



## **The PART THE CLOUD –Bioenergetics/ Mitochondria, Clearance Related, Vascular Contributions and Inflammation Clinical Trials**

**Program Goal:** The **PART THE CLOUD [PTC] Bioenergetics/ Mitochondria, Clearance Related, Vascular Contributions and Inflammation Clinical Trials Program** will accelerate the testing of innovative therapy, including experimental or repurposed drug and/or experimental or repurposed device in the earliest stages of neurodegeneration. For this program, therapeutic approaches to Alzheimer's disease (AD) and related dementias (ADRD) should have a focus on biological mechanisms related to vascular pathology, mitochondrial/ bioenergetics, clearance related mechanisms (autophagy, lysosomal and lymphatic/ glymphatic systems) and inflammation. Projects will be considered that move experimental or repurposed drug candidates and/or experimental or repurposed trial ready devices into Phase 1 or Phase 2 clinical trials for AD and/or ADRD

**Background:** Presently there are no effective interventions that delay or stop the progression of AD and ADRD. To date, clinical trials based on current theories of the disease pathogenesis have not resulted in viable treatments. The strategic goal of Part the Cloud, in collaboration with Bill Gates, is to increase the options for potential interventions in early stages of neurodegeneration and to encourage the discovery and development of a wide-range of interventions that target biology with strong scientific rationale for AD and ADRD.

Despite the pivotal role for processes downstream of beta amyloid and tau accumulations as the 'final common pathway' for dysfunction of neurons, the precise mechanisms of synapse loss in AD, dendrite pruning and/or cell death that occur in disease remain uncertain. There are urgent and pressing needs to identify therapeutic strategies capable of preventing additional neuronal damage, targeting the pre-existing damage, or a combination of the two. There is growing evidence that dysfunction -- and even death -- of other types of cells may contribute to disease pathology. Thus, as an example (in addition to neuronal targets or other cellular types), there are opportunities to target cellular mechanisms of astrocytes, oligodendrocytes, microglia and even endothelial cells on blood vessels in order to halt, diminish and/or reverse the brain cell degeneration seen in AD or ADRD.

The Alzheimer's Association, in collaboration with Bill Gates, believes that there are urgent unmet needs for discovering and developing novel therapeutic targets, as well as addressing new paradigms for testing potential interventions that target these three biological areas of investigation. Given the uncertainty regarding the precise mechanisms of neurodegeneration, **PTC** will advance potential therapeutics (an

experimental or repurposed drug and/or experimental or repurposed device) and accelerate our understanding of the processes involved in neurodegeneration. Identifying therapies that target vascular pathology, mitochondrial/ bioenergetics, clearance-related mechanisms (autophagy, lysosomal and glymphatic systems) and inflammation may have the potential to treat complex underlying biology of AD and ADRD, while also gaining a deeper understanding of multiple diseases that affect the brain.

**Program Description:** PTC aims to accelerate the translation of possible therapeutics in the clinical setting. PTC will promote human studies to advance innovative ideas for early phase human trials (Phase 1 or Phase 2) that address therapies (an experimental or repurposed drug and/or experimental or repurposed device) to address vascular pathology, mitochondrial/ bioenergetics, clearance-related mechanisms (autophagy, lysosomal and lymphatic/ glymphatic systems) and inflammation.

Additional details on what this could include are provided below. Projects will be funded up to \$1 million (Phase 1) or up to \$2 million (Phase 2) to launch and advance the clinical trials; considerations of increased budget are possible and additional instructions on how to make such an inquiry are included below. Applications for the PTC program will be accepted that include lead candidate therapeutic agents (novel or repurposed drug candidates; including biologic or small molecule approaches) or trial ready devices targeting vascular pathology, mitochondrial/ bioenergetics or clearance related (autophagy, lysosomal and lymphatic/ glymphatic systems), and related biological mechanisms within these areas (i.e. inflammation response).

**Mitochondrial/ Bioenergetics:** Mitochondria are a primary source of cellular energy that supports the formation of lipids, nucleotides, and proteins. The formation and breakdown of these molecules result in the energy flow through the complex signaling cascade that are tightly regulated and conserved. Mitochondria regulate both cell survival and apoptosis (cell death) signaling through a series of signals and gene expression pathways that influence metabolic reactions. Recent insights reveal that mitochondria can also adjust rates of metabolic reactions, which can help regulate cell signaling and gene expression.

