Alzheimer’s Combination Therapy Opportunities (ACTO)
Requests for Proposals

Collaboration of Alzheimer’s Drug Discovery Foundation, Alzheimer’s Association and Alzheimer’s Society UK

**Competition Objectives:** This new grant mechanism, Alzheimer’s Combination Therapy Opportunities (ACTO), aims to provide pilot funding to explore combination therapy opportunities in Alzheimer’s disease. This program will support a biomarker-based combination clinical trial testing repurposed drug combinations through Phase II proof of concept.

**Background:** The initiation and progression of Alzheimer’s disease is not completely understood, but evidence suggests they are influenced by a multitude of factors. Aging is the greatest risk factor for Alzheimer’s and there are multiple causes of aging-induced brain degeneration. In addition, recent advances in understanding the genetics underlying sporadic Alzheimer’s disease point to a number of pathways being involved in increasing the risk of Alzheimer’s disease. Targeting these pathways together, in combination, has the potential for synergistic benefit for Alzheimer’s disease patients.

Combination therapy has been effective and often essential in treating many chronic health conditions – heart disease, HIV/AIDS, rheumatoid arthritis and cancer, for example. There are currently many drugs on the market today for the treatment of age-related comorbidities that target pathways relevant to Alzheimer’s. In this RFP, Alzheimer’s Drug Discovery Foundation, Alzheimer’s Association, and Alzheimer’s Society UK (the Partners) challenge the research community to propose combinations of repurposed and/or repositioned drugs that have the potential to be disease-modifying for Alzheimer’s disease and are hypothesized to work synergistically to provide a large effect in slowing or reversing Alzheimer’s disease progression. This RFP will support biomarker-based combination clinical trials testing this combination through Phase II proof of concept. Studies that target the full continuum of disease, preclinical through Alzheimer’s dementia will be considered, symptomatic and disease modifying to stop or slow progression of disease.

**Potential Themes:** This new grant mechanism aims to provide pilot funding to explore combination therapy opportunities in Alzheimer’s disease. Priority will be given to projects that:

1. Target biological mechanisms with a strong rationale for these mechanisms to be relevant in treating AD in combination, including but not limited to drugs that target multiple biological mechanisms such as:
   - Inflammatory response
   - Protein homeostasis
   - Energy utilization and mitochondria function
   - Lipid/membrane repair
   - Epigenetics
   - Synaptic maintenance/neuroprotection

2. Explore the combination of two repurposed drugs; repurposing refers to studying compounds developed and/or approved to treat another disease or condition to determine safety/efficacy for treating other diseases.
Although important for further investigation, strategies used in combination with repurposed or experimental drugs such as nutraceuticals, vitamins, exercise or other lifestyle interventions are considered outside the remit of this RFA.

It is not a requirement that proposed compounds have already been tested singly in placebo controlled trials. Applicants may choose their trial design as best suited to the evidence available, including 2 by 2 designs, single arm, or multiple arm studies. If the combination of the two repurposed or experimental drugs have never been tested together in humans, a Phase I safety trial will need to be included in the preliminary data or in the proposal design, if applicable. A successful Phase II trial would show either additive or synergistic effects of the drug combination.

**General Considerations and Eligibility:** Applications will be accepted from academic investigators and small companies with candidate therapies ready for early phase human clinical trials. Applicants are required to assemble an interdisciplinary team, including but not limited to, biology, pharmacology and clinical trial experts.

**Eligibility:** Both non-profit and small for-profit agencies are eligible. Small for-profit agencies must submit documentation that demonstrates net assets and annual earnings for consideration during the letter of intent process. Not-for-profit organizations must submit documentation verifying status for consideration during the letter of intent process. Applications will be accepted from organizations 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, Alzheimer’s Society (UK) at james.pickett@alzheimers.org.uk or ADDF at dshineman@alzdiscovery.org

**Funding and award period:** The Partners anticipate funding up to two Alzheimer’s disease Combination Therapy Opportunity (ACTO) awards in this cycle. Realizing the complexity of combination trials, the Partners will consider awards up to $2,000,000 (direct costs only, no indirect costs will be supported) for two or three years; however budgets must be adequately justified. The per annum budget must match the proposed plan for the study. In instances where a project may have a budget exceeding $2,000,000 in value, please contact the Alzheimer’s Association at grantsapp@alz.org for possible special programmatic or budgetary considerations.

