Discovery-Validation of Therapeutic Targets for Developing Novel Interventions of Alzheimer’s disease (DVT)

**Competition Objectives:** This Request for Applications (RFA) by the Alzheimer’s Association aims to stimulate the discovery-validation of a broad spectrum of potential therapeutic targets and/or agents that could be tested in human subjects as putative disease modifying interventions for Alzheimer’s disease. The goal of this RFA is to foster ideas or areas of research beyond those already in various stages of development. The applicants may address any phase of drug discovery-validation; ranging from pre-clinical discovery of potential targets or therapeutic agents [validation of targets/screening/development of drugs]. 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:** The development of novel therapeutics aimed at slowing and eventually preventing progression of Alzheimer’s disease (AD) remains a critically important international public health goal. Recent clinical trials for AD have not met their primary or secondary outcome measures to significantly alter the course of the disease. Despite this, modifying the clinical course of AD and/or delaying the onset of disabling symptoms remains an important strategic objective. The Alzheimer’s Association - through this RFA - aims to initiate or encourage the process of re-evaluating current concepts and approaches to therapy development. This call for proposal intends to promote the identification of alternative ideas for exploration of potential directions for development of more effective treatments. The Association aims to expand the pipeline for new and novel drugs with the potential to significantly improve the treatment and prevention of Alzheimer’s, either as monotherapy or in combination with drugs that are or may soon be available.

**Potential themes:** The primary objective of this RFA is to identify, discover and/or validate ‘novel therapeutic targets’, defined as a clearly different drug target that has not yet been published or extensively evaluated for treatment of AD. Applications that pursue strategies targeting beta amyloid biology in ways that have already been extensively evaluated and applications targeting the cholinergic system will not be considered novel. The following are examples areas that projects could address, although projects are not limited to these ideas. Examples include:

1. **Discovery therapeutic targets for neurodegeneration -dementia -Alzheimer’s.** Research projects in this category may propose exploration of therapeutic targets based on novel hypothesis on pathogenesis or new conceptual models of dementia derived from general systems theory. Applicants are encouraged not only to propose new hypothesis based on systems biology approaches but also to offer experiments to test or validate these ideas. The primary objective of this solicitation is to stimulate, by applying principles of systems theory, the exploration of complex interactions between several ‘systems’, neural networks or ethological factors either working in parallel or in sequence in the expression of clinical phenotypes of the disease. Traditional approaches to the discovery and validation of therapeutic targets have relied on search and amelioration of a single ethologic factor [i.e. either replacement of a needed molecule or blocking the harmful
effects of toxin/pathogen], in contrast this RFA aims to introduce a different approach where interactions of multiple variables are explored. A possible example: the respective roles of multiple molecules and/or cell types in the central nervous system through cascade of events that implicate the vascular and/or metabolic systems or cell signaling pathways that link multiple hallmarks of AD. Projects may include human subjects, human samples, animal models, samples from such models and/or cell culture models.

2. Validation of disease modifying therapeutic targets. One of the specific aims of this RFA is to stimulate the formulation and validation of hypotheses on novel modes of actions or biological mechanism of potential disease modifying therapies. The explorations may focus on discovery of new therapeutic targets as well as new agents. Research projects in this category should aim to demonstrate some level of target modulation/effect and/or an outcome measurement in pre-clinical models that might have a clear relevance to neurodegeneration/dementia. A possible example may be to test and validate targets that promote intracellular clearance through the autophagy and lysosomal pathway or other cellular degradative pathways. Projects may include not only non-human models but also human samples/subjects.

3. Screening - development of putative therapeutic agents. Research projects in this category may include preliminary projects designed to bridge work between early preclinical ‘drug discovery research’ and ‘early phases of drug development’. The proposal may include a variety of approaches in drug discovery-development including but not limited to: medicinal chemistry to synthesize new comp; rational-drug design; development of high-throughput assays; drug screens or efforts to modify promising scaffolds.