Growing research underscores that in Alzheimer's and other neurodegenerative diseases, these mitochondria/ bioenergetics pathways are known to be dysfunctional. Other pathways affected in aging include (but are not limited to):

- Biological pathways that lead to decreased glucose utilization (Blass et al 2001; Mosconi et al 2008);
- Decreased ketoglutarate, pyruvate dehydrogenase (Gibson et al 1999; Blass et al 2001; Casley et al 2002);
- Decreased cytochrome c oxidase and increased reactive oxygen species (ROS) levels (Kish et al, 1992, Mutisyo et al 1994, Cardose et al 2004);
- Decreased mitochondrial nuclear-coded proteins (Liang et al 2008);
- Increased oxidative stress – increased protein oxidation/ nitration and decreased anti-oxidant enzymes (Aksenov et al 1998, Perry et al 2000);

- Decreased mitochondrial dynamics
- Increased mitochondrial morphology/ abnormal distribution (Wang et al 2008, Cho et al 2009, Hirai et al 2001).

There is also the possibility of repurposing drugs and/or targeted approaches developed for other diseases (e.g. cancer and diabetes).

There are examples in oncology drug development to target these biological mechanisms that may have an influence in Alzheimer's and related dementia. Leveraging learnings from cancer research that, mitochondria have their own protein biosynthesis machinery that can be inhibited by antibiotics like doxycycline (with higher doses). This presents potential druggable targets possible or offers an opportunity to develop an analog to mimic this effect. Numerous drugs have been developed in oncology targeting inhibition of mitochondria to force the cell to use non-mitochondrial metabolic pathways to generate energy. Another example, Metformin is a mitochondrial inhibitor and both Metformin as well as drug analogs of Metformin are being explored as possible therapies for cancer (Klii-Drori AJ et al) and for Alzheimer's.

Proposals in this area of interest should include targeted Phase 1/ Phase 2 studies that advance an experimental therapeutic (novel experimental therapeutic, repurposed drug or trial-ready device) targeting mitochondria and mitochondria-related mechanisms, including the potential of repurposed drugs developed for cancer or other conditions. Some examples of focus areas could include -- but is not limited to -- direct mitochondria targets, cell cycle, apoptosis related, metabolism linked to bioenergetics (i.e. insulin receptor, alternative energy source, and related).

**Clearance Related (autophagy, lysosomal and lymphatic/ glymphatic systems):**

Autophagy is a highly conserved degradation and clearance pathway that controls numerous cellular functions, including elimination of protein aggregates and damaged organelles. Autophagy utilizes lysosomal function for these processes, and is essential in development and cellular differentiation (Ravikumar et al. 2010; Mizushima N et al. 2010). Increasing evidence is also implicating lymphatic/ glymphatic clearance pathways are key driving mechanisms in AD and ADRD.

Several diseases have demonstrated dysfunction in autophagy and related clearance mechanisms, including metabolic diseases, neurodegenerative disorders, infectious diseases and cancer. In some instances, autophagy is inhibited and can enhance disease, whereas in other diseases, autophagy yields to disease pathogenesis (Rubinsztein et al. 2012). These pathways may be prime targets for therapeutic development, and learnings from other therapeutic areas may provide a rich resource of target strategies for repurposing a potential therapeutic approach.

In neurodegeneration, and specifically Alzheimer's where the disease is characterized by the presence of increased protein aggregates, activation or upregulation of autophagy-related mechanisms may have a therapeutic benefit (Hara et al, 2006; Komatsu et al, 2006). Metabolic diseases are also a potential risk or contributing factor to dementia, which means an approach that targets autophagy pathways may also be beneficial for metabolic diseases. An example, rapamycin induces autophagy;

however, due to its side effects, may be less desirable in a pre-symptomatic population of Alzheimer's (Berger et al, 2006). Metformin, although a mitochondrial inhibitor, also is thought to activate AMPK (AMPK activates the ULK1 complex); this may also impact increased autophagy. Other drugs that have been or are being developed for other therapeutic areas include, but are not limited to: Ins(1,4,5)P3R antagonists, Valproic acid, Lithium or other Glycogen synthase kinase 3 inhibitors, phosphor-diesterase inhibitors targeting cyclic adenosine monophosphate (cAMP) and BH3 mimetics.

Proposals in this area of interest should include targeted Phase 1/ Phase 2 studies that advance an experimental therapeutic (novel experimental therapeutic, repurposed drug or trial-ready device) targeting biology implicated in autophagy, lysosomal and lymphatic/ glymphatic clearance mechanisms. The Phase 1 or Phase 2 studies should aim to evaluate experimental or repurposed drugs or a trial ready device that include, but is not limited to target autophagy related signaling pathways and/ or mechanisms impacting cellular clearance.

