

SUMMARY STATEMENT

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(Privileged Communication)

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Application Number: 1 R15 AI126395-01A1

Principal Investigator

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Applicant Organization: WESTERN UNIVERSITY OF HEALTH SCIENCES

Review Group: ZRG1 IDM-S (81)
Center for Scientific Review Special Emphasis Panel
AREA applications in Infectious Diseases and Microbiology

Meeting Date: 11/07/2016 *RFA/PA:* PA16-200
Council: JAN 2017 *PCC:* M32A
Requested Start: 04/01/2017

Project Title: Preferential translation of host cell factors by hantavirus nucleocapsid protein

SRG Action: Impact Score:21
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: 10-No human subjects involved
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Project Year	Direct Costs Requested	Estimated Total Cost
1	[REDACTED]	[REDACTED]
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.

1R15AI126395-01A1 Mir, Mohammad

RESUME AND SUMMARY OF DISCUSSION: This resubmitted application proposes to determine the mechanism by which Hantavirus nucleocapsid (N) protein regulates selective translation of certain host transcripts and the potential impact of this phenomenon on viral replication. The application will also examine if N protein modulates protein kinase R (PKR) and its downstream target eIF2 α to counteract the host antiviral responses. The application will advance the basic biology of Hantavirus and may also identify novel targets for antiviral drug development. The investigator has adequately addressed the previous concerns. This submission has a clear prioritization plan. The strengths are that the investigator is highly talented with an excellent publication track; preliminary data, though not required, provide a solid premise for the two independent specific aims; novel mechanism of selective translation may be revealed; the proposed experiments are well within the expertise of the investigator and feasible; multiple strategies used and proper controls ensure adequate rigor; and the environment is appropriate. The potential of student involvement in research is addressed. One concern is that Aim 2 is somewhat unfocused. Another concern is that the hypothesis that modulation of PKR by the N protein does not involve the direct interaction between these two proteins may not be correct. Despite these concerns, the overall enthusiasm is high for this application proposing to study the functions of Hantavirus N protein in translation of certain host mRNA and viral replication.

DESCRIPTION (provided by applicant): Hantaviruses, members of the Bunyaviridae family are enveloped negative strand RNA viruses and category A pathogens that are transmitted to humans through aerosolized excreta of infected rodent hosts. Hantaviruses have evolved a unique translation mechanism for the preferential translation of their mRNAs. This preferential translation is carried out by hantavirus nucleocapsid protein (N-protein) which specifically binds to the mRNA 5' cap and ribosomal protein S19 (RPS19), a structural component of the 40S ribosomal subunit. In addition, a trimeric N-protein molecule specifically binds to a highly conserved triplet repeat sequence (UAGUAGUAG) of the viral mRNA 5' UTR. Our results suggest that N-protein associated ribosomes are selectively loaded on viral mRNA 5' UTR to boost the translation of viral transcripts in the host cell cytoplasm where cellular transcripts are competing for the same translation machinery. Interestingly, our preliminary data shows that N-protein mediated translation strategy also favors the translation of certain host cell factors by an unknown mechanism. Using multifaceted experimental avenues we will determine the mechanism for the selective translation of certain host cell mRNAs by N-protein mediated translation strategy. We will determine whether preferential translation of host cell factors plays a role in virus replication. As antiviral response, host cells transiently shutdown the host translation machinery to create roadblocks for the synthesis of viral proteins. This antiviral response is triggered by the activation of protein kinase R (PKR), which phosphorylates its downstream target eIF2 α , causing translational shutdown. Our preliminary results show that N-protein inhibits PKR activation in virus-infected cells to ensure continuous synthesis of viral proteins during the course of infection. We will test the hypothesis that N-protein requires the assistance from endogenous host cell factors to inhibit PKR antiviral response. These studies will reveal new targets for therapeutic intervention of hantavirus disease.

PUBLIC HEALTH RELEVANCE: There is no treatment for hantavirus associated disease at present. The major goal of this application is to delineate the mechanism of hantavirus replication in cells. In addition, the proposed studies will help in the identification of new host targets for antiviral drug design.

