SUMMARY STATEMENT

Principal Investigators (Listed Alphabetically):

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Applicant Organization: STARWISE THERAPEUTICS, LLC

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

Meeting Date: 06/29/2017  RFA/PA: PAS17-065
Council: AUG 2017  PCC: 3CCDDRL
Requested Start: 01/01/2018

Project Title: Study of the New HDAC6i SW-100 as a Treatment for Alzheimer's Disease and Other Tauopathies
SRG Action: Impact Score:18
Next Steps: Visit https://grants.nih.gov/grants,next_steps.htm
Human Subjects: 10-No human subjects involved
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted

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<th>Project Year</th>
<th>Direct Costs Requested</th>
<th>Estimated Total Cost</th>
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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.
RESUME AND SUMMARY OF DISCUSSION: This outstanding Phase I STTR application proposes to test the therapeutic potential of SW100 for rescuing the synaptic degeneration and tauopathy underlying Alzheimer's Disease (AD). SW100 is an inhibitor for the histone deacetylase 6 (HDAC6) which, amongst other targets, promotes deacetylation of tubulin, HSP90 and tau. The study hypothesizes that increases in acetylated forms (Ac) of these proteins will: slow synaptic degeneration (mediated by stabilization of microtubules containing Ac Tubulin), increase proteasomal degradation of tau (by Ac HSP90) and perhaps directly inhibit aggregation of tau (by Ac tau). The application addresses an unmet need for treating tauopathies. Moreover, an improved HDAC6 inhibitor will have broader therapeutic application compared to the limited therapeutic potential of the currently available HDAC6 inhibitor, Tubastatin A (TA). Therefore, the high significance and potential impact are notable strengths of the application. The scientific premise is based on the rescue of tauopathies due to inhibition of HDAC6 activity and it is strongly supported by compelling preliminary data. In a comparative analysis between TA and SW100, their data show that SW100 displays similar selectivity, provides better rescue for tau phenotype in Tg4510 mouse models and displays both higher affinity, longer half-life and increased brain permeability. The research team is excellent. Dr. Kozikowski has expertise in medicinal chemistry and drug discovery, while USF collaborators will bring expertise to studies with animal models for AD. However, reviewers noted a couple of minor issues, such as a lack of SBIR/STTR experience within the team. Also, SW100 will be orally administered and the taste of the drug may be a challenge. In summary, the panel was highly enthusiastic during the discussion of the application, which was considered excellent in all evaluated aspects.

DESCRIPTION (provided by applicant): Alzheimer's and other tauopathies are medical problems growing to historical proportions that threaten the long term viability of medical care systems worldwide. Alzheimer's costs today are 1.2% of the US GDP, and growing as the population ages. Effective disease-modifying treatments have yet to be developed. A number of drugs in clinical testing target amyloid, but very few have been developed to target tau. We expect that like heart disease, cancer and HIV, effective Alzheimer's management will require combination treatment using multiple therapeutic modalities. Prior work by our research team has determined that part of the tau phenotype can be reduced using a histone deacetylase 6 (HDAC6) inhibitor, Tubastatin A (TA). This involved treatment of Tg4510 mice that develop tau deposits by 3 mo and forebrain atrophy by 6 mo of age. We treated mice from 5 to 7 mo and found improved behavioral performance and reduced total tau deposition. However, other components of the tau phenotype in this model were not significantly impacted. Here we propose to test whether an improved HDAC6 inhibitor, SW-100, can more completely rescue the tau phenotype in this mouse. SW-100 has a higher affinity, slightly longer half-life and substantially increased brain permeability than TA. SW-100 is a new HDAC6 inhibitor with selectivity similar to that of TA, but increased CNS penetration. SW-100 further lacks mutagenicity in the Ames test (in which TA was positive). Thus, we wish to evaluate if this compound, as well as a newly designed back-up analog, can more fully reverse the phenotype of the Tg4510 mouse by pursuing the three aims below. Aim 1. Prepare 4 new analogs of SW-100 as potential back-up compounds, and conduct HDAC isozyme testing, tubulin acetylation assays, and ADMET assays. Advance the best of these to animal studies in Aim 2. Aim 2. Conduct a dose range finding study of SW-100 and the best back-up compound from Aim 1 to identify a dose in mouse chow that causes maximal CNS impact and is well tolerated. Aim 3. Test SW-100 and the back-up analog from Aim 1 in Tg4510 mice starting at two ages to ascertain the extent to which these new chemical entities can retard the development of the tau phenotype, and whether benefits can be observed even after tau deposition has started. Assessments will thus be made of drug effects on cognition, histological tau deposition, and neurochemical tau accumulation. Any positive effects observed using these drugs after tau deposition would suggest benefit for people who already have dementia. There are several potential mechanisms by which HDAC6 may produce benefits. First, it may lead to more stable microtubules and enhance axonal transport through increased tubulin acetylation. Second, it may increase tau degradation in the proteasome through increased HSP90
acetylation. Third, it may inhibit tau aggregation through increased tau acetylation. We will monitor acetylation of each of these HDAC6 substrates to begin understanding the mechanism(s) most responsible for benefiting the tau phenotype in this model.

PUBLIC HEALTH RELEVANCE: There are no effective treatments for the accumulation of abnormal proteins, loss of memory and brain shrinkage that occur in Alzheimer's disease and other tauopathy-related neurodegenerative diseases. This project will further establish the ability of brain penetrant HDAC6 inhibitors to serve as potential AD therapies using a relevant mouse model. Success in this project will provide further validation of this therapeutic approach and lay a strong foundation for moving such NCEs to the clinic.

CRITIQUE 1

Significance: 1
Investigator(s): 2
Innovation: 3
Approach: 2
Environment: 3

Overall Impact: Proposal investigates the question of whether excessive deacetylation of tubulin and other proteins make a major contribution to the synaptic degeneration underlying the progressive dementia in AD and other tauopathies. HDAC6 removes acetyl groups covalently attached to lysine residues in tubulin and HSP90. Several factors drive scores in a positive direction. Evidence provided for partial rescue and reduced total tau by tubastatin in 6 month old Tg4510 mice with substantial tau pathology. However, tubastatin is Ames pos and a poor ADMET profile for a druggable molecule. This study proposes to test whether another HDAC6 inhibitor, SW-100, and a related analog to be identified might achieve better rescue of the Tg4510 phenotype. SW-100 is Ames neg and has better pk profile including much better brain penetration, better HDAC inhibition and a longer half-life. Scientific premise and rigor both high and the investigative team and environment strong. The study is well designed to show if a next gen HDAC6 inhibitor can block synaptic degeneration. If so, this work in an aggressive model of tau accumulation will indicate when treatment is most likely to achieve a positive outcome. Success could stimulate pharma to strongly consider clinical trials of HDAC6i.

1. Significance:

Strengths

- Increasing tubulin acetylation via HDAC6i could slow synaptic degeneration by stabilizing microtubule function and increase axonal transport.
- Possible MOAs include increasing tau degradation in the proteasome through increased HSP-90 acetylation and/or directly reduce tau aggregation through increased microtubule acetylation.
- Positive finding could open new directions for AD treatments and strengthen the investment potential for clinical testing of next-gen HDAC6 inhibitors.

Weaknesses

- None noted.

2. Investigator(s):
Strengths
- PI has extensive experience in medicinal chemistry and drug discovery with strong current interest in epigenetics, esp. inhibitors of HDAC6 for treating host of diseases.
- He has founded several companies for further development of lead compounds identified by his research.
- Collaborators at USF have deep expertise in evaluating behavioral and histopathological phenotypes in animal models of AD.

Weaknesses
- Neither the PI nor co-investigators provide evidence of prior SBIR activity for this or any other project.
- Proposal fails to state a clear vision for their STTR program, other than advanced work would be conducted by application for Phase II funding.