**Vascular Pathology and Related Mechanisms:** Molecular mechanisms associated with both vascular and AD pathologies have been linked in several ways and may act together to increase the possibility of neuronal death observed in individuals (Snyder et al. 2015). Mechanisms such as changes in blood flow, integrity blood brain barrier, hints from genomic assessments, and others, have contributed to this growing linkage and understanding. The National Institutes of Health ADRD Summit in 2016(<https://aspe.hhs.gov/alzheimers-disease-related-dementias-adrd-summit-2016-prioritized-research-milestones#Topic6>), and again in 2019, recommend the need to advance human studies that target mechanisms related to small vessel disease related biological pathways.

There are examples of vascular-related mechanisms being targeted in clinical studies, particularly focused on lifestyle interventions. However, the PTC program is seeking novel or repurposed lead candidates that are focused on addressing vascular-related biology and pathology mechanisms for Phase 1 or Phase 2. This would include experimental pharmacological drug candidates that address known mechanisms of pathological significance, including but not limited to, small vessel disease, blood-brain barrier related targets or mechanisms of delivery, pericyte derived or other cell-specific targets, blood flow or oxygenation-related interventions.

**Targeting Common Underlying Mechanisms, specifically Neuroinflammation:** Notably there are likely common mechanisms that link vascular, bioenergetics/ mitochondria and clearance/ autophagy dysfunction in AD and ADRD that are highlighted in this RFA. This could include many potential pathways, but several with the most evidence in support of these links include aging, immune pathways and others. Clearly, aging is the most significant risk factor for AD and would likely underlie common biological mechanisms and accumulating genetics. Systems biology studies have provided further support that immune pathways likely play a key contributing role to AD and ADRD pathogenesis.

Neuroinflammation is involved in the neurodegeneration process, but the role it plays is enigmatic. Simultaneously, the immune system in the brain seems to be both injurious

as well as beneficial. There is a great need for better understanding in this area. Only recently have we discovered that cells involved in inflammation originate both from within the brain and from peripheral blood cells that migrate to the brain.

New information about the role of microglia and proteins have advanced to make them potential therapeutic targets. Microglia are responsible for removing damaged cells from the brain, however in AD, evidence suggests that beta amyloid may cause microglia to overstimulated and overactive, causing further damage to the brain and increased inflammatory response. Studies have also found microglia may be underactive and not clearing enough cellular debris and waste.

Further, several genes linked to immune cell function have been identified that increase the risk for neurodegeneration, but little is also known about their function. For instance, variations in one gene called triggering receptor expressed on myeloid cells 2 (TREM2), was identified as playing a major role in how microglia are expressed in the brain, and specific variations in TREM2 are linked to increased risk of late-onset Alzheimer's. Finally, there is evidence that external factors like systemic inflammation, the microbiome and obesity can influence the immune response within the brain. The challenge is to understand these processes in a way that leads to drug development in order to ameliorate the detrimental effects or redirect them for beneficial outcomes.

PTC, in collaboration with Bill Gates, will accelerate our understanding of immune processes involved in neurodegeneration. Because neuroinflammation is prevalent in so many diseases of the brain, identifying therapies that target this process could have broad implications for treating Alzheimer's disease and a large number of related disorders. The current PTC program seeks drug candidates and/ or trial ready devices that target these common underlying biological pathophysiological neuroimmune mechanisms and applicants need to provide evidence and/ or preliminary data in support of these linkages. The PTC program is seeking novel or repurposed lead candidates that are focused on addressing vascular-related biology and pathology mechanisms for Phase 1 or Phase 2.

**Additional Award Information:** Awards should be able to demonstrate significant advancement of the drug candidate or trial-ready device within two years (24 months) of the award. Funding will support Phase 1 or Phase 2 studies of experimental or repurposed drug and/or experimental or repurposed device that target appropriate biological processes in normal individuals or individuals with preclinical or symptomatic Alzheimer's disease (i.e. human studies to set the stage for efficacy studies), including single ascending dose (SAD) and multiple ascending dose (MAD) studies to establish safety, brain penetration and/or target engagement and larger proof of concept trials. Any proposal must have a clear relevance to AD and ADRD 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 should focus at least 90% of effort and budget on the human clinical trial aspect of the proposal design for eligibility.

In addition, proposals should include a plan for how participants are being selected; for instance providing discussion that outlines the study participant selection, with careful consideration to confirm that the disease related changes or neuronal or other cell death

pathology are present in the study participants; this can include fluid, imaging or other biological measures. All proposals should clearly outline and explicitly notate the type of study, the rationale for the study, the participant selection process, the methods for study, and outcomes. This can include the use of appropriate biomarker measures (fluid, imaging or other) to identify participants and/or to confirm target engagement and/or pharmacodynamic effect throughout the study as well, as applicable.