CRITIQUE 1:

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

Environment: 2

Overall Impact: This application examines two different functions of the HANTV N protein: 1) promoting enhanced translation of specific cellular mRNAs, and 2) preventing activation of the cellular PKR-eIF2a pathway in response to infection. Information obtained from the completion of the proposed studies should contribute to a better understanding of HANTV-host cell interactions and associated pathogenesis. The application is by a very talented investigator with an excellent publication track record in this area of research. The productivity of the investigator over the years generates a high level of confidence that the project will be successfully completed. In this revised application, the investigator has been very responsive to the criticisms made by the study section. Studies proposed in specific aim 1 have now included a clear prioritization plan, whereas studies proposed in specific aim 2 have included alternative approaches. The research content of this application should facilitate exposure of undergraduate and graduate students at Western University Of Health Sciences to high quality research in the field of virology and it is very appropriate for AREA. The overall great enthusiasm for the application is slightly diminished because the distinct possibility that HTNV N protein-mediated increased expression levels of several host cell genes may not have a significant contribution to HTNV multiplication, and studies based on the use of MTH and confocal microscopy might demonstrate an interaction between HTNV N and PKR, a finding that will negate the most exciting hypothesis proposed by the investigator that N-mediated inhibition of PKR activation does not require a direct N-PKR interaction.

1. Significance:

Strengths

- Infection with the bunyaviruses cardiopulmonary syndrome (HCPS) and hemorrhagic fever with renal syndrome (HFRS) hantaviruses (HTNV) cause serious diseases in humans for which currently there are not vaccines or effective treatments. Improved understanding of HTNV-host cell interactions may generate valuable information to facilitate the development of novel antiviral strategies to treat HTNV human infections and associated disease.
- HTNV have a non-cytolytic strategy of multiplication and HTNV-infected cell do not exhibit protein synthesis shutoff typically observed with most cytolytic viruses like VSV. Intriguingly, HTNV proteins are efficiently produced in infected cells, suggesting that HTNV have developed strategies that allow viral mRNAs to efficiently compete with cellular mRNAs for the translational machinery of the cell. Published work by the investigator has documented that HTNV N protein promotes translation of capped viral mRNAs via a novel mechanism in which N functionally replaces the activity of the eIF4F complex to mediate interaction between the 43 S pre-initiation and the cap structure at the 5'-end of the viral mRNA, where N also interacts with a specific viral sequence (UAGUAGUAG) that promotes translation of the mRNAs. The investigator has observed that a subset of host cellular mRNAs appears to be also responsive to N-mediated enhanced translation. This finding raises the interesting possibility that HANTV N protein promotes translation of host cell factors that contribute to virus multiplication, a hypothesis that will be examined in this application.
- Activation of PKR and subsequent PKR-mediated phosphorylation of eIF2a is very common cellular response to virus infection, with eIF2a phosphorylation reducing protein translation that results in a diminished production of virus infectious progeny and hence restricted virus propagation within infected hosts. Accordingly, many viruses have evolved mechanisms to counteract PKR activation, thus preventing PKR-mediated eIF2a phosphorylation to maintain a cellular environment that permits efficient translation of both viral and host cell mRNAs. The investigator has presented convincing evidence that HTNV N protein prevents the activation of the PKR-eIF2a pathway by mechanisms that do not appear to involve a direct interaction of HTNV N protein with PKR. The identification of host cell factors that may contribute to HTNV N-

mediated inhibition of PKR activation, and the elucidation of the underlying mechanisms, may uncover novel aspects of HANTV-host cell interactions with potential important implications for HTNV induced disease, as well as for the development of novel strategies to treat HTNV infections and associated diseases.

Weaknesses

- The distinct possibility that HTNV N protein-mediated increased expression levels of several host cell genes may not have a significant contribution to HTNV multiplication and propagation. This issue may be difficult to address using RNAi knock down approaches, as this will result in protein expression levels of the corresponding host cell genes below those that are physiological, which could result in inhibition of HTNV multiplication but without proving that increased protein expression of these host cell genes is required for efficient HTNV multiplication.
- The possibility that studies based on the use of MTH and confocal microscopy will effectively demonstrate an interaction between HTNV N and PKR. This finding would be itself interesting and with implications for understanding HTNV-host cell interactions, but it will negate the most exciting hypothesis proposed by the investigator that N-mediated inhibition of PKR activation does not require a direct N-PKR interaction.