4. Proof of concept evaluation of novel therapeutic targets and/or agents. Research projects in this category may focus on the evaluation of putative therapeutic targets and/or agents in either well-established pre-clinical models or small pilot studies [early clinical work] with human volunteers that have mild cognitive impairment or cognitively normal elderly individuals. Outcome measures might include not only clinical or behavioral outcome measures but also neuroimaging, biological-biochemical alterations associated with Alzheimer’s. Studies focusing on cognitively normal individuals should not be preventive trials per se but should target alterations of physiological processes that have relevance to Alzheimer’s and can be tracked (e.g., with biomarkers) whether or not there is an accompanying change in cognition.

[** NOTE – The aim of this RFA is to encourage: a) the expansion of ongoing efforts in drug-discovery/validation beyond those that are underway in industrial setting and b) build-up capabilities-resources for early s phases of R&D in therapy development in academic settings. Proposals from biotech of pharmaceutical companies will not be accepted.]
5. Evaluation of potential efficacy and/or added value combination therapy. Research projects in this category may evaluate the potential effects or unique benefits combinations of interventions, which may include several therapeutic targets and agents including the combination of non-biological with various chemical agents. The preliminary projects prosed in this section might include pre-clinical studies as well as small scale clinical studies. Although both therapeutic components may not be novel, the combination must be new [i.e., they have not have been explored before]. The proposal should be based on a defensible rationale e.g., pertinent preliminary data. See point 4 for details on experimental design.

6. Bench-to-bedside models. Research projects in this category may focus on pioneering translational programs or mechanisms that could facilitate and expedite the path that leads from the identification of novel targets to clinical trials of drugs aimed at the novel targets. Although projects may focus on academic or industrial settings, of particular interest are projects that focus on the academic/industrial interface.

**General considerations:** Any proposal must have a clear focus on Alzheimer’s disease and on a novel therapeutic target 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 delay, halt, reverse or prevent Alzheimer’s disease.

Because the principle idea is to encourage studies into new technologies and high-risk ventures 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:** Each *Discovery-Validation of Therapeutic Targets for Developing Novel Interventions of Alzheimer’s disease* award is limited to $250,000 (direct and indirect costs) for two to three years. Requests in any given year may not exceed $100,000 (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 (Assistant Professor and above) are encouraged to apply. *Applications from post-doctoral candidates will not be accepted.*
**Please note:** If the applicant institution does not have an Assistant Professor Position, the letter of employment should include sufficient information to allow the Alzheimer’s Association staff to evaluate the eligibility of the applicant.

**Ineligibility:** The Alzheimer’s Association will not accept new grant applications from currently funded investigators who are delinquent in submitting required reports and other deliverables on active grants. Investigators that have previous Alzheimer’s Association awards closed as ‘Incomplete’ are not eligible to apply without exception. This policy will be strictly adhered to with no exceptions.

**Submission and Review Procedures:** The grant submission process will follow a two stage procedure. First, applicants will submit a LOI. These LOIs will be reviewed and a select number of the top rated LOIs will be invited to submit a full grant application. The exact number of full applications invited for full submission will be determined by available funding, with a target of more than 10% funding rate for full submission.

**Both LOI and the full submissions will be reviewed based on:**

1) Alignment with the research priorities as outlined in the RFA
2) Demonstrable innovation/novelty of the proposed project (especially in the context of the PIs recently funded work).
3) Impact of project on Alzheimer’s disease and related dementia research.
4) Established investigators from other fields new to Alzheimer’s and related dementia research.
5) Evidence of methodological rigor that address the research question(s) being proposed.

**Deadlines and award dates:** Letters of Intent must be received by 5:00 PM EASTERN STANDARD TIME, March 6, 2015. 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, May 1, 2015.

Scientific and technical review will be conducted from May through June 2015. The second-level review by the Medical and Scientific Advisory Council will be conducted during June 2015. Funding will be awarded by August 30, 2015.

**Applications will be reviewed with special attention to:**

- Significance of the question being studied
- Applicant information
- Quality of the work plan
- Quality and adequacy of available resources and budget
- Impact-Risk
**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 progress and financial reports are required. Continuation of the grant over the awarded duration is contingent upon the timely receipt of scientific 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 ($250,000 for *Discovery-Validation of Therapeutic Targets for Developing Novel Interventions of Alzheimer’s disease* projects).

**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:

- 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 interviewers, interventionists, data entry staff, technicians, and administrative support staff whose work is directly related to the funded project)
- Manual production/development/website, etc.

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

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