HARTY, R

SUMMARY STATEMENT

PROGRAM CONTACT: [redacted]

(Privileged Communication)

Release Date: **11/22/2020**
Revised Date:

Application Number: **2 R42 AI138630-03**
Formerly: **3R41AI138630-02**

Principal Investigator

HARTY, RONALD N

Applicant Organization: FOX CHASE CHEMICAL DIVERSITY CENTER, INC

Review Group: **ZRG1 BCMB-G (10)**
Center for Scientific Review Special Emphasis Panel
Small Business Applications: Drug Discovery and Development

Meeting Date: **11/16/2020**
Council: **JAN 2021**
Requested Start: **04/01/2021**

RFA/PA: **PA20-265**
PCC: **M55A B**

Project Title: **Development of Small Molecule Therapeutics Targeting Hemorrhagic Fever Viruses**

SRG Action: **Impact Score:** [redacted]
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Age: **7A-Only Adults, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
3	[redacted]	[redacted]
4		
5		
TOTAL	[redacted]	[redacted]

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.

2R42AI138630-03 HARTY, RONALD

RESUME AND SUMMARY OF DISCUSSION: A very strong and experienced in drug discovery group from the Fox Chase Chemical Diversity Center proposes to continue the development of small molecules for the treatment of hemorrhagic fever viruses. The significance of the proposed work is exceptionally high as effective therapies for emerging human RNA viruses are urgently needed. The Phase I portion of the project was very successful and yielded a lead series with promising properties, including in vivo proof-of-concept. There is a solid foundation for further optimization of drug-like properties and demonstration of in vivo efficacy. The overall approach is well-conceived, logically presented and sufficiently detailed; supplemental information shows that the lead molecule also blocks release of live infectious SARS-CoV-2 from infected human lung cells, which is consistent with the mechanism of action. Few minor weaknesses associated with the unclear 'new' scaffolds do not detract from the very high enthusiasm the panel expressed for this comprehensive and likely impactful proposal.

DESCRIPTION (provided by applicant): The ultimate goal of this Phase II application is to develop novel small molecule, broad-spectrum therapeutics against viral infections caused by filoviruses, arenaviruses, and other viruses that depend on the PPxY L-domain motif for egress and spread of infection. Some of these viruses, including Ebola (EBOV), Marburg (MARV), and Lassa fever (LAFV) viruses, are highly pathogenic and classified as Category A bioterror pathogens. We and others have determined that efficient budding of these emerging human pathogens depends on the subversion of host proteins, such as neural precursor cell expressed developmentally down-regulated protein 4 (Nedd4), by PPxY L-domains in the matrix proteins of these RNA viruses. The identification and development of small molecule inhibitors that interfere with these virus-host interactions should effectively block virus egress, disease progression, and transmission. In these efforts we have discovered several chemical series of small molecule inhibitors of the host Nedd4/virus PPxY complex important for viral egress which led to one analog possessing proof of concept in vivo activity in a Marburg virus challenged mouse model. As FDA approved therapeutic agents for the treatment of these most of these viral infections are not available, our identification of virus-host inhibitors that may prevent virus spread will fill a significant unmet need. Moreover, these inhibitors will be broad-spectrum, and therefore will likely be effective against newly emerging viruses as well as viral variants. As described below, we will use a rigorous multifaceted approach to identify, develop, and validate PPxY budding inhibitors identified in Phase I as potent, broad-spectrum antivirals. The goal of this Phase II STTR grant application is to optimize our lead inhibitors of VP40 PPxY-Nedd4 interactions to generate full- fledged predevelopment drug candidates ready for IND directed studies. This will be accomplished by combining the pharmaceutical and medicinal chemistry expertise of the scientists at the Fox Chase Chemical Diversity Center, Inc. (FCCDC) with the expertise and experience in the experimental aspects of antiviral therapy of the Harty Lab at the University of Pennsylvania. We will realize this goal by optimizing our existing series of inhibitors, exemplified by in vivo active FC-10696, for improved potency and oral drug properties (Aim 1), evaluating new compounds based on two potent series for their ability to specifically inhibit PPxY-Nedd4 interactions and subsequent VLP and surrogate virus egress (Aim 2), identifying compounds having suitable drug properties and selectivity using in vitro and in vivo ADMET evaluation (Aim 3), and evaluating compounds for their antiviral efficacy against authentic BSL-4 viruses in vitro and in vivo (Aim 4).

PUBLIC HEALTH RELEVANCE: There is an urgent need to develop antiviral therapy against emerging human RNA viruses that represent potential agents of bioterrorism (Ebola, Marburg, and Lassa fever). We have discovered small molecule compounds that disrupt budding and spread of live viruses; a process that is critical for virus dissemination and disease progression. Here, the Harty group at the University of Pennsylvania, experts in the antiviral technology of this proposal, have partnered

with the small business Fox Chase Chemical Diversity Center, Inc. to further develop these broad spectrum antiviral budding inhibitors by using medicinal chemistry, live virus budding assays, and live cell imaging techniques.

CRITIQUE 1

Significance: [redacted]
Investigator(s): [redacted]
Innovation: [redacted]
Approach: [redacted]
Environment: [redacted]

Overall Impact: The overall impact of this Phase II STTR proposal to develop effective therapies for RNA viruses caused by Marburg and Ebola, is very high. These are also rare diseases, and the investigators can benefit from that designation along with being eligible for the US neglected disease voucher program. The scientific rigor from the data obtained from the Phase I study is strong with the identification of two lead series of compounds and an advanced lead compound with very good potency. The strategy to block the viral-host interactions between the matrix protein PPxY and select host proteins for efficient virus egress (cellular budding) and spreading infection appears innovative. The strong premise of the project plan with the potential to identify a preclinical candidate that could lead to acute toxicity study phase of the pre-IND. The details of a screening cascade, target product profile and go no-go decisions, and a robust commercialization plan with options, provide confidence that this well rounded team can execute the current objectives and has the high potential to nominate a clinical candidate from this project. The resources lined up and the facilities that will be used to conduct the proposed studies and the strength of a world class team assembled around this project has made this a highly impactful proposal.

1. Significance:

Strengths

- There is an unmet need to develop effective therapeutics to protect immunologically naïve individuals form the RNA virus infections as the Marburg and Ebola viruses cause hemorrhagic diseases, which is a rare disease.
- Currently available vaccines are not a complete defense since they must be given pre-exposure.
- The therapeutic development program for these diseases is eligible for the US neglected disease voucher program.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- Excellent team of interdisciplinary scientists spanning computation chemistry, medicinal chemistry, virology, with extensive experience in drug discovery and development in Pharma.
- The team also has collaborated for the Phase I STTR grant and on other projects.

- Business Development expertise is included, which is essential for executing the commercialization strategy.

Weaknesses

- None noted.

3. Innovation:

Strengths

- Developing therapeutics to block viral-host interactions.
- Novel series of Nedd4:PPxY inhibitors targeting the virus-host interactions, of a conserved host:virus complex to develop broad spectrum antivirals to treat Marburg and other emerging RNA viruses.

Weaknesses

- None noted.

4. Approach:

Strengths

- Advanced lead compound has nanomolar potency with no potential Cy P450 3A4 activity and good metabolic stability.
- The proposed optimization of advanced lead FC-10696 to identify 2-3 compounds with improved aqueous solubility while continuing to improve their potency, TI, ADME, PK and safety properties specific criteria (screening cascade given), testing for potency and in vitro/in vivo evaluation of promising inhibitors against other RNA viruses is executable.
- The proposed work has the potential to develop improved analogs that inhibit RNA viral egress, due to inhibition of viral matrix protein PPxY interaction with cellular Nedd4.

Weaknesses

- As the Phase I grant is currently under a no-cost extension, it is not clear if the Phase II grant will be contingent on completing the proposed Phase I objectives.

5. Environment:

Strengths

- The facilities at the Texas Biomedical Research Institute, and the resources available at the CRO are adequate for executing the project.

Weaknesses

- None noted.

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

Acceptable

- The progress made from the Phase I study shows robust data with POC in vivo reduction of Marburg virus challenged mouse models.

- A clear product development plan with desired TPP and a robust commercialization plan options, with strong IP protection on composition of matter (issued).

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

Vertebrate Animals:

YES, all criteria 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

CRITIQUE 2

Significance: [redacted]
Investigator(s): [redacted]
Innovation: [redacted]
Approach: [redacted]
Environment: [redacted]

Overall Impact: This Phase II STTR application aims to develop novel small molecule, broad-spectrum antivirals against infections caused by filoviruses, arenaviruses, and other viruses that depend on the PPxY L-domain motif for virus egress and spread of infection [Marburg (MARV), Ebola (EBOV), and Lassa fever (LAFV)]. There are no commercially available small molecule therapeutics for these viral infections. The proposed anti-virals will fill a significant unmet need. The team has discovered several chemical series that block the host Nedd4/virus PPxY complex (critical regulator of viral transmission) and have identified an analog capable of blocking in vivo activity in a Marburg virus challenged mouse model as proof of concept. In the current proposal they will use their current lead inhibitor series, (e.g., FC-10696) to generate novel candidates for IND-enablement studies. To accomplish this goal,

scientists at the Fox Chase Chemical Diversity Center, Inc. (FCCDC; pharmaceutical and medicinal chemistry), the Harty Lab at the University of Pennsylvania (experimental aspects of antiviral therapy), and the lab of Olena Shtanko at Texas Biomedical Research Institute (evaluating compounds against live viruses in vitro and in vivo under BSL-4 conditions) have combined their considerable experience and expertise. The team of researchers has extensive expertise in relevant areas and are a major strength. Preliminary data provided in the proposal indicate that the approach is promising and newly designed leads exhibit antiviral activity. The overall approach is well conceived, is based on solid literature precedent, and addresses the major aspects required of a drug discovery program. In addition, supplements (Additional Materials) recently submitted by the PI suggest the compounds under development may have the potential to serve as broad-spectrum antivirals against emerging pathogens (e.g., SARS-Co-V-2). There is considerable enthusiasm for the project with only minor concerns.

1. Significance:

Strengths

- The project addresses an important, current need for effective anti-viral therapy.
- The novel agents presented potently interrupt the host Nedd4: viral PPxY interaction to inhibit virus budding and spread.
- If the project is successful it could lead to a novel, much needed antiviral treatment.
- The scientific premise is well supported by literature reports.
- The team has experience with antivirals and a history in the drug discovery area.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- The PI and the team of scientists are highly qualified to carry out the proposed work.
- The team has a successful track record of productivity in this area of research.

Weaknesses

- None noted.

3. Innovation:

Strengths

- Interrupting the host Nedd4: viral PPxY interaction to inhibit virus budding and spread is innovative.
- The small molecule inhibitors being proposed in the current proposal are novel.
- The potential for the newly discovered, novel inhibitors to have broad antiviral indications is high.

Weaknesses

- None noted.

4. Approach:

Strengths

- Efforts to improve PK/PD profiles of leads (metabolic stability, solubility, etc.) via molecular modification in the medicinal chemistry plan is rational and clearly described.
- The group has experience with the assay used to test compounds for their ability to specifically inhibit the PPxY-Nedd4 interaction and subsequent virus egress.
- A well designed, three-pronged approach is utilized under BSL-2 conditions to identify the best compounds (Aim 2) to be advanced to the more challenging and hazardous studies in the BSL-4 laboratory (Aim 4).
- In vitro and in vivo ADMET evaluation of lead compounds will be performed to ensure suitable drug properties and selectivity (FCCDC).
- In vitro and in vivo analyses of lead inhibitors against authentic hemorrhagic fever viruses is performed in a BSL4 laboratory at Texas Biomedical Research Institute (TBRI; Dr. Olena Shtanko).
- A high level of scientific rigor is evident throughout the proposal.

Weaknesses

- The rationale for the “new” scaffolds proposed in Aim 1 (increase basicity) is unclear and may present additional challenges following incorporation into inhibitors.

5. Environment:

Strengths

- The resources available at each of the sites are more than adequate to carry out the proposed work.

Weaknesses

- None noted.