3. Innovation:
Strengths
- Increasing tubulin acetylation could slow synaptic degeneration by stabilizing microtubule function and increase axonal transport.
- In past decade, numerous studies have used AD mouse models to test whether HDAC6 inhibition can block synaptic degeneration. Though “promising” still inconclusive and require further study.
- Thus, far lack of strong results from patients trials showing whether clinical benefits can be achieved by HDAC6 inhibition in MCI or AD.

Weaknesses
- None noted.

4. Approach:
Strengths
- The approach has strong scientific rigor.
- Likelihood of useful outcome improved by starting prior to the onset of tau deposition and through the time of massive accumulation.
- Monitor acetylation of HDAC6 substrates to understand the mechanism(s) most likely responsible for rescuing the tau phenotype in the Tg4510m mouse.
- Increasing tubulin acetylation could slow synaptic degeneration by stabilizing microtubule function and increase axonal transport.

Weaknesses
- Questionable whether analogs to SW-100 will have favorable profiles. If not, entire study would focus only on SW-100.

5. Environment:
Strengths
- SW-100 were initially developed at UI-Chicago and licensed to the PI’s SBC (Star Therapeutics). It’s likely similar arrangement will exist for any other HDAC6 inhibitors developed in this project.
Weaknesses

- PI is “planning to” lease space adjacent to Northwestern University in Chicago for medicinal chemistry studies, ostensibly if this and/or other fund-raising activities pan out.

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

Direct Phase II (Type 1 R44 applications See Face Page):

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

 Protections for Human Subjects:
 Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Inclusion of Women, Minorities and Children:
- Sex/Gender:
- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion of Children under 18:

Vertebrate Animals:

Biohazards:

Authentication of Key Biological and/or Chemical Resources:

Budget and Period of Support:
Recommended budget modifications or possible overlap identified:

CRITIQUE 2

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

Overall Impact: Effective disease-modifying treatments for tauopathies such as AD have yet to be developed. Preliminary work by the applicant in relevant mouse models has revealed that some of the tau phenotype can be reduced using commercially available inhibitors of histone deacetylase (HDAC) 6, such as tubacin and tubastatin, though these compounds have properties to make them not useful therapeutically. With NIH funding Dr Kozikowski has derived a larger number of novel entities based on tubastatin, some of which are selective HDAC6 inhibitors, and provides preliminary data showing that
SW-100 can more completely rescue the tau phenotype, has higher affinity, longer half-life and substantially increased brain permeability. In this Phase 1 application StarWise and a group at USF propose to evaluate SW-100, together with 4 newly designed back-up analogs, in a relevant mouse model (Tg4510) at two ages, to see whether development of the tau phenotype can be delayed and/or benefit can occur even after tau deposition begins. This is a well-thought out and timely application. Lead compounds exist and new entities will be readily produced. The strength of the application is the synthetic chemistry track record of Dr Kozikowski and the ongoing collaboration with the group at USF. Minor concerns include the potential variability of drug dosing when presented via diet, lack of indication of testing efficacy in both sexes, and the wide scope of the work which could be constrained by focusing on efficacy at the expense of mechanism.

1. Significance:
**Strengths**
- Unmet clinical need in tauopathies
- Broad therapeutic application of HDAC6 inhibitors
- Strong premise as indicated by effectiveness of commercially available selective inhibitors
- Plausible mechanisms of action
- HDAC6 inhibitors may not only delay onset but also reduce burden of tauopathy
- IP of new compounds with StarWise

**Weaknesses**
- None noted.

2. Investigator(s):
**Strengths**
- StarWise founder and CEO Dr Kozikowski is an outstanding synthetic chemist with a long history of NIH funding, albeit not yet through STTR/SBIR mechanisms
- USF collaboration for in vivo screening of novel compounds is long standing

**Weaknesses**
- None noted.

3. Innovation:
**Strengths**
- Novel therapeutic entities in addition to SW-100
- Properties of compounds make them druggable

**Weaknesses**
- None noted.

4. Approach:
**Strengths**
- Strong preliminary data
- Ongoing process to derive new analogs
- Appropriate animal model and tests of cognition
Considering actions that both delay and/or decrease pathology
Simple outcome measure –effects on tau burden

Weaknesses
- Administration via diet may be problematically variable, whereas gavage should be non-stressful and dosing is more certain
- Rigor not specifically addressed
- Needs to focus on efficacy >> potential mechanisms in Phase 1

5. Environment:

Strengths
- Continuing and complimentary collaboration between Dr Kozikowski and USF

Weaknesses
- None noted.

Phase II (Type 2 R42 and Type 2 R44 applications):
Not Applicable

Direct Phase II (Type 1 R44 applications See Face Page):
Not Applicable

Fast Track (Type 1 R42 and Type 1 R44 applications):
Not Applicable

Protections for Human Subjects:
Not Applicable (No Human Subjects)

Inclusion of Women, Minorities and Children:
- Sex/Gender:
- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion of Children under 18:

Vertebrate Animals:
YES, all four points addressed
- SABV not addressed

Biohazards:
Not Applicable (No Biohazards)
**Resource Sharing Plans:**
Acceptable

**Authentication of Key Biological and/or Chemical Resources:**
Acceptable

**Budget and Period of Support:**
Recommend as Requested

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**CRITIQUE 3**

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

**Overall Impact:** Alzheimer’s and neurodegenerative tauopathies represent one of the largest unmet medical needs in elderly population. Although the idea of using HADC inhibitor for the treatment of AD has been around for a while, the field has been hampered by the lack of selective and brain penetrant HDAC inhibitors. The proposed study will test a highly selective HDAC6 inhibitor SW100. The compound displays an impressive b/p ratio of 2.5 and very favored pharmacological profile. The experiments were well thought out and will be carried out at labs with extensive experience of tau transgenic mice and behavior assessment. HDAC6 inhibitor would be a high-risk approach with still a lot of biology needs to be sort out. However, this study will provide important information on the validation of this target.

1. **Significance:**

**Strengths**
- Targeting tauopathy will have a significant impact on the treatment of AD and related neurodegenerative diseases.

**Weaknesses**
- None noted.

2. **Investigator(s):**

**Strengths**
- This is a great team with complementary expertise in chemistry and biology, industry and academics.

**Weaknesses**
- None noted.

3. **Innovation:**

**Strengths**
• Although many HDAC inhibitors have been described in literature, testing a brain penetrable HDAC6 selective compound represent a new approach to tauopathies.

Weaknesses
• None noted.

4. Approach:
Strengths
• The experimental designs were well thought out.
Weaknesses
• None noted.

5. Environment:
Strengths
• USF have excellent environment to conduct the efficacy studies in Tg4510 mice.
• StarWise is in an incubator space well equipped to support the proposed studies.
Weaknesses
• None noted.

Phase II (Type 2 R42 and Type 2 R44 applications):
Not Applicable

Direct Phase II (Type 1 R44 applications See Face Page):
Not Applicable

Fast Track (Type 1 R42 and Type 1 R44 applications):
Not Applicable

Protections for Human Subjects:
Not Applicable (No Human Subjects)

Inclusion of Women, Minorities and Children:
• Sex/Gender:
• Race/Ethnicity:
• For NIH-Defined Phase III trials, Plans for valid design and analysis:
• Inclusion/Exclusion of Children under 18:

Vertebrate Animals:
YES, all four points addressed

Biohazards:
Acceptable

Select Agents:
Acceptable

Resource Sharing Plans:
Acceptable

Authentication of Key Biological and/or Chemical Resources:
Acceptable

Budget and Period of Support:
Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS’ WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

VERTEBRATE ANIMALS: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R41 AG058283-01; PI Name: kozikowski, alan P.

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-A (11)
06/29/2017 - 06/30/2017

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

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