2. Investigator(s):

Strengths

- The investigator has recently (2015) moved from the Department of Microbiology, Molecular Genetics and Immunology at the University of Kansas Medical Center to the College of Vet Medicine at Western University of Health Sciences at Pomona, CA.
- The investigator has an impressive publication record in the field hantaviruses, specifically in the area related to the multiple functions played by hantavirus N protein in infected cells.
- The investigator has all the expertise in the areas of biochemistry, cell biology and virology required for directing this project.

Weaknesses

- None noted

3. Innovation:

Strengths

- The key innovative component of this application relates to its conceptual framework. The investigator will investigate two novel concepts regarding the activity of HTNV N protein-host cell interactions: 1) How HTNV N protein mediates enhanced translation of a specific subset of host cell mRNAs, and whether these proteins contribute to HTNV multiplication. 2) A possible novel mechanism by which HTNV N protein can mediated inhibition PKR activation and subsequent eIF2 phosphorylation in response to infection, thus facilitating continue efficient translation of viral proteins in infected cells.

Weaknesses

- None noted

4. Approach:

Strengths

- The investigator has presented compelling preliminary findings; most of them already published in excellent peer review journals that provide strong support for the studies proposed within this application.
- The application consists of two distinct, but related, aims each one addressing important questions regarding the effects of HTNV N protein in translational control of mRNAs in HTNV-infected cells.
- The proposed experiments are feasible and the publication track record of the investigator clearly shows he is knowledgeable and highly experienced in the different experimental procedures.

Weaknesses

- None noted

5. Environment:

Strengths

- The environment and resources provided by the College of Veterinary Medicine at Western University Of Health Sciences (WUHS) are appropriate, including the access to BSL3 facilities required to handle live HANTV, to facilitate the successful completion of the proposed research.

Weaknesses

- WUHS has a strong faculty roster, but the program at the College of Veterinary Medicine at WUHS does not appear to have other virologists working in areas with close affinity to the research interests of the investigator

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

- The facility comply with the requirements to work with BSL2 agents, but it would be helpful to provide a brief description of the SOP on place to handle HTNV.

Resubmission:

- The investigator has been very responsive to the critiques made by the study section during the previous review. Studies proposed in specific aim 1 have no included a clear prioritization plan, and a good justification of the subset of candidates that will be first examined to validate the concept being explored prior extending the research to the large collection of candidates. Likewise, studies proposed in specific aim 2 of this revised application have included alternative approaches, besides CoIP assays, to thoroughly investigate whether HTNV N protein interacts with PKR, and whether this interaction is required for HTNV N-mediated interference with PKR activation.

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Unacceptable

- No specific information was provided about this component.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Significance: 2

Investigator(s): 2

Innovation: 3

Approach: 3

Environment: 2

Overall Impact: This is a revised application that has been significantly bolstered since the previous submission. The organization and prioritization have been improved, several scientific nuances have been clarified, and the environment at Western University of Health Sciences, and incorporation of students in the research have been clarified. Overall there is strong enthusiasm for Aim 1, which will shed light on mechanisms of selective translation, including potentially targeted translation enhancement of certain host-encoded mRNAs. The second Aim is somewhat less focused, as it strives to understand the involvement of nucleocapsid protein in the suppression of the host PKR-mediated antiviral response. Older data suggested that N may be responsible for preventing dimerization and activation of PKR, but preliminary and recently published data suggest that there is no direct interaction between N and PKR. Thus the experimental approach becomes a bit diffuse in trying to first confirm a lack of N-PKR interaction, then to test a hypothesis that a virally co-opted host protein suppresses the PKR response, then to explain virus tropism in the context of a presumed PKR suppression difference between new and old-world hanta viruses. The investigator has an excellent track record for producing meaningful advances in the field and for involving students in modern molecular virology research.

1. Significance:

Strengths

- Hantaviruses cause severe disease in humans globally. Because there are no current proven or licensed treatments or vaccines, understanding the molecular virology of hanta viruses is of imminent importance.
- Elucidation of mechanisms of selective translation and for evading the PKR antiviral response would represent significant achievements in the field and in related fields in virology.
- The interplay of host and viral proteins is of paramount importance to survival of the virus, and for developing new antiviral strategies that target host proteins or host-viral protein interactions. The application is likely to elucidate new host proteins involved in arresting PKR activation.