**Review Process:** Both letters of intent and applications will be reviewed by a joint steering committee composed of biology, pharmacology and clinical trial experts. The review committee will work with the top applicants to refine the application before final selection and joint funding by the Foundation Partners. Proposed candidate therapies will be evaluated using the following decision matrix:

<table>
<thead>
<tr>
<th>Drug source/ IP status (if relevant)</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Combination</th>
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<tbody>
<tr>
<td>Pathway(s) targeted</td>
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<td>Rationale/supporting data for dose selection</td>
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<td>Safety/Toxicity</td>
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<td>Pharmacodynamic</td>
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### Patient Selection Strategy

**Disease Subtype/Genotype**

**Experimental Gaps:** Any non-clinical studies required?

**Clinical Trial Design (i.e. 2X2)**

**Use of Biomarkers in Non-clinical and/or Clinical Trial**

**Evidence for Brain Penetration**

**Expertise of Team**

**Pharmacokinetics** (including relevant tissue distribution, half-life, % bioavailability, etc.)

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<th>readout for target engagement</th>
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Both letters of intent and applications will be reviewed based on the rationale of the study design and drug candidate selection, quality of the study design components, expertise and resources of the applicant and key study personnel. Further, LOIs will be evaluated on the following criteria:

- Biological rationale for the combination to treat AD
- Non-clinical team to define dose and evaluate the PK, safety and toxicity of the combination
- Biomarker strategy which may include translatable biomarkers to provide data on target engagement
- Clinical team to define the patient population, exclusion/inclusion criteria and clinical trial design
- Regulatory expertise in order to gain NDA approval for the combination
- Patent expertise to provide clarity on intellectual property issues for the combination of repurposed drugs
- A strong and consistent source and supply for the drugs to be used in the program

During the study design and delivery of the proposed study, the partners suggest to involve people affected by Alzheimer's disease or related dementia.

**Deadlines and Award Dates:** Letters of intent must be received by 5:00 PM EASTERN STANDARD TIME, May 20, 2016 and must address the specific parameters of this RFA. Late or incomplete letters of intent will not be accepted after this date (no exceptions).

All Letters of intent must be submitted online thru Proposal Central at [http://proposalcentral.altum.com](http://proposalcentral.altum.com)

Full applications must be received by 5:00 PM EASTERN STANDARD TIME, August 10, 2016 and must be submitted online thru Proposal Central at [http://proposalcentral.altum.com](http://proposalcentral.altum.com). Award notifications will be made by November 15, 2016.
**Reporting requirements:** Awardees will be required to provide sixth month milestones, including go/no-go decision making criteria for each stage of the study. In addition, awardees will have bi-annual discussions with the funding partners. Annual scientific progress and financial reports are required. Continuation of the grant over the awarded duration is contingent upon the meeting 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. Your budget must not exceed the maximum amount of the award ($2,000,000) unless you have received special consideration from the funding partners. Questions can be addressed to the Alzheimer’s Association at grantsapp@alz.org or call 1.312.335.5747 or 1.312.335.5862 or ADDF at dshineman@alzdiscovery.org or call 1.212.901.8007. UK applicants may contact AS at james.pickett@alzheimers.org.uk.

**Costs not allowed under this award include:**
- Tuition
- Computer hardware or software for investigators
- Rent for laboratory/office spaces
- Construction or renovation costs
- Investigator travel

**For more information:** Contact the Alzheimer’s Association at grantsapp@alz.org or call 1.312.335.5747 or 1.312.335.5862 or ADDF at dshineman@alzdiscovery.org or call 1.212.901.8007. UK applicants may contact AS at james.pickett@alzheimers.org.uk.