The PART THE CLOUD to RESCUE (REverse, reStore, Cease and UndErstand) Brain Cell Degeneration in Alzheimer’s disease Program

Program Goal: The PART THE CLOUD to RESCUE (REverse, reStore, Cease and UndErstand) Brain Cell Degeneration in Alzheimer’s disease program will accelerate the discovery and testing of innovative compounds to be used for interventions in the earliest stages of neurodegeneration-dementia-Alzheimer’s disease.

Background: Presently there are no effective interventions to delay or prevent the progression of neurodegenerative processes that underlie the disabling symptoms of Alzheimer’s dementia. To date, clinical trials based on current theories of the disease pathogenesis have not resulted in viable treatments. The strategic goal of the Alzheimer’s Association is to increase the options for potential interventions in early stages of neurodegeneration. In light of these aims the primary focus of PTC to RESCUE Brain Cell Degeneration in Alzheimer’s disease program is to encourage the discovery and development of a wide-range of interventions to maintain and/or restore the health and functionality of neurons and/or connectivity of neural networks.

The rationale for emphasizing healthy functions of a neuron stems from the compelling evidence, which now indicates the ‘loss of neuronal connectivity’ as the most proximal neurobiological event(s) that account for the expression of the clinical features [i.e., cognitive impairment, changes in an individual’s affect, motor dysfunction, etc.] of Alzheimer’s dementia. Brain atrophy, one of the characteristic pathologic indices along with amyloid beta (A-beta) fibrillar plaques and tau neurofibrillary tangles, is caused by massive dendrite pruning; severe synapse loss and/or demise of large numbers of neurons. This phenomenon [i.e., the loss of synapses and/or decline in neuron functionality] is often assigned a critical role or invoked as a central explanation in virtually all major ideas and theories on the disease pathogenesis.

Despite this significant role as the ‘final common pathway’ for multiple upstream etiologic factors that trigger the dysfunction of neurons the precise mechanisms of synapse loss, dendrite pruning and/or cell death remain uncertain. For example, multiple lines of evidence suggest that both A-beta and tau accumulation trigger a complex cascade of events that result in neuronal demise. Thus, there is a pressing need to identify therapeutic strategies capable of preventing additional neuronal damage, reversing pre-existing damage or some combination of the two. Further there is growing evidence that dysfunction and even death of other types of brain cells may contribute to pathology, thus, there may be opportunities to target the health of astrocytes, oligodendrocytes and even microglia in order to halt and/or reverse the brain cell degeneration seen in Alzheimer’s.
The Alzheimer’s Association believes that discovering and developing novel therapeutics targets as well as addressing new paradigms for testing potential interventions of neuronal fitness and regeneration are urgent unmet needs. Further, given the uncertainty regarding precise mechanisms of neurodegeneration, the PTC to RESCUE Brain Cell Degeneration in Alzheimer’s program will not only advance potential therapeutics, but will accelerate our understanding of processes involved in neurodegeneration. Identifying therapies that target brain cell health may have the potential to impact multiple aging-related diseases that impact the brain.

Program Description: The PTC to RESCUE Brain Cell Degeneration in Alzheimer’s disease program will promote human studies to advance innovative ideas for early phase human trials (Phase 1 or Phase 2a proof of concept) that addresses therapies to target neuron health in Alzheimer’s disease – this could include, but is not limited to, therapies to address synaptic dysfunction, neurogenesis, restoring glial homeostatis and neuronal protection. Projects will be awarded $1 million to launch and carry forward the Phase 1 or in appropriate circumstances, Phase 2, study in Alzheimer's disease over 2 years (24 months). PTC aims to accelerate our knowledge of neuronal brain health and rapidly advance therapeutics in the clinical setting.

Applications for the PTC program will be accepted that include lead candidate therapeutic agents targeting neuronal growth factors, cell survival and cell cycle pathways, anti-apoptotic or anti-cell death mechanisms and related mechanisms. These targets should be at a stage that require early stage phase 1 testing prior to Proof of Concept (POC) Phase 2 or 3 efficacy studies, or with lead therapeutic agents that have already established human safety data and require a small-scale pilot Proof of Mechanism (POM) phase 2 study in preparation for larger-scale POC trials. Awards should be able to demonstrate significant advancement of the compound within two years (24 months) of the award. Funding will support Phase 1 or early Phase 2 studies (Phase 2a, including proof of concept, proof of mechanism) of new or repurposed drugs in normal individuals or individuals with preclinical or symptomatic Alzheimer’s disease (i.e. early human studies to set the stage for efficacy studies), including single and multiple dose studies to establish safety, brain penetration and/or target engagement and POM in preparation for larger proof of concept trials. Any proposal must have a clear relevance to Alzheimer’s disease and be translational in nature. While preliminary preclinical animal studies can be a component of the larger proposal and as a part of the study design, proposals must include human clinical trials for eligibility. Proposals should include a plan for how participants are being selected, for instance confirming that there are already Alzheimer’s disease related changes or neuronal or other cell death pathology in the individual; this can include fluid, imaging or other biological measures. All proposals should clearly and explicitly outline the type of study, the rationale for the study, the participant selection process, the methods for study, and outcomes. This can include use of appropriate biomarker measures (fluid, imaging or other) to identify participants and/or to confirm target engagement throughout the study as well, as applicable.
The PTC will fund best in class projects that effectively demonstrate that their proposal will translate into human trials of an experimental drug or drugs targeting neuronal health, with the future promise of improving cognition/function in individuals with neurodegenerative diseases.

**Selection of Finalists:** Projects will be selected as a finalist for this program. These projects will receive up to $1,000,000 (total) over 2 years to support their proposed study. Funding should span over two years with maximum per year of $700,000. Projects will be evaluated throughout the 2 years and at the conclusion for satisfactory progress and overall success toward achieving the milestones.

Projects will be evaluated with special attention to clinical translational details for moving through the development pipeline, as well as their innovation and out of the box thinking to address these challenging questions.

**Eligibility:** Both non-profit and for-profit agencies from the international scientific community are eligible. Small for-profit agencies must submit documentation of net assets and annual earnings for consideration during the letter of intent process. Not-for-profit organizations must submit documentation verifying status during the letter of intent process. Researchers with full-time staff or faculty appointments are encouraged to apply. Applications from post-doctoral candidates will not be accepted. For questions as to whether an investigator or organization is eligible, please contact the Alzheimer’s Association at grantsapp@alz.org.

**Funding and award period:** The PTC to RESCUE Brain Cell Degeneration in Alzheimer’s grants will be for up to $1,000,000, funded over two years to make significant advancements of their compound through clinical trials. These awardees will be evaluated throughout the two years. Indirect costs are capped at 10 percent (rent for laboratory/office space is expected to be covered by indirect costs paid to the institution).

**Letter of Intent (LOI) Review Procedures:**
All LOIs will be evaluated prior to invitation to submit a full application. LOIs will be reviewed by the Alzheimer’s Association and select experts for relevance to the RFA and goals of the RFA. Only LOIs that meet program specific guidelines as outlined in this request for applications will be invited to submit full applications.

**Deadlines and award dates:** Letters of Intent (LOI) must be created and submitted through the proposalCENTRAL online application system at [http://proposalcentral.altum.com](http://proposalcentral.altum.com).

Letters of Intent must be received by March 5, 2018, 5:00 PM EASTERN STANDARD TIME, and must address the RFA in scope. Late or incomplete LOIs will not be accepted after this date (no exceptions).
For those invited, full applications must be received by April 18, 2018, 5:00 PM EASTERN STANDARD TIME. Scientific and technical review will be conducted from mid-April – mid-June, 2018. A specialized review panel will evaluate each project. Funding is anticipated to be awarded by June 30, 2018.

The full grant application consists of the following:
1. Problem Statement – 1 page
2. Work Plan – 5 pages
3. Available Resources & Budget Justification – 2 pages
4. Biosketch or Curriculum Vitae (PI/Co-PI) – 4 pages each
5. Documentation of access to agent for testing in the clinical study

Applications will be reviewed with special attention to:
• Rationale of the target being pursued
• Quality of the proposed trial design, including participant selection criteria and trial methodology
• Applicant information
• Quality and adequacy of available resources and budget
• Impact-Risk

Reporting requirements: Projects that receive the PTC awards will be required to provide sixth month milestones, and have bi-annual discussions with the Alzheimer’s Association, including select experts identified by the Association. In addition, annual scientific progress and financial reports are required. Continuation of the grant over the awarded duration is contingent upon meeting the scientific milestones, and upon timely receipt of scientific and financial reports. At the conclusion of two (2) years, the projects will be evaluated for overall success of milestones.

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.

Direct 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.

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