Weaknesses

- The notion of confirming a published negative result that showed a lack of interaction between PKR and N does not sound like a large step forward in the field. In fact, it is possible that an interaction between N and PKR will be found using other methodologies.

2. Investigator(s):

Strengths

- Dr. Mir is a strong contributor his field. The discovery of hantaviral nucleocapsid protein as a translation factor has made an impact in the hantavirus field. Dr. Mir, despite a couple of moves, has maintained a high level of productivity and has consistently included students in his research.
- The investigator has the necessary expertise to carry out the experiments described.

Weaknesses

- The investigator's recent move makes it difficult to assess how the new environment may affect productivity, although he reports that he has already recruited students to work on the project.

3. Innovation:

Strengths

- The investigator's discovery several years ago that the hantaviral nucleocapsid protein can substitute for a large complex of eukaryotic translation initiation factors to enable viral protein translation during a cellular antiviral state remains an exciting innovative area of research. The current application delves into mechanistic aspects of this phenomenon.
- Viral evasion of cellular immune defenses is vital for virus survival. The notion that hantaviruses prevent the PKR cellular antiviral response by inhibiting PKR dimerization is novel.
- The notion that nucleocapsid protein could co-opt the functions of host proteins to help arrest PKR activation and subsequent translational shutoff.

Weaknesses

- Because of Dr. Mir's rapid progress in these areas, some concepts are not novel, but the efforts to elucidate mechanisms are.

4. Approach:

Strengths

- The preliminary data provide a sound scientific premise for the selective translation studies in Aim 1, and the experiments proposed are logically presented and achievable.
- Aim 2 addresses an apparently surprising recent result that nucleocapsid protein, while shown to limit the antiviral PKR response, does not interact directly with the PKR machinery. This is an interesting and unexpectedly challenging task.

Weaknesses

- Aim 2 is rather diffuse. It is unclear that expending that much effort to confirm published data that indicate a lack of interaction between PKR and N using a two-hybrid approach is worthwhile.

- The knockdown of several host proteins that are already known to be suppressors of the PKR response would likely give increased eIF2 α phosphorylation, but this result may prove to be difficult to trace back to a viral N effect.
- The notion that tropism of new and old-world hantaviruses is linked to the PKR suppression effect is intriguing, but may also be difficult to prove. If there are other restriction factors involved, one could see an increased or decreased PKR suppression phenotype in different cell types that result secondarily from more or less robust infection.

5. Environment:

Strengths

- Western University of Health Sciences provides an excellent environment for engaging students in research. Facilities should be more than adequate to carry out this kind of work. Letters are included in the application to support the role of biomedical research and student research at WUHS.

Weaknesses

- It appears that Western University students are mostly professional school students who may not naturally pursue careers in biomedical research.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Authentication of Key Biological and/or Chemical Resources:

Unacceptable

- There is no statement about authentication.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 2

Investigator(s): 1

Innovation: 1

Approach: 2

Environment: 2

Overall Impact: This application is focused on understanding the effects of the hantavirus N protein on host cell translation. The hantavirus N protein allows translation to occur in the absence eIF4 α . The study of this protein activity will make important contributions to the understanding of normal cellular processes as well as our understanding of hantavirus biology. The investigator has a strong record of training students, and is expected to continue to train students, drawing on students from multiple institutions.

1. Significance:

Strengths.

- Hantaviruses are emerging pathogens, with episodic occurrences of disease world-wide. The novel translation mechanism has the potential for broad implications in molecular biology.

Weaknesses.

- None noted.

2. Investigator(s):

Strengths.

- The investigator is well trained and productive and has experience with the model system in the application.

Weaknesses

- None noted

3. Innovation:

Strengths.

- The novel translation mechanism used by the virus.

Weaknesses.

- None noted

4. Approach:

Strengths.

- The application includes multiple strategies and controls to maximize the significance of the results that will be obtained.

Weaknesses:

- In specific aim 1, the investigator proposes to examine the expression of cellular genes that are translationally up-regulated by the N protein, hypothesizing that the cellular genes will contain similar sequences to viral transcripts. In silico analyses would be appropriate here. Also the cloning of cDNAs of the mRNAs of interest can be more easily accomplished using Genestrings (or something similar). Additