REQUEST FOR PROPOSALS: ACCELERATING DRUG DISCOVERY FOR FRONTOTEMPORAL DEGENERATION

There are currently no FDA approved disease-modifying treatments available for frontotemporal dementia (FTD) and symptomatic treatments only provide limited benefit for patients. Recent scientific advances have provided an increased understanding of pathogenic mechanisms underlying FTD and are driving the development of potential disease-modifying therapies. The Alzheimer's Drug Discovery Foundation (ADDF) and The Association for Frontotemporal Degeneration (AFTD) seek to accelerate this progress by supporting innovative small molecule and biologic (antibodies, oligonucleotides, peptides, gene therapy etc.) drug development programs for FTD through this request for proposals (RFP). Drug targets in the areas of inflammation and proteostasis will be considered high priority.

The Association for Frontotemporal Degeneration
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Deadlines

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

Letter of Intent: May 28th, 2021

Invited Full Proposal: July 30th, 2021

Average Duration

One year with potential for follow-on funding.

Average Award

$100,000-$150,000 based on stage and scope of research.

Eligibility

Funding is open to researchers and clinicians in the U.S. and worldwide working in:

- **Academic** medical centers and universities or nonprofits. Industry partnerships are encouraged.
- **Biotechnology companies** that demonstrate a clear need for nonprofit funding. Funding is provided through mission-related investments (MRIs) that require return on investment based upon scientific and/or business milestones. Existing companies and new spinouts are both eligible.

Please review our **Funding Policies** before applying.

FUNDING PRIORITIES

The RFP supports:

- **Lead optimization** of novel disease-modifying compounds, including medicinal chemistry refinement and in vitro ADME.
- ***In vivo* testing of novel lead compounds, biologics, vaccines, or repurposed drug candidates** in relevant animal models for pharmacokinetics, dose-range finding, target engagement, in vivo 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 ADDF's PACT RFP.

Drug Targets

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

- Inflammation
- Proteostasis
- Autophagy
- Epigenetics
- Genetic Causes of Disease (*C9ORF72, MAPT, GRN, etc.*)
- Misfolded proteins (TDP-43, tau, FUS etc.)
- Mitochondria & Metabolic Function
- Neuroprotection
- Synaptic Activity & Neurotransmitters

EXPECTATIONS

Novel Drugs

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

- Chemical structures of hits and leads have been assessed for structural liabilities
- 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 FTD population have been evaluated
- A supplier that will provide sufficient quantities of the drug or compound to complete the study aims
- Plans to develop novel IP around the repurposing/repositioning strategy have been considered

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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 the proposal)
- Include measures of target engagement in the proposed animal study design
- Include measures to assess off-target effects with the potential to interfere with behavioral outcome measures (e.g., sedation)

Applicants are encouraged to follow the recommendations outlined in Shineman (2011), Roberson (2012) and Snyder (2016) when developing the animal study design.

EVALUATION

All proposals will be evaluated for:

- Rational biological connection of the target to the disease pathophysiology
- Strength of the preliminary data
- Feasibility, research design and methodology, including justification of the proposed animal model for efficacy studies, particularly its relevance to FTD clinical phenotypes
- Appropriate data analysis strategy
- 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 FTD disorders? Targets without a defined genetic link will also be considered.
- 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 from FTD disorders, and do they correlate with disease severity and cognitive or behavioral 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 eventually in humans?
- How is the target more compelling than other related targets that have been tested for FTD disorders?

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 dementia, including 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 FTD-relevant pathology and FTD cognitive/behavioral symptoms (e.g., apathy, disinhibition, social disinterest, perseverative behavior, overeating/carbohydrate craving) or motor deficits (instability, gait changes, maintain balance, strength, reflexes, coordination, unilateral motor changes, decline in overall mobility)?
- 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. abnormal protein accumulation, synaptic changes, neuronal loss, cognitive defects, etc.)?

APPLICATION SUBMISSIONS

Review the Application Instructions* for steps on applying.

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

**Please note that you will be following the same application instructions as the Core RFPs.*

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