

Alzheimer's Disease Strategic Fund: APOE Biology in Alzheimer's (ABA) - *Implications for Biological Underpinnings, Risk, Progression and Outcomes*

Program Objective:

The Alzheimer's Disease Strategic Fund (ADSF), established in 2019 by the Alzheimer's Association and an anonymous foundation, aims to support innovative, high-risk, collaborative team science opportunities that investigate and focus on outstanding questions related to the biological underpinnings of Alzheimer's disease (AD). The ADSF expects timely sharing of data and resources generated from funded projects in accordance with the sharing principles detailed below. In this second call for proposals to advance scientific understanding, the ADSF will focus on the role of APOE in diverse populations and the impact of this gene and its product on biological underpinnings, risk, progression and individual outcomes.

Although Alzheimer's research has made many advances in recent years, the field still faces gaps in our knowledge and ability to translate basic science discoveries into effective treatments and evidence-based clinical practices for dementia care. Some of these overarching questions focus on understanding of disease causes, need for models and other tools to evaluate disease biology, early and accurate detection and diagnosis procedures and diverse treatment modalities.

Program Overview:

Variants in the APOE gene, which is the major cholesterol carrier in the brain, are the biggest risk factor for AD in some populations after age. Although the risk due to APOE in some populations has been known for decades, the Alzheimer's research community does not fully understand how differences in the APOE gene confer risk of AD. Advances in tools and technology are now allowing research teams to probe the role of APOE in a much more sophisticated way, and scientists are beginning to develop new hypotheses for the way APOE contributes to disease. As technologies evolve and are now able to increase or decrease levels of specific forms of APOE, however, the use of these technologies requires a greater understanding of the biological underpinnings to deploy these potential therapeutics. Additional understanding of this target could enable timely clinical trials.

The **APOE Biology in Alzheimer's (ABA) Grant Program** solicits projects that aim to address some of the key challenges in Alzheimer's research today as related to APOE contributions and biology, including but not limited to:

- **Cause(s) of the Disease:** What are the biological mechanisms by which APOE genotype is altering overall risk for AD? For example, how is APOE contributing to the following basic questions of AD pathophysiology: How and why do specific sets of neurons in select brain structures become dysfunctional in disease? Why is there selective vulnerability in specific brain regions and not in others? What initiates these processes and are they cell autonomous or non-cell autonomous in nature? How do other identified risk/resilience genes interact with APOE-related biology? This could include projects aimed to address the biological significance of APOE to risk and resilience in different populations, including impact on risk and mutations, impact on resilience, and links to cardiovascular/ cerebrovascular related pathways or metabolic disorders, or studies

aimed to understand the biological role of APOE as relates to transport metabolism. **Importantly, how genetic background influences the contribution of APOE genotype to disease in different ethnic groups, and an understanding of the underlying biology underlying this altered risk is of particular interest.**

- Experimental Models of Disease: Considerable advances have been made in the development of cellular and animal models for AD that incorporate APOE contributions and APOE-related genes; however, these model systems do not capture the full complexity of the human condition. This has been problematic in applying these models to predict the success of specific therapeutic interventions in individuals with AD. Are there novel technologies or approaches that recapitulate disease progression and/or pathogenesis to support model applications that will particularly help to address the role of APOE?
- Early and Accurate Detection and Diagnosis: What are the most sensitive, specific and cost-effective diagnostic procedures or methods for assessing change throughout the course of the disease? How might APOE genotype affect specific biomarkers of disease? Projects may include work aimed to develop novel biomarkers and/or drug discovery and development (pre-IND) related to APOE to advance understanding of biological implications and contributions of APOE and related measures
- Treatment: Should therapeutic development be specifically targeted towards different APOE genotypes or specific trial designs? We would be interested in proposals that would provide support to help inform these types of decisions.
- Tool development: What are key tools and/or resources that if developed will benefit a broader range of scientific questions and/or studies related to APOE biology? Tools and resources developed through this funding would be made broadly available to the scientific field.

The ABA Grant Program aims to fund concerted and collaborative efforts that will explore these questions as they relate to APOE to advance our understanding of disease.

