Sample Application for Small Business Funding

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Application Number: 1 R42 AG049562-01

Principal Investigators (Listed Alphabetically):
SOTO, CLAUDIO PHD
VOLLRATH, BEN (Contact)

Applicant Organization: AMPRION, INC.

Review Group: **ZRG1 ETTN-M (11)**
Center for Scientific Review Special Emphasis Panel
Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders

Meeting Date: **06/23/2014**   *RFA/PA:*   **PA14-072**
Council: **OCT 2014**   *PCC:*   **3CCDPKT**
Requested Start: **09/01/2014**

Project Title: **Blood-based diagnostics for Alzheimer's Disease**

SRG Action: Impact Score: 27
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: E4-Human subjects involved - Exemption #4 designated
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	████	████
2	████	████
3	████	████
TOTAL	████	████

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R42AG049562-01 Vollrath, Ben

RESUME AND SUMMARY OF DISCUSSION: This Fast Track STTR application proposes to develop a specific, blood-based biomarker to detect misfolded Aβ oligomers in the plasma from Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) patients, using the protein misfolding cyclic amplification (PMCA) technology in transgenic mouse model of AD. There is an urgent need for developing specific and sensitive biomarkers for early diagnosis and prediction of AD. The panel recognized several strengths of this application including the substantial expertise of the investigators in development of the PMCA technology, the novelty of targeting Aβ oligomers, based on the rationale that the presence of oligomers in blood may be early indicators of AD, the supportive preliminary results, and the thorough description of the milestones in the proposed Phase I and of the commercialization plan. A few minor weaknesses were also noted, such as the lack of samples from other type of dementia, the uncertainty regarding regulatory discussion with FDA, and a concern whether the proposed method is capable of detecting Aβ oligomers in humans. Overall, majority of the panel members viewed the strengths as outweighing the weaknesses and expressed high enthusiasm for the technology that could bring about a specific and sensitive biomarker for AD.

DESCRIPTION (provided by applicant): This proposal is for a phase I/II fast track project for the STTR program with the main goal to develop a blood test for Alzheimer's disease (AD) diagnosis. AD is the most common dementia in the elderly population and one of the leading causes of death in the developed world. One of the main problems in AD is the lack of an early, sensitive and objective laboratory diagnosis to identify individuals that will develop the disease before substantial brain damage. Compelling evidences point that the hallmark event in AD is the misfolding, aggregation and brain accumulation of amyloid-beta (Aβ) protein. Aβ aggregation follows a seeding-nucleation mechanism and involves several intermediates, including soluble oligomers and protofibrils. Recent evidence has shown that Aβ oligomers are circulating in biological fluids and these structures appear to be key for inducing brain degeneration in AD. Our working hypothesis is that detection of misfolded Aβ oligomers circulating in blood may be the basis for an early biochemical diagnosis for AD. Our approach is to use the functional property of misfolded oligomers of being capable to catalyze the polymerization of the monomeric protein as a way to detect them. We have recently invented the protein misfolding cyclic amplification (PMCA), which represent a platform technology to detect very small quantities of seeding-competent misfolded oligomeric proteins associated with various protein misfolding diseases. Currently, PMCA has been adapted to detect misfolded prion protein implicated in prion diseases in various biological fluids, including blood and urine and more recently soluble Aβ oligomers in cerebrospinal fluid of AD patients. The major goal of this project is to adapt the PMCA technology for specific and highly sensitive detection of misfolded Aβ oligomers in human blood, perform studies of specificity and sensitivity using large number of samples and evaluate the utility of Aβ-PMCA for pre-clinical identification of people in the way to develop AD. The results generated in this project may lead to the first biochemical test for blood-based diagnosis of AD. The studies included in this project will constitute the basis for regulatory approval of the test that Amprion will commercialize.

PUBLIC HEALTH RELEVANCE: Development of a blood-based biochemical assay for the sensitive, early and non-invasive diagnosis of Alzheimer's disease is a top medical priority, essential to permit efficient treatment of this devastating disease. This project proposes to develop the protein misfolding cyclic amplification (PMCA) technology to detect with high sensitivity and specificity amyloid-beta oligomers which are considered the key molecules responsible for neurodegeneration in AD. In this project we have put together the relevant technical and business expertise and secured the availability to key samples to permit the successful development, validation and approval of the test.

