DRUG DEVELOPMENT PROGRAM

FUNDING OPPORTUNITY DESCRIPTION

The Drug Development RFP seeks to support in vivo preclinical studies that advance lead molecules developed for Alzheimer's disease and related dementias to IND-enabling studies. The proposed studies should be structured to deliver a compound with strong potential for clinical and commercial application.

This funding opportunity prioritizes novel drug mechanisms and modes of action related to the biology of aging and other emerging therapeutic areas for dementia. For this reason, amyloid targeted approaches and cholinesterase inhibitor proposals will not be considered for this RFP.

Stage of discovery:

- Preclinical pharmacokinetics (PK) and pharmacodynamics (PD) (primarily to inform dose selection for in vivo efficacy studies), as well as preliminary rodent tolerability studies
- *In vivo* efficacy or proof-of-concept studies in animal models of disease or aging, with a focus on direct and indirect markers of target engagement and downstream pharmacologic effects
- **Please note:** Applications that focus on basic research (including target discovery), assay development, and screening to identify hit compounds are not a priority for this RFP and will be withdrawn
- **Please note:** IND-enabling work and clinical trials are supported through the **Program to Accelerate Clinical Trials (PACT) RFP**

Therapeutic modalities: Includes small molecules, biologics, gene therapies, antisense oligonucleotides, and stem cells. Development of novel devices or delivery systems will not be considered for this RFP.

Drug mechanisms or modes of action: Novel drug mechanisms and modes of action related to the biology of aging and other emerging therapeutic areas for dementia are considered high priority. These include, but are not limited to:

- Epigenetics
- Inflammation
- Mitochondrial & metabolic function
- Neuroprotection
- Proteostasis
- Synaptic activity and neurotransmitters
- Vascular function
- Other mechanisms and modes of action related to the biology of aging (e.g. senescent cells)
- Other novel mechanisms or modes of action that are supported by compelling evidence demonstrating a rational biological connection to the disease process
- **Please note:** Anti-amyloid approaches (e.g. anti-amyloid aggregation, beta-amyloid vaccines, beta- or gamma-secretase inhibitors) and cholinesterase inhibitor proposals will not be considered

UPCOMING DEADLINES

ELIGIBILITY

AWARD INFORMATION

EXPECTATIONS AND EVALUATION

The strongest proposals will provide a clear rationale for targeting the proposed mode or mechanism of action and include supportive preclinical data, study outcomes that can measure pharmacokinetic/pharmacodynamic relationships and evidence of target engagement, a testable hypothesis with well-defined go/no-go decision points, an experienced team with appropriate expertise and resources necessary to carry out the proposed research. A detailed landscape analysis to compare competition related to the mode or mechanism of action is strongly encouraged.

The following guidance may assist you in developing a strong application that allows reviewers to better evaluate the science and merit of your proposal. The strongest proposals will contain many or all of the aspects listed below. Any approaches with a sound biological rationale and well justified outcome measures will be considered.

Mechanisms or modes of action: Applicants are encouraged to provide a clear rationale and compelling evidence for targeting the proposed mode or mechanism of action in AD or related dementias and should specifically address these questions in their proposal:

- Is the mechanism or mode of action novel? How is the target biology more compelling than other related targets that have been tested for the disease?
- Is there human genetic evidence linking the target biology 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.

Chemistry: For non-biologic entities, applicants are encouraged to include data around the following:

- 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

Preclinical efficacy studies: Applications that include preclinical efficacy should:

- Provide data demonstrating blood-brain barrier penetration in cases of CNS targets
- Justify dosing administration and regimen with in vivo PK/PD data. **If these data are not yet available, a PK/PD study aim should be included in the proposal. In most cases, a PK/PD study should be performed prior to efficacy studies to inform the dosing regimen selected.**

- Include measures of direct and indirect target engagement that can be used preclinically and clinically. Outcomes that assess pharmacodynamic responses related to the target biology will be prioritized. For example, inflammation targeted drug proposals should prioritize biochemical and immunohistochemical markers related to inflammatory processes over behavioral outcomes.
- **Please note:** Applicants are expected to follow the recommendations outlined in **Shineman (2011)** and **Snyder (2016)** when developing the animal study design.
- **Please note:** The ADDF strongly encourages researchers to use the Alzheimer's Disease Preclinical Efficacy Database (**AlzPED**), to survey the literature on the preclinical testing of drugs for Alzheimer's disease and, to raise their awareness about the critical data, design elements, and methodology required for rigorous, reproducible and translatable preclinical studies.

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 are 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.

For programs testing **repurposed/repositioned** drugs, provide a clear rationale for the need to perform the proposed aims in animal models instead of testing directly in human clinical studies. Proposals testing repurposed or repositioned therapies should provide a discussion around the known side effects and how well tolerated the therapy is by the intended clinical population. Plans to develop novel IP around the repurposing/repositioning strategy should be considered.

Investigative team: The preclinical drug development process will likely require resources beyond those available at a single organization and collaborations with other investigators, CROs, and consultants are encouraged.

APPLICATION SUBMISSIONS

Review the **Application Instructions** for steps on applying.

LOG IN OR CREATE ACCOUNT

We encourage you to contact us if you would like to discuss your proposed project and receive initial feedback.

For scientific inquiries, please contact:

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For inquiries related to contracting and the online funding portal, please contact:

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