Funding and award period:

The maximum grant amount is \$300,000; with anticipated funding ranges to be \$150,000 to \$300,000 depending on the project scope. Budget spending should be appropriately aligned to the specific aims and proposed milestone of the project. No indirect costs are allowable for this funding program. The maximum project duration is 3 years, and there is no minimum timeframe. The ADSF will evaluate projects on progress toward specific milestones; continued disbursement of funds is dependent on demonstrated progress toward key milestones.

Eligibility:

The ABA Grant Program is open to researchers at academic institutions as well as small companies. Both non-profits and small for-profit organizations are eligible. For-profits and non-profits must provide documentation verifying status. The Principal Investigator of the project must be a full-time faculty member or paid employee of the organization submitting the proposal. If the applicant is not a paid employee, they must demonstrate that they are part of the company and a listed employee. Applications from post-doctoral researchers will not be accepted.

Investigators that have received Alzheimer's Association funding and are currently delinquent in submitting required reports or have awards closed as "Incomplete" are not eligible to apply. For questions about eligibility, please contact the Alzheimer's Association at grantsapp@alz.org.

Submitting a Letter of Intent:

The Letter of Intent (LOI) is a required step in the application process. LOIs must be completed online at <https://proposalcentral.com>. First-time users must register and complete a Professional Profile to begin the LOI process. No hard copies will be accepted. The LOI is completed through the online interactive system; you will need to complete the required sections and upload any required documents. The main section will have a limit of 10,000 characters, approximately 3 pages, and should include the information below (no figures/graphics or images are allowed):

- Brief project description, including methodology
- Specific aims of the project
- Innovation/novelty of the project
- Project team
- Plan for data sharing

For U.S. entities, the LOI materials will include proof of your organization's not-for-profit status and a W9 signed and dated by the signing official. Non-US entities must provide a W8-BEN-E signed and dated by the signing official. **Your LOI will not be accepted without these documents.** Current awardees of Alzheimer's Association are eligible provided current funded grant does not overlap with this proposal.

Evaluation of LOIs:

All LOIs will be evaluated prior to invitation for a full proposal. Only LOIs that meet program specific guidelines and meet review criteria, including the goals of the ADSF call, will be invited to submit full applications. LOIs will be reviewed by a panel of experts with special attention to:

1. Demonstrable innovation/novelty of the proposed project (especially in the context of the PI/PIs and team recent work)
2. Alignment with the research priorities of the RFA
3. Impact of project on AD research
4. Evidence of methodological rigor that address the research question(s) being proposed
5. While not required, priority will be given to studies that leverage interdisciplinary and/or inter-institutional teams to accomplish the proposed project in a way no one group would be able to do independently.

Feedback is not provided for LOIs that are not invited to submit a full application.

Submitting a Full Application:

For those invited to submit a full application, additional materials will be required. Templates and instructions will be provided after LOI approval.

Full applications will include:

- Executive Summary (1 page)
- Background/ Rationale (1 page): should include background and clearly defined hypothesis and/or rationale addressing why strategy is expected to be fruitful. This should also note the specific aims.
- Work Plan (up to 5 pages): should include goals/specific aims, methods and project plan and should be organized in alignment with the milestones as outlined in the application.
- Project Milestones: workplan should be separated into one-year intervals with specific milestones to be accomplished within that timeframe. Milestones should align with the overall project goals and be designed for easy progress evaluation and for clear

determination on whether or not milestones have been met. For each milestone, indicate the relevant Project Aim. (No upload required)

- Principal Investigator(s) and Key Personnel Curriculum Vitae or Biosketch (no more than 5 pages per person); there is no limit on the number of CVs to be included
- Available Resources and Budget Justification (2 pages):
 - Expenses that will not be allowed under this award include: tuition for full degree programs, rent for laboratory/office space, construction or renovation costs, liability insurance, networking and communication fees, and any facilities fees and laboratory/supply costs not directly relevant to the project. If awarded, a full budget of planned expenses will be required.
 - Include a list of tools/models available (if appropriate, list critical tools and models to be used or needed in the course of the research)No indirect costs will be allowed. Budget should be broken down in 1year increments and align with project milestones.
- Data sharing plan (1page): it is expected that data generated through this funding mechanism will include a robust plan for sharing data as well as appropriate included budget to accommodate this plan. Data sharing is a key component of the application and will be considered in the review and evaluation. Information on timelines, feasibility and the platform(s) and/or mechanisms of sharing should be included. Failure to share data appropriately may prevent investigators from being eligible for future funding.
- Citations/References (1 page): Use the reference style that is most common in the major journal(s)
- W9/W8 Documentation

Deadlines and Award Timeline:

Key Dates for this program include:

- Letter of Intent Launch..... January 12 on proposalcentral.com
- Letter of Intent Deadline..... February 24 at 5:00 pm Eastern Time (No Exceptions)
- Application Deadline.....May 3 at 5:00 pm Eastern Time (No Exceptions)
- Application Review.....Throughout May and June
- Award Notifications.....By July 15

LOIs will be accepted through 5:00 PM EST February 24. Letters of Intent will not be accepted after this date. **No exceptions will be made.**

All LOIs must be completed online at <https://proposalcentral.com>. No hard copies or emails will be accepted.

For those invited to submit a full application, the full application must be received by 5:00 PM EST, May 3, 2022. Applications will not be accepted after this date. **No exceptions will be made.** No hard copies or emails will be accepted.

Award announcements will be made by July 15, 2022.

For More Information: Contact grantsapp@alz.org

Additional Details

It is the responsibility of the applicant to ensure and verify that:

- The application is submitted by the receipt date/time deadline. Once submitted, you will receive a confirmation email from proposalcentral.com that your application was successfully submitted. If you do not receive a confirmation, click the Proposals tab and

under the “Status” column, make sure it says Submitted and not In Progress, which indicates you have not yet submitted your application.

- The application is complete and accurate before submission. Only a single copy of an application will be accepted. We do not require signatures at the time of submission. The signature page provided is for use should your institution/organization require signatures; we do not override any institutional policies and/or procedures. Please do not submit the signature page with your application.
- Revisions, additional materials, and/or reference, manuscripts, appendices, etc., are not allowed and, if attached, will be removed from your application. Up to 3 letters of support (no more than 2 pages each) are allowed. Additional letters will be removed.

Multiple and Overlapping Submissions:

Multiple submissions from one applicant is not permitted. This includes multiple submissions from the same group and/or collaborators.

Allowable costs under this award include:

- Small pieces of laboratory equipment and laboratory supplies (**purchases over \$10,000 require prior approval, even if included in the project proposal budget**).
- Computer software if used strictly for data collection and/or analysis.
- Salary for the principal investigator, scientific (including postdoctoral fellows) and technical staff (including modest administrative support).
- Research supplies needed for the proposed studies.
- Support for travel to scientific and professional meetings, not to exceed \$1,000 in any given year.
- Open access publications fees are appropriate and reasonable for the project budget.

Not allowable as direct costs under this award include:

- Computer hardware or standard software (e.g., Microsoft Office).
- Construction or renovation costs.
- Tuition.
- Rent for laboratory/office space.
- Salary and/or compensation for Alzheimer’s Association staff or for current members of the Alzheimer’s Association Medical and Scientific Advisory Group (MSAG), International Research Grant Program (IRGP) Council.
- No indirect costs are allowed.

Additional Information

Ethical/regulatory approvals and reporting requirements

If awarded for funding, the Alzheimer’s Association require that any necessary ethical and/or regulatory approvals are kept current, and may require specific reporting throughout the lifetime of the award. This includes, but is not limited to, the following:

Human Subject Assurances

Human subject assurances are not required at the time of application. Investigators have up to 90 days after receipt of their award notification to submit these documents. However, the Alzheimer’s Association encourages investigators to initiate their certification applications on a schedule that recognizes that approvals at many institutions can take more than 90 days. We will accept only certifications that apply specifically to the funded project and must include the name of the awardee. An award letter will not be issued unless the appropriate certifications are in place and include the name of the awardee within the 90 days from award notification. The same applies for animal ethical approvals, if applicable.