PTC will fund best-in-class projects that effectively demonstrate a proposal to translate an experimental or repurposed drug and/or experimental or repurposed device into human clinical trials. The goal of PTC is to advance promising ideas that have promise of stopping or slowing the progression of neurodegenerative disease.

**Selection of Finalists:** Projects will be evaluated with special attention to the clinical and translational strategy provided, as well as their innovative and out-of-the-box approach for addressing these challenging questions.

**Eligibility:** Both not-for-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. Collaborations between not-for-profit and for-profit organizations are strongly encouraged. 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](mailto:grantsapp@alz.org).

**Funding and award period:** PTC projects should be for Phase 1 or Phase 2 human trials; for Phase 1 studies, budgets can be up to \$1,000,000 (total) over 2 years to support their proposed study. For Phase 2 studies, budget can be up to \$2,000,000 (total) over 2 years to support their proposed study. Funding can span up to two years. Projects will be evaluated every 6 months throughout its duration for satisfactory progress and overall success toward achieving the milestones (as detailed in the application and award documentation). PTC recognizes the wide range of per participant cost for Phase I and Phase 2 studies (estimated ranges of \$10,000 - \$150,000 per participant); considerations for increased budgets to accelerate a study will be considered, however, strong rationale for the budget allocation should be made and prior approval is needed. Please contact [grantsapp@alz.org](mailto:grantsapp@alz.org) for approval. PTC anticipates funding up to 20 clinical studies through this program. 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).

**Submitting a Letter of Intent:** The Letter of Intent (LOI) is a required step in the application process. LOIs must be completed online at <https://proposalcentral.com>. First-time users must register and complete a Professional Profile to begin the application process. No hard copies will be accepted.

**LOI Review:** All LOIs will be evaluated prior to invitation to submit a full application. The Alzheimer's Association and a select panel of experts will review LOIs for relevance to the RFA and goals of the RFA. Applicants will need to provide the area of therapeutic target (i.e. Bioenergetics/ Mitochondria, Clearance Related, Vascular Contributions and Inflammation) and will need to identify if experimental/ repurposed drug or device. Only LOIs that meet program specific guidelines as outlined in this request for applications will be invited to submit full applications. ***Feedback is not provided for LOIs that are not invited to submit a full application.***

**Submitting a Full Application:** For those invited to submit a full application, additional materials will be required. Templates and instructions will be provided after LOI approval.

**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. Milestones – no upload required– completed online
  - The budget must be broken down into 6-month increments, with key milestones listed for each 6-month budget period
  - Milestones should align with your overall project goals and be designed such that it can be clearly determined if each one has been met
  - For each milestone, indicate the relevant Project Aim of which it is a part of
  - Next to each Project Aim, include the amount of budget allocated to that Aim
5. Gantt Chart of proposed study, including go/no-go decision steps -1 page
6. Therapeutic Rationale - 1 page
7. Biosketch or *Curriculum Vitae* (PI/Co-PI) – 4 pages each for PI and other key personnel
8. Plan for Data Sharing – 1 page

**The full grant application will be reviewed by a panel of experts on both scientific and trial design 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 the available resources and budget
- Impact-Risk

**Deadlines and award dates: Letters of Intent must be received by 5:00pm EST, January 6, 2020** and must address the RFA in scope. Late or incomplete LOIs will not be accepted after this date (no exceptions). All LOIs must be completed online at <https://proposalcentral.com>. No hard copies or emails will be accepted.

**For those invited, full applications are due by 5:00pm EST, March 2, 2020.**

Scientific and technical review will be conducted from March – April 2020. A specialized review panel will evaluate each project. Funding is anticipated to be awarded by April 30, 2020. The second tier of review will consist of representatives from the Alzheimer’s Association and a panel of select experts will convene, discuss the merits (strengths and weaknesses of each application) and provide recommendations to the Association on funding priorities.

**Reporting requirements:** Projects that receive the PTC funding will be required to provide sixth month milestones, and have bi-annual discussions with the Alzheimer’s Association and Bill Gates’ team, including select experts identified from the larger field, as applicable. 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.

**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. Indirect costs are limited to no more than 10% of the total award budget.

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](mailto:grantsapp@alz.org)

**Made possible through the generous funding of  
The Part the Cloud, benefiting the Alzheimer’s Association.**

**Key Dates - 2020 New Part the Cloud (PTC)**

**Letter of Intent Opens:** Open now on <https://proposalcentral.com>

**LOI Deadline:** January 6, 2020

**Application Invitations Sent:** Week of January 27, 2020

**Application Deadline:** March 2, 2020

**Award Notifications:** By April 30, 2020