viii. Understanding the Development and Devising Treatments for Alzheimer’s Disease in Individuals with Down Syndrome (DS/AD)

**Competition Objectives:** The Alzheimer’s Association, in collaboration with the Linda Crnic Institute for Down Syndrome and the Global Down Syndrome Foundation, is launching a new initiative to understand the development of Alzheimer’s disease (AD) in individuals with Down syndrome (DS). We are interested in understanding the mechanism(s) that lead to the initiation of AD in this specific population, with the intent to identify novel therapeutic strategies to treat AD in both the DS and non-DS populations. The Association’s Request for Applications (RFA) is aimed at identifying and developing therapeutic strategies to reduce AD and evaluate 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 to obtain additional research support from other funding agencies.

**Background:** Down syndrome (DS) occurs in 1 out of 691 infants in the U.S and is caused by the mis-segregation of chromosome 21 leading to three copies of this chromosome, or by abnormal translocations. In addition to early physical and intellectual disabilities, individuals with DS are at a high risk for developing Alzheimer’s disease (AD). Individuals with DS develop the two hallmarks of AD, plaques and tangles, in their 30s and 40s. Due to improved clinical care, these individuals are living into their 6th decade of life, causing the majority of individuals with DS to develop AD. The high incidence of AD in people with DS is thought to be due to the extra copy of chromosome 21, which contains the gene that encodes the amyloid precursor protein (APP). APP is the protein that is cleaved to form the amyloid-β (Aβ) peptide; the major protein found in plaques. It has been presumed that the extra copy of the gene produces an abnormal amount of Aβ, leading to its aggregation and deposition. However, there are hundreds of genes on chromosome 21 that may also play a role in the development of DS by affecting gene transcription, cell-cell interaction, synaptic activity, or induction of abnormal cell division. Even though there are developmental abnormalities that occur early in life which are unrelated to AD development, there is little research into whether or not other genes that are over-expressed by this genetic abnormality play a role in AD pathophysiology. This RFA is to explore what is known about DS with respect to how it may relate to the development of familial and sporadic AD. We are interested in understanding the similarities and differences between these conditions to help us identify new targets and potential therapies. We want to explore whether DS models could identify targets not available in current AD models. Finally, of critical importance is the fact that these individuals with DS can be identified early in life, before the onset of AD, allowing individuals to be used to develop predictive AD biomarkers and in the designing of practical interventional trials.

**Potential themes:**
1) Can DS animal models provide new insights into the initiation and development of AD? The current AD models only reproduce the early features of AD. Animal models that reproduce the full spectrum of the disease are required to test therapeutic strategies that may be needed in the mid to later stages of the disease. Researchers have genetically engineered mouse models of DS. Can these mice provide more insight into the
development of AD? How similar or different are the pathologies in the DS and AD mouse models?

2) Are there key biochemical pathways that may be responsible for the induction and progression of AD in DS? There are specific genes on chromosome 21 other than APP that alter CNS physiology through their effects on transcription, cell-cell interactions, redox balance, and channel physiology. Can this increased gene dosing identify proteins involved in AD pathogenesis?

3) Are pre-clinical therapeutics capable of slowing or blocking the development of AD in DS models? Both pharmacological and non-pharmacological therapies have been developed to ameliorate AD pathology in pre-clinical models. Are these efficacious in a DS model?

4) Could early, non-pharmacologic interventions used in other child disabilities not only reduce the early physical and intellectual disabilities, but slow and/or reduce the onset of AD? Physical activity, mental stimulation and social interactions are suggested to reduce the risk of AD. Often children with disabilities are enrolled in specific physical and educational programs to reduce deficits or learn compensatory skills. Do these programs reduce the risk of AD in individuals with DS or animal models as well as reducing (or lessening) these early disabilities?

5) Does the initiation and progression of the conditions in human tissue show similar or different characteristics in DS in comparison to AD? More information is needed concerning the progression of the pathophysiology of AD in the brain of persons with DS. Do Aβ and Tau spread in the brain of a person with DS in the same manner as in AD? Are the affected areas of the brain similar or different when comparing DS vs. sporadic AD brain tissue?

6) Can the development of AD biomarkers be used in DS to identify the pre-clinical onset of the disease? Because people with DS are readily identified at a very early age and the majority eventually convert to AD, this population is ideal for monitoring biomarkers to determine their ability to predict the onset of AD. Can CSF markers recently being developed in AD be used to follow pre-clinical AD in individuals with DS? This could include Aβ, Tau, or brain imaging. These studies would be needed to devise future interventional trials.