CRITIQUE 1:

Significance: 3
Investigator(s): 3
Innovation: 3
Approach: 3
Environment: 3

Overall Impact This proposal seeks to develop a "PCR"-like amplification system of misfolded proteins in blood as a potential biomarker of AD. Repeated cycles of elongation and sonication (to generate seeds) will permit sensitive detection of misfolded proteins such as Abeta/amyloid. Seeds may be captured by antibody as an initial step to remove contaminants and confounding proteins in blood. Considering that this is a fast-track application, the investigators should have already met with regulatory agencies to discuss required criteria for approval of a new diagnostic.

1. Significance:

Strengths

- A biomarker of AD would be useful for screening, diagnosis, prognosis, and evaluation of new therapies.

Weaknesses

- None.

2. Investigator(s):

Strengths

- Excellent and experienced PI and investigative team.

Weaknesses

- None

3. Innovation:

Strengths

- The proposal is innovative in developing a novel protein amplification system to detect misfolded Abeta/amyloid protein. A similar strategy may be developed for prion protein, alpha-synuclein, etc.

Weaknesses

- None noted

4. Approach:

Strengths

- The specific aims are focused and feasible.
- The rational is good and the preliminary data supportive of the aims.
- The approach may be exploited to sensitively detect other misfolded proteins in biologic samples.

Weaknesses

- For a fast-track proposal, more preliminary data would be supportive – for example, with samples from transgenic AD mice.
- Similarly, discussions with regulatory officials for approval requirements of a new diagnostic should begin early to guide the experimental plan.

5. Environment:

Strengths

- Excellent research environment.

Weaknesses

- none

Phase II (Type 2 R42 and Type 2 R44 applications):

Not Applicable

Fast Track (Type 1 R42 and Type 1 R44 applications):

Acceptable

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C3A - No Children Included, Acceptable [NIH defines a child as anyone under the age of 21]

Vertebrate Animals:

Acceptable

Biohazards:

Not Applicable (No Biohazards)

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Significance: 3
Investigator(s): 2
Innovation: 2
Approach: 3
Environment: 3

Overall Impact This is an interesting and promising study by an established investigator. The application is to detect misfolded Aβ oligomers by Aβ-PMCA in the plasma from AD and MCI patients. The identification of Aβ oligomers in the blood is important as they are related AD progression. The company seems to have expertise in detecting Aβ oligomers in the brain as well as in body fluids, i.e. CSF and the plasma from AD and MCI patients, which are novel. The PI has assembled a strong and outstanding team, including the support from the established and well known scholar, Dr. Claudio Soto from University of Texas Health Sciences at Houston, who will provide major technical support as well as clinical samples. There are some concerns: (1) the Aim 1 seems still need to further optimize the experimental conditions to increase the sensitivity for detecting Aβ oligomers in AD blood. Hopefully it will turn out clean results which will be able to detect low levels of Aβ oligomers from AD blood, (2) there are no imaging parameters to correlate with the plasma Aβ oligomers, which should be important to validate the biomarkers, and (3) it would be much stronger to have a sample quality control protocol shared among the 4 independent clinical centers as well as ▬▬▬▬▬▬Inc.

1. Significance:

Strengths

- Discovery of new misfolded Aβ oligomers by Aβ-PMCA in the blood from AD and MCI patients compared to normal controls is desperately needed in the clinical as there is no effective biomarker to effectively screen initial patients with cognitive decline.

- This is an interesting and promising Fast Track application from an established well-known PI as well as co-PIs. The application is to detect misfolded Aβ oligomers by Aβ-PMCA in the plasma from AD and MCI patients. The identification of misfolded Aβ oligomers may be related progress of the disease. The company seems to have strong expertise in detecting misfolded Aβ oligomers from the blood of AD and MCI patients.

- The company has outstanding expertise in detecting misfolded Aβ oligomers in the blood. The technology and methods are solid and the results are appealing. If successfully accomplish this project, it would be important and critical in the field and may provide effective and reliable and inexpensive assay for initiate screening patients with cognitive decline, which is highly needed in the market.

Weaknesses

- Since Aβ protein aggregation or Aβ oligomers can be found not only in pure AD, but may be other neurodegenerative disorders, it may be a good idea to include patients with some other types of neurodegenerative disorders.

- There is no imaging parameter to be used correlate with the plasma Aβ oligomers, which is critical for validating the biomarkers.

2. Investigator(s):

Strengths

- This is a multiple PI project lead by Dr. Vallrath, CEO of Amprion Inc and Dr. Soto, Professor of University of Texas Health Science Center at Houston. It has assembled a strong team to measure misfolded Aβ oligomers in the blood of AD, MCI and normal cohorts.