Annual Scientific and Financial Reports

Interim Scientific and Financial Reports must be submitted at the end of each reporting period as long as the grant remains active. Final Scientific and Financial Reports must be filed within 90 days of the grant's end date. All reports must be submitted electronically via proposalcentral.com. The Financial Report must be approved and signed by someone with financial authority in the Office of Research and Sponsored Programs at the recipient's institution.

Data Sharing:

The ADSF expects and requires timely sharing, based on the following principles:

- Make useful datasets and supporting information available to the broader research community every 12 months, at minimum, through an appropriate data sharing platform and other repositories, noting that not all experimental datasets are useful at early or intermediate stages of generation, exceptions may be made on a case-by-case basis if the ADSF agrees that the data are not yet ready to be shared.
- Use a streamlined data access process for the data sharing platform to allow high-throughput management of data access request approvals; make novel tools and research reagents (including, but not limited to, research models, cell lines, plasmids, viral vectors, antibodies, code/analysis methods, etc.) available as quickly as possible to academic and industry researchers either directly, or preferably through an appropriate and accessible distribution platform (e.g. Jackson Laboratory, Addgene, and GitHub) with minimal costs and restrictions.
- Whenever possible, avoid use of reagents, tools, samples, or data that cannot be easily shared; pre-approval for use of animal models that cannot be freely shared is required.
- Rapidly bring research findings and results to the research community through presentations at meetings and open-access publication (e.g. preprint servers, open access journals, or making papers available on the investigator's website).

The research team's clear commitment to sharing in a timely manner will be part of both application and project evaluation throughout the project duration.

Recruitment Efforts for Clinical Studies:

Projects involving human participants must address the appropriate inclusion or exclusion of individuals in the proposed research project and describe recruitment efforts to represent the community in which the study is planned or being conducted. Prior to distribution of funding, the researcher must provide a description of their recruitment plan; including an outline describing how their recruitment efforts will ensure diversity in their participants (see <https://www.nimhd.nih.gov/about/overview/> for NIH operationalization). Recruitment efforts should focus on diversity within key target groups, including a diverse representation of, but not limited to: sex, gender identity, sexual orientation, socioeconomic status, race, and ethnicity. This will be tracked throughout the duration of the grant and continued funding is contingent on applications addressing these goals.

Financial Responsibility:

Funding is awarded to the institution and/or organization, not to the individual principal investigator. The principal investigator or a first-degree relative cannot be listed as the signing official or financial officer, or have checks sent to their attention if awarded.

Appeals of Scientific Peer Review:

To maintain a fair and rigorous review system, the Alzheimer's Association have a process for appeal of funding decisions. Appeals will be not be considered for the letter of intent stage. Regarding applications, an appeal is intended to address extraordinary circumstances. Appropriate reasons for initiating an appeal might include:

- Evidence that a reviewer has an undeclared conflict of interest.
- An egregious error or misunderstanding in the review process.
- Active malfeasance or demonstrable lack of due diligence.

The appeal process is not intended to provide a mechanism for routine protest of failure to receive a grant. It is anticipated that funding through ABA Grant Program will be extremely competitive and is limited by availability of funds.

If an applicant believes an extraordinary circumstance has contributed to failure to receive funding, the principal investigator may send a two-page, double-spaced formal letter of appeal (Word document) to grantsappeals@alz.org. Any supporting documents included must be submitted as a PDF. **Appeals must be submitted within 2 weeks from the date your application outcome notification is sent.** Notification of action on the appeal will be made via email, usually within 90 days of the appeal deadline.

Nondiscrimination and Harassment Statement:

Alzheimer's Association is committed to providing an environment free from harassment and discrimination. Alzheimer's Association strictly prohibits harassment and discrimination based on race; creed; color; religion; sex; sexual orientation; national origin; ancestry; age; Veteran status; citizenship status; marital status; physical or mental disabilities; pregnancy, gender identity or expression (including transgender status); genetic information; and any other characteristic protected by federal, state or local law.