

2024 Part the Cloud Translational (PTC) Gene Targeting Challenge

Competition Objectives: Part the Cloud, a program through the Alzheimer's Association, announces a targeted challenge funding program focused on increasing early phase human trials (Phase 1 and Phase 2) of potential therapies tailored to the genetic underpinnings of Alzheimer's disease and related dementias internationally.

Background: A number of factors and processes likely contribute to the development of brain diseases such as Alzheimer's disease, and these may not be the same for every individual. More than 100 genes have been associated with the development of Alzheimer's as either risk or protective factors, each one influencing biological changes in the brain. Because of this variation in disease processes between individuals, there is a significant opportunity for personalized gene editing and therapy in Alzheimer's. Evidence from the trials that led to the recent approvals for two new therapies targeting the abnormal accumulation of beta-amyloid "plaques" suggest potential subpopulations of responders and non-responders. The complex interplay of factors and processes leading to the development of neurodegenerative disease points towards combination therapy of two or more drugs — with behavioral interventions that target distinct biological processes as the likely future of treatment for Alzheimer's and the other brain diseases that cause dementia. Personalized medical approaches to address an individual's biological circumstances is the future of treatment for Alzheimer's throughout the disease continuum.

Gene targeting therapies have existed for some time, but only recently have they become viable for clinical use. The COVID-19 vaccines utilized novel mRNA technology. Other new technologies such as small interfering RNA (siRNA), antisense oligonucleotides (ASOs), and CRISPR are being evaluated in the clinic for a range of diseases like sickle-cell anemia and heart disease. In early 2023, the U.S. Food and Drug Administration (FDA) approved ASO approaches for treatment of amyotrophic lateral sclerosis (ALS) and in late 2023, the FDA approved a CRISPR based therapy for sickle cell anemia, moving these approaches to care in real time. These recent approvals demonstrate the timeliness of leveraging approaches that build on the technological advances of ASOs, siRNA and CRISPR, as well as other approaches for gene modifications for Alzheimer's and other brain diseases that cause dementia. The Alzheimer's Association and Part the Cloud are already leading the way in these therapeutic approaches for Alzheimer's disease and other related dementias. Previous Part the Cloud awards include an ASO therapy targeting tau, a gene therapy targeting brain derived neurotrophic factor (BDNF), and an adult stem cell therapy. The BDNF gene therapy trial has shown that a single injection can lead to prolonged increases in brain BDNF levels. While these advances are pushing the field forward, a greater emphasis on these approaches, or combinations of these approaches with other therapies, could lead to unprecedented acceleration in the treatment of Alzheimer's.

Slowing or preventing Alzheimer's disease is a major public health need, and it is essential that the field begin to examine these promising new approaches. While many academic investigators and companies have successfully discovered candidate therapeutics, and have succeeded in the non-clinical stages of development, funding for the next phase to transition into human testing can be a major stumbling block. Most government and non- government grant mechanisms support preclinical development or mid to later clinical trials testing drug efficacy in humans, but there are few mechanisms for supporting the critical earlier Phase I trials in humans or have restrictions on funding that limit the forward momentum for therapeutic approaches.

Potential themes: This new grant mechanism aims to fill the gap in Alzheimer's disease and related dementia clinical trials for advancing potential gene targeting therapeutics forward by providing support for early phase studies (Phase 1 and Phase 2).

General considerations and Eligibility: Applications will be accepted from academic investigators and small companies with lead candidate therapeutic agents that require early stage testing prior (Phase 1) 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) study in humans to begin proving the scientific concept in humans. This award will support Phase 1 studies or pilot small- scale Phase 2a studies for new or repurposed drugs in cognitively impaired individuals or individuals with asymptomatic, early stage, or Alzheimer's and related dementia (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. The funding request should focus on the human clinical trial component. Outcomes proposed should be in line with Phase 1 or Phase 2 study being proposed (i.e. safety, tolerability, dosage); proposals should not have efficacy as the primary outcome, and should have clear Go/No Go criteria for advancing to the next stage of development. It is recognized that these studies are a necessary step to the larger efficacy study, so proposals may include those measures as exploratory or as secondary outcomes. The application must make a case as to how the data from the current study will inform the future trial. Specific to this challenge, we encourage applicants to consult [FDA guidance on cellular and gene therapies](#) when designing their trials. Any proposal must have a clear focus on Alzheimer's disease and related dementias and be translational in nature. All proposals should clearly and explicitly outline the measure to be investigated, the methods for study, the study population, and outcomes. Researchers from underrepresented groups are encouraged to apply.

Studies funded by Part the Cloud with results justifying further development (e.g. Phase 2b, or 3) may be eligible to apply to the Alzheimer's Clinical Trials Consortium (ACTC) (U24 AG057437). ACTC provides comprehensive infrastructure and expertise on AD/DRD clinical trials. ACTC and the proposer will work in collaboration to develop a grant application to National Institute on Aging, NIH. If funded, ACTC will conduct the trial.

Mentorship and Principal Investigator training in Alzheimer's Clinical Trials is provided by ACTC. Read more at: <https://www.actcinfo.org/submit-a-proposal/>.

Eligibility: Both non-profit and small for-profit organizations are eligible. Open to International Applicants. Small for-profit organizations must submit documentation of net assets and annual earnings during the letter of intent process as a part of the review process. Not-for-profit organizations must submit documentation verifying status during the letter of intent process.

Applications will be accepted from organizations conducting studies around the world. 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.

Note: Alzheimer's Association grants are generally open to scientists and researchers across the globe; however, as a U.S.-based charity, the Alzheimer's Association is subject to, and complies with, U.S. law. As a result, the Alzheimer's Association cannot award, and will not award, grants in violation of applicable U.S. statutes and regulations. This means, among other things, that the Alzheimer's Association cannot, and will not, fund any individual or entity (i) that is subject to U.S. comprehensive or targeted sanctions or if awarding funding would result in a violation of such sanctions, (ii) that is on the U.S. List of Specially Designated Nationals or entities owned or controlled by such persons, or (iii) when doing so is otherwise prohibited by U.S. laws related to combating terrorism.

Funding and award period: Each grant is limited to \$1,000,000 (direct and indirect costs) for Phase 1 studies and \$2,000,000 for Phase 2 studies over two or three years. We anticipate funding a mix of phase 1 and phase 2 studies with available funding, minimum of 10 clinical trials. Indirect costs are only allowed for not-for-profit institutions, and are capped at 10 percent (rent for laboratory/office space is expected to be covered by indirect costs paid to the institution). No indirect costs are allowed for profit organizations.

Letter of Intent (LOI) Review Procedures:

All LOIs will be evaluated prior to invitation to submit a full application. 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 received by 5:00pm EST, October 24, 2024. Letters of Intent will not be accepted after this date. No exceptions will be made. All LOIs must be completed and submitted online through our interactive system Proposal Central at <http://proposalcentral.com>. (No paper copies or emailed versions will be accepted)

The on-line LOI is approved and invited to submit a full proposal, an email notification will be sent from Proposal Central granting access to the on-line application. The online system must be used to submit a grant application—hard copies of the application will not be accepted.

Each LOI is evaluated with attention to:

- Demonstrable innovation/novelty of the proposed project (especially in the context of the PIs recently funded work)
- Alignment with the research priorities of the PTC request for applications and the Alzheimer's Association, including population, proposed therapeutic, outcome measure(s) and overall scientific rationale
- Evidence of methodological rigor of the trial, including patient selection, target engagement, outcome measures, etc. being proposed

For those invited to submit, Full applications must be received by 5:00pm EST, January 9, 2025.

The full grant application consists of the following:

1. Problem Statement – 1 page
2. Work Plan – 5 pages; Efficacy should not be the primary outcome for studies at phase 1 and phase 2; however, it may be an exploratory outcome. All applications should have clear Go/No Go criteria to the next phase of clinical development of the therapy, which should be clearly outlined in the application. The application must demonstrate how data from the proposed study will inform future trials.
3. Available Resources & Budget Justification – 2 pages; If awarded, a full budget of planned expenses will be required.
4. Data Management and Sharing Plan – 3 pages; we recommend using the provided amended NIH template. When data sharing may be limited, applicants must explain such limitations at the time of application.
5. Recruitment Plan - 1 page; the Association expects all trials to match or exceed the diversity of their local population at a minimum. **Award must maintain at least 20% minimum representation of minoritized participants. The Association will withhold payments if recruiting does not achieve this level of diversity.**
6. Milestones – 3 pages max
7. Reference and Citations – 1 page
8. Response to review comments – For resubmissions only – 1 page
9. Therapeutic Rationale – 1 page
10. Gantt Chart – 1 page (Optional)
11. Biosketch (PI/Co-PI/Key Personnel) – 5 pages max for each
12. Research Project Leadership Plan – 5 pages max

Applications will be reviewed with special attention to:

- Significance of the question being studied & rationale of the target being pursued
- Applicant information
- Quality of the proposed trial design
- Quality and adequacy of available resources and budget
- Impact-Risk

Scientific and technical review will be conducted from **January - March, 2025**. The second-level review by the Alzheimer's Association and subject matter experts in September 2024 and funding is anticipated to be awarded by **April 30, 2025**.

Reporting requirements: Awardees will be required to provide sixth month milestones, and have bi-annual discussions with the Alzheimer's Association. Annual scientific progress and financial reports are required. Continuation of the grant over the awarded duration is contingent upon meeting the scientific milestones, achieving a minimum participant recruitment of 20% minimum representation from minoritized participants, and upon timely receipt of scientific and financial reports. Representation of study participants should be reflective of the communities that are being engaged for this study.

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, \$1,000,000 (inclusive of direct and indirect) over two or three years.

Allowable Costs include:

- purchase and care of laboratory animals;
- small pieces of laboratory or clinical research equipment;
- special use computer hardware and software for neuropsychological or imaging studies;
- laboratory or clinical supplies;
- salary for the Principal Investigator;
- salary for scientific staff (including post-doctoral fellows and graduate students) and technical staff (including laboratory technicians and modest secretarial support);
- open access publication fees for journal articles related to the funded research project;
- participant remuneration adhering to the NACC ADRC Best Practices located here: <https://naccddata.org/adrc-resources/best-practices>
- membership to ISTAART, the professional society of the Alzheimer's Association and other scientific associations
- professional development and communication training; and
- support for travel to scientific and professional meetings and additional support for travel expenses necessary to carry out research planned— this may include

site visits. A total of \$12,500 over a three year period may be requested for travel purposes and is not to exceed \$7,000 in any given year.

- costs associated with the management and sharing of research data are allowable.

Costs not allowed under this award include:

- Computer hardware or software for investigators (e.g. Microsoft Office, mouse, monitor, computer parts)
- Laboratory equipment such as freezers, ultracentrifuges, RT-PCR, Microscopy/imaging equipment
- Service contract fees for equipment
- Construction or renovation costs
- Tuition
- Rent for laboratory/office spaces
- Visa costs and fees
- Expenses such as Data Network Recharges and Computing and communication devices support services
- General liability insurances, such as GAEL
- Wire and currency exchange fees
- Salary and/or compensation for Alzheimer's Association Staff or current members of the Alzheimer's Association Medical and Scientific Advisory Group (MSAG) and the International Research Grant Program (IRGP) Council. A complete list of MSAG and IRGP Council members can be found on our website alz.org/grants.

For more information: Contact grantsapp@alz.org

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Part the Cloud, benefiting the Alzheimer's Association.***