- ███
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███
████████████████████████████

Weaknesses

- There are no supporting letters from ███████████████████ although they are responsible to provide AD plasma samples from ██████████████ to this project, respectively

3. Innovation:

Strengths

- Identification and large scale screening of misfolded Aβ oligomers the plasma from AD and MCI and controls is relative novel although misfolded Aβ oligomers in AD have been published by several independent groups.

Weaknesses

- None

4. Approach:

Strengths

- Identification of misfolded Aβ oligomers in the brain and the CSF has been done in AD. Measuring misfolded Aβ oligomers in the blood does have good advantages and is significant.

- There are three specific aims: Aim 1 is to optimize the experimental conditions for detection of Aβ oligomers in AD blood. Aim 2 to evaluate the sensitivity and specificity in large number of plasma samples from AD patients. Aim 3 is study the usefulness of Aβ-PMCA to monitor disease progression and for pre-clinical diagnosis of AD. The aims seem logically connected. The experiments in the Aim 1 are pretty much completed. It seems to be a good assay to continue.

Weaknesses

- Although the project will use samples from several independent centers, it would be better to have a table to show how samples (AD, MCI and controls) are selected from which medical center, instead of just listing total 500-700 AD and 2000-2200 control samples. Particularly, the control cohorts include age-matched and young controls as well as controls of neurodegenerative diseases and non-neurodegenerative diseases.

- It would be stronger to include some "golden standards" such as CSF tau or Aβ 42 or imaging to validate the midfolded Aβ oligomers.

5. Environment:

Strengths

- The company has productive environment with scientific motivation.

Weaknesses

- None

Fast Track (Type 1 R42 and Type 1 R44 applications):

Acceptable

- The company has expertise to measure misfolded Ab oligomers by Aβ-PMCA in the plasma of patients. Moreover, the company has definitive goals and commercial plans. Once these potential biomarkers are truly effective for AD early diagnosis, it would have great potential in the market with significant commercial value.

Vertebrate Animals:

NO, animal welfare concerns or incomplete

- two types of APP transgenic mice (APP and APP/PS1) will be obtained from Taconic. Total of 200 mice will be used for experiments in Aim3. However, no justification of sex and number were included in the protocol.

Budget and Period of Support:

Recommend as requested

CRITIQUE 3:

Significance: 1
Investigator(s): 2
Innovation: 1
Approach: 1
Environment: 2

Overall Impact This new STTR Fast-Track application is proposing to develop a blood test for Alzheimer disease using protein misfolding cyclic amplification to detect misfolded abeta oligomers. The rationale of focusing on abeta oligomers is based on the notion that oligomers present in blood may be early indicators of AD. There is a need for an AD blood test and if successful in development such a test would have high impact both in terms of diagnosis and treatment. This application has much strength. Development of an AD blood test focused on abeta oligomers has high significance. The PMCA technology developed by Soto and colleagues is innovative and provides specificity that lacking in other assays. The research team is well-qualified, and Dr. Soto is an internationally recognized leader in AD. Preliminary data showing seeding activity in human CSF samples from controls and AD patients by AbetaPMCA demonstrates the sensitivity and specificity of the assay and data indicated that AD samples could be differentiated from patients with other neurodegenerative diseases. Moreover, similar results were observed in plasma. However, an important issue identified by the PIs is that due to the low levels of abeta in blood and interfering compounds and additional procedure is needed involving use of ELISA plates coated with various antibodies specific for the sequence of abeta or the conformation of abeta oligomers. This procedure captures abeta species from plasma and removes potential interfering compounds and the material is then used in the PMCA assay. This extra procedure does present potential problems (e.g., antibody quality and specificity) but a well-described assay optimization plan is presented. There are clearly-defined milestones for Phase 1 and based on the preliminary data in support of the proposed experiments feasibility for obtaining the milestones is

high. A comprehensive commercialization plan is included. The potential impact of this project high and it could be a major advancement in diagnosing AD.

Fast Track (Type 1 R42 and Type 1 R44 applications):

Acceptable

- Commercialization plan is well-described.

Vertebrate Animals:

Acceptable

- NIH 5 issues addressed.

Resource Sharing Plans:

Unacceptable

- No plan

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

VERTEBRATE ANIMAL (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders
ZRG1 ETTN-M (11) B
June 23, 2014 - June 24, 2014

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.