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

Acceptable

- The team successfully completed a phase I grant that supplied proof of concept for their antiviral leads. The current proposal builds on that work to provide drug-like anti-viral agents for IND-enabling studies.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- The research involves human subjects as a source of blood obtained by venipuncture to isolate peripheral blood mononuclear cells. Studies in primary human macrophages (targets of MARV, EBOV, LASV) are important to understand whether antiviral treatment affects virus replication and spread in clinically relevant cells. Subjects are limited to normal healthy adult (18-50 years old) volunteers without symptoms. Both genders are studied and there is no discrimination of race or ethnicity. Participant recruitment will also be monitored. Risks will be explained to the subject by the principal investigator or an appropriate physician representative.

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion Based on Age: Distribution justified scientifically
- Subjects are limited to normal healthy adult (18-50 years old) volunteers without symptoms. Both genders are studied and there is no discrimination of race or ethnicity. Participant recruitment is monitored. Risks will be explained to the subject by the principal investigator or an appropriate physician representative.

Vertebrate Animals:

YES, all criteria addressed

- Justifications for animal use, protection of animals during studies and method of euthanasia are described (where appropriate).

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

Recommended budget modifications or possible overlap identified:

- The budget goes beyond the statutory guidelines for Phase II STTRs. The budget waiver is elected.

CRITIQUE 3

Significance: [redacted]
Investigator(s): [redacted]
Innovation: [redacted]
Approach: [redacted]

Environment: [redacted]

Overall Impact: This is a strong proposal for the development of small molecules for treatment of hemorrhagic fever viruses. Their Phase I work yielded a lead series with promising properties, including in vivo proof-of-concept. Phase II is focused on further optimization of drug-like properties and demonstration of in vivo efficacy. The supplemental information shows that the lead molecule also blocks release of live infectious SARS-CoV-2 from infected human lung cells, which is consistent with the MOA. Overall, a strong proposal with clear goals for optimization and an effective screening tier that will give confidence in the develop-ability of an optimized lead.

1. Significance:

Strengths

- High unmet medical need for treatment of highly pathogenic viruses such as Ebola, Marburg, and Lassa viruses; potential for application to SARS-CoV-2 (supplementary material).
- Application to viral treatment in both community settings and in response to bioterrorist use of the hemorrhagic viruses.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- Strong expertise in all aspects of the project. Harty is an expert in the area of RNA virus-host interactions and virus egress/transmission. Investigators have impressive track records of success in their disciplines.

Weaknesses

- None noted.

3. Innovation:

Strengths

- Novel mechanism of action via blocking the host Nedd4/virus PPxY complex, a critical regulator of viral transmission.
- Lead series identified; one member has demonstrated in vivo proof-of-concept in a Marburg virus mouse model.

Weaknesses

- None noted.

4. Approach:

Strengths

- Plan for optimization is clearly laid out and logical in progression; timelines are reasonable.

- Challenges in the lead structure are acknowledged (e.g., high logD, likely low aqueous solubility) and plans to address are specifically mentioned. Criteria for success are clearly delineated.
- Ability to screen in an in vivo viral infection model is a significant strength.
- Early consideration of a prodrug strategy is reasonable given that the SAR may not permit modifications that give increased solubility.

Weaknesses

- None noted.

5. Environment:

Strengths

- All appropriate facilities are available.
- Access to ABS-L4 labs is critical to evaluation of the lead molecules.

Weaknesses

- None noted.

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

Acceptable

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- The need for human blood samples is clearly described (human peripheral blood mononuclear cells are needed to study antiviral efficacy), as are protection of privacy and protection against risks.

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion Based on Age: Distribution justified scientifically
- Subjects are limited to normal healthy adult (18-50 years old) volunteers without symptoms. Both genders are studied and there is no discrimination of race or ethnicity.

Vertebrate Animals:

YES, all criteria addressed

- Acceptable; mice will be used for DMPK and in vivo efficacy studies; animal care and use is appropriately documented, as is the need for use of animals.

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:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE

INCLUSION OF WOMEN PLAN: ACCEPTABLE

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

INCLUSION ACROSS THE LIFESPAN: ACCEPTABLE

VERTEBRATE ANIMALS: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 2 R42 AI138630-03; PI Name: HARTY, RONALD N

NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.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.