DRUG DEVELOPMENT PROGRAM

UPCOMING DEADLINES

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

Letter of Intent
January 17, 2020

Invited Full Proposal
February 7, 2020

Letter of Intent
April 10, 2020

Invited Full Proposal
May 8, 2020

Letter of Intent
July 10, 2020

Invited Full Proposal
August 7, 2020

Letter of Intent
October 9, 2020

Invited Full Proposal
November 6, 2020

FUNDING OPPORTUNITY DESCRIPTION

The goal of this RFP is to develop therapeutics for Alzheimer's disease and related dementias. This RFP focuses on building preclinical evidence in animal models and on advancing lead molecules to the clinical candidate selection stage. The proposed studies should have a high probability of reaching IND-enabling studies within two years.

Specifically, the Drug Development RFP supports:

- Preclinical pharmacokinetics, pharmacodynamics, target engagement, and preliminary rodent tolerability
- *In vivo* efficacy or proof-of-concept studies
- **Please note:** *IND-enabling work and clinical trials are supported through the* **Program to Accelerate Clinical Trials** (PACT) RFP

Applications that focus on basic science, target identification, target validation, assay development, and high-throughput screening are not a priority for this RFP and will be withdrawn.

The ADDF is interested in small molecules and biologics (e.g. antibodies, peptides, gene therapies). Both novel programs and repurposing/repositioning of approved or clinically safe therapies from other disease indications are appropriate for this RFP.

Current target areas of interest include:

- Epigenetics
- Inflammation
- Mitochondria & metabolic function
- Neuroprotection
- Proteostasis
- Synaptic activity and neurotransmitters
- Vascular function
- 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

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

AWARD INFORMATION

Average Award:
Up to $600,000 based on stage and scope of research.
Payment structure will be negotiated and based on milestone achievements.

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

Allowable Cost
Only direct costs are allowed. Please review our **Funding Policies**.

ELIGIBILITY

Funding is open to researchers and clinicians worldwide at:

- **Academic medical centers and universities or nonprofits.** Industry partnerships are 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 ADDF prioritizes later-stage preclinical programs that own or plan to generate novel composition of matter intellectual property (IP).

For programs testing **novel drugs**, the ADDF will prioritize applications that meet the below 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
- A biomarker(s) has been identified that can measure target engagement, both in animal models and in human clinical trials

For programs testing **repurposed/repositioned** drugs, the ADDF will prioritize applications that meet the below criteria:

- There is a clear rationale to perform the proposed aims in animals, instead of going directly in a human clinical studies
- 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 considered

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 the 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

All proposals will be evaluated for:

1. Rational biological connection of the target to the disease pathophysiology

- Is this a novel target? How is the target more compelling than other related targets that have been tested for the disease?
- 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?
- 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.

2. Strength of the preliminary data

- Are physiochemical and ADMET properties of the lead compounds sufficiently “drug-like”?
- Are there compelling in vitro and in vivo data to justify the proposed study?

3. Feasibility, research design and methodology

- Are there direct measures of target engagement that can be used preclinically and clinically?
- Is the dose, frequency and route of administration well-justified?
- Are the experiments well designed, powered and with the right controls?
- Are milestones and go/no-go criteria well defined?

4. Rationale for the for proposed animal model

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.

5. Investigative team, organizational capabilities, and project budget

- Do the PI(s) and collaborators have the appropriate experience to design and execute the project? Note: The preclinical drug development process will likely require resources beyond those available at a single organization and collaboration with other investigators and contract research organizations and consultants are encouraged.
- Do the investigators have complementary and integrated expertise?
- Is the budget appropriate for the proposed aims?

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 would be happy to talk to you about your drug development program.

For program-related inquiries, please contact:
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For application submission inquiries, please contact:
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Alzheimer's Drug Discovery Foundation

A GuideStar-Rated Charity

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