DRUG DISCOVERY PROGRAM

UPCOMING DEADLINES

Must be received by 5:00 pm ET on the deadline date.

Letter of Intent
January 18, 2019

Invited Full Proposal
February 8, 2019

Letter of Intent
April 12, 2019

Invited Full Proposal
May 10, 2019

Letter of Intent
July 12, 2019

Invited Full Proposal
August 9, 2019

Letter of Intent
October 11, 2019

Invited Full Proposal
November 8, 2019

Average Duration

One year with potential for follow-on funding. Multi-year proposals can be considered.

Average Award

$150,000-$600,000 based on stage and scope of research. For studies requiring additional support, co-funding from other funding agencies or investors is encouraged.

Eligibility

Funding is open to researchers and clinicians worldwide at:

- **Academic medical centers and universities or nonprofits.** Industry partnerships are strongly encouraged.
- **Biotechnology companies.** Funding is provided through mission-related investments that require return on investment based upon scientific and/or business milestones. Existing companies and new startups are both eligible.

FUNDING PRIORITIES

The Alzheimer's Drug Discovery Foundation (ADDF) has long recognized the need to bridge the translational funding gap between early-stage drug discovery and clinical development for Alzheimer's disease, related dementias, and cognitive aging by supporting promising therapeutic approaches.

The Drug Discovery RFP supports:

- **Novel drug programs** aiming to advance novel lead molecules to the clinical candidate selection stage. This includes small molecules and biologics (e.g., antibodies, peptides, gene therapies).
- **Repurposed/repositioned programs** aiming to build preclinical evidence in relevant animal models for repurposed drugs (existing drugs that are approved for other diseases and conditions) and repositioned drugs (existing drugs that have entered clinical trials for other indications and have not yet been approved).

Drug Targets

Current target areas of interest include, but are not limited to:

- Neuroprotection
- Inflammation
- Proteostasis
- Mitochondria & metabolic function
- Vascular function
- Epigenetics
- APOE
- Synaptic activity and neurotransmitters
- Other aging target (e.g. senescent cells)

Other novel targets or pathways that are supported by compelling evidence demonstrating a rational biological connection to the disease process are encouraged.

NOTE: This RFP does not support anti-amyloid approaches (e.g., anti-amyloid aggregation, beta-amyloid vaccines, beta- or gamma-secretase inhibitors) or cholinesterase inhibitors.

Stage of discovery

This RFP supports in vivo pharmacokinetics, preclinical target engagement, preclinical efficacy, and/or preliminary rodent tolerability studies.

This RFP does NOT support target identification, target validation, assay development, high-throughput and high-content screening. IND-enabling work is supported through the PACT RFP.

EXPECTATIONS

Novel Drugs

The strongest applications will test a compound that has met many or all of the following criteria:

- Lead molecule or series has *in vitro* biological activity in the nanomolar range for biochemical assays (where the molecular target is known) and <10μM in cell-based/phenotypic assays based on the target
- Chemical structures of leads have been assessed for structural liabilities
- Adequate solubility and scale-up feasibility has been demonstrated
- Selectivity among related and unrelated family members has been assessed
- Initial *in vitro* ADMET (absorption, distribution, metabolism, excretion, toxicity) profiling indicates sufficient drug-like properties
- Novel composition of matter patents have been filed or plans to generate novel composition of matter intellectual property (IP) have been developed

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Repurposed/Repositioned Drugs

The strongest applications will test a repurposed or repositioned drug that has met many or all of the following criteria:

- The known side effects of the drug and how well they would be tolerated by the intended clinical population have been evaluated
- A supplier that will provide sufficient quantities of the drug or compound to complete the study aims has been identified

- Plans to develop novel IP around the repurposing/repositioning strategy have been demonstrated

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Preclinical Efficacy Studies

Applications that include preclinical efficacy studies should:

- Provide data demonstrating blood-brain barrier penetration (if the intended target is in the CNS)
- Justify dosing administration and regimen with in vivo PK/PD data. (If this data is not yet available, a PK/PD study aim should be included in your proposal)
- Include measures of target engagement in the proposed animal study design

Applicants are expected to follow the recommendations outlined in Shineman (2011) and Snyder (2016) when developing the animal study design.

EVALUATION

The strongest applications will test a compound that has met many or all of the following criteria:

- Rational biological connection of the target to the disease pathophysiology
- Physiochemical and ADMET properties of the drug
- Strength of the preliminary data
- Feasibility, research design and methodology, including justification for proposed the animal model for efficacy studies
- Investigative team, organizational capabilities, and project budget

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Targets

The following criteria will be used to assess the proposed drug target(s):

- Is there human genetic evidence linking the target to the disease?
- Is the target expressed in disease-relevant regions of the brain (or where applicable, in the periphery) in humans and/or animal models?
- Are there changes in target mRNA/protein expression or activity in human disease specimens, and do they correlate with disease severity and cognitive functions?
- Does genetic and/or pharmacological manipulation of the target in disease-relevant *in vitro* (e.g., primary cultured neurons/glia or cells derived from patient iPSCs) or *in vivo* models alter disease phenotypes?
- Are there direct measures of target engagement that can be used experimentally and in humans?
- How is the target more compelling than other related targets that have been tested for the disease?

If the molecular target is unknown, the strength of the evidence for the mode of action and its link to disease pathophysiology will be evaluated. The applicant should summarize the existing evidence in the proposal.

Animal Models

There are numerous available models of Alzheimer's disease and related dementias, including aged animals and transgenic models with a host of different transgenes expressed alone or in combination. Each of these models reflect different aspects of disease, which vary from the number and types of phenotypes observed to their onset and severity; however, none of these models recapitulate all aspects of human disease. Instead, the appropriate model can provide valuable information on how the therapeutic engages with its target and its ability to modify phenotypes related to its mode of action.

Reviewers will evaluate the rationale for the proposed animal model using the following criteria:

- How well characterized is the animal model? Has it been characterized in the applicant's or collaborator's lab, or is there historical control data available from the contract research organization (CRO) that will run the study?
- Does the model mimic one or more human symptoms of the primary disease indication?
- Does the model exhibit the appropriate phenotype(s) to measure target engagement (e.g. a drug intended to reduce pro-inflammatory cytokines in the brain should be tested in a model shown to exhibit elevated pro-inflammatory cytokine levels)?
- Does the model exhibit other phenotypes relevant to the mode of action that can be measured as secondary outcomes (e.g. synaptic changes, mitochondrial defects, neuronal loss, plaques, tangles, cognitive defects, etc.)?

Please visit Alzforum's Research Model Database for a select listing of rodent models of neurodegenerative diseases. On occasion, the ADDF will consider canine and non-human primate models for preclinical efficacy testing if there is sufficient justification for testing in larger animals at this stage of development.

APPLICATION SUBMISSIONS

Review the Application Instructions for steps on applying.

ADDF FUNDING PORTAL

LOG IN OR **CREATE ACCOUNT**

The ADDF considers its application process an iterative one, and we would be happy to talk to you about your program.

For program-related inquiries, please contact:
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For application submission inquiries, please contact:
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grants@alzdiscovery.org

Alzheimer's Drug Discovery Foundation

A GuideStar-Rated Charity

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