7) Can cognitive tests be developed for the DS population to measure memory impairment and early dementia? Because clinical outcomes such as cognition are important in judging the effectiveness of therapeutics, do specific cognitive tests need to be developed due to the intellectual disabilities prior to the onset of AD in individuals with DS? This can be a challenge because of the large variation in the severity of these disabilities.

**General considerations:** Any proposal must have a clear focus on the relationship between DS and AD and what therapeutic approaches can be identified. 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 at risk to develop AD.

Because the principal 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.

**Funding and award period:** Funding will be considered from both more established investigators (investigator initiated) and new investigators independently.

**Eligibility:** Researchers with full-time staff or faculty appointments are encouraged to apply (Assistant Professor and above). Applications from post-doctoral candidates will not be accepted (see below DS/AD New Investigator program for exception).

**DS/AD Investigator Initiated program:**
Researchers with full time staff or faculty appointments (Assistant Professor or above) are encouraged to apply. Applications from postdoctoral or junior faculty (below assistant professor) are not eligible to apply for this program.

**DS/AD New Investigator program:**
Eligibility to apply as a new investigator is restricted to investigators who have less than 10 years of research experience after receipt of their terminal degree. The 10-year period applies to the date of submission of the grant application. Adjustments for career interruptions can be made. Applicant must contact the Alzheimer’s Association regarding any possible exception (grantsapp@alz.org). These would include, but are not limited to: family leave, military service, and major illness or injury. It is the responsibility of the applicant to point out and document such interruptions within their application.

In general, postdoctoral fellows and junior faculty (below Assistant Professor) are not eligible to apply for Alzheimer’s Association grants at this time. For the DS/AD New Investigator program, applications will be accepted from postdoctoral fellows and other junior faculty members (for example: Instructor, Research Associate Scientist, etc.) who can provide a letter of employment verification indicating you will have a full-time faculty position of an Assistant Professor and above by the award deadline. The letter of employment must be uploaded to your application, printed on the hiring institution letterhead, signed by an authorized institutional signature (i.e. Grants and Contracts officer) and must indicate that the position will be activated by the grant award date. If the anticipated position is not activated by the award date for any reason, any offer of funding will be withdrawn. There will be no exceptions. In the event your application is funded, you will be required to provide an official letter on organizational letterhead, signed by an institutional signing official, stating you will have a full-time faculty position of an assistant professor and above.

**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.**

**Deadlines and award dates:** Letters of Intent must be received by 5:00 PM EASTERN STANDARD TIME, February 1, 2013. 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, April 1, 2013. Scientific and technical review will be conducted from March through June 2013.

The second-level review by the Medical and Scientific Advisory Council of the Alzheimer's Association and the Scientific Advisory Board of the Linda Crnic Institute will be conducted during June 2013. Funding will be awarded by August 30, 2013. Applications received by investigators at the Linda Crnic Institute for Down Syndrome will be reviewed solely by the Medical and Scientific Advisory Council of the Alzheimer's Association.

**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. Budgets must not exceed the maximum amount of the award ($300,000 or $150,000 for the Investigator Initiated vs. New Independent Investigator) in the “Development and Devising Treatments for Alzheimer’s Disease in Individuals with Down Syndrome” grant program.

**DS/AD Investigator Initiated Awards:**
Investigator Initiated awards are limited to $300,000 (direct and indirect costs) for 2-3 years. Requests may not exceed $125,000 (direct and indirect costs) in a given year. Indirect costs are capped at 10 percent (rent for laboratory/office space is expected to be covered by indirect costs paid to the institution).

**DS/AD New Investigator Awards:**
New Investigator award applications are limited to $150,000 (direct and indirect costs) for 2-3 years. Requests may not exceed $60,000 (direct and indirect costs) in a given year. Indirect costs are capped at 10 percent (rent for laboratory/office space is expected to be covered by indirect costs paid to the institution).
Allowable costs under this award: It is required that most of the funds awarded under this program be used for direct research support. Indirect costs are capped to 10 percent.

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 or call 1.312.335.5747 or 1.312.335.5862.

The Understanding the Development and Devising Treatments for Alzheimer’s Disease in Individuals with Down Syndrome (DS/AD) is being co-funded by the Linda Crnic Institute for Down Syndrome, Global Down Syndrome Foundation and the Alzheimer’s Association.