**Budget:** A “budget summary” for the proposed research project is required and must be submitted with the application and within the allowable page limits. However, if the application is to be awarded, a more detailed budget will be required and must be approved before the disbursement of funds. Your budget must not exceed the maximum amount of the award (\$400,000 for research investigating the role of neuronal hyper excitability and seizures in Alzheimer’s disease).

**Allowable costs under this award:** It is required that most of the funds awarded under this program be used for direct research support.

**Allowable costs under this award include:**

- Purchase and care of laboratory animals
- Small pieces of laboratory equipment and laboratory supplies
- Computer equipment if used strictly for data collection
- Travel (up to \$1,000 per year)
- Salary for the principal investigator, scientific (including post-doctoral fellows) and technical staff (including laboratory technicians and administrative support staff whose work is directly related to the funded project)

**Costs not allowed under this award include:**

- Tuition
- Computer hardware or software for investigators
- Rent for laboratory/office spaces
- Construction or renovation costs

**For more information:** Contact [grantsapp@alz.org](mailto:grantsapp@alz.org) or call 1.312.335.5747 or 1.312.335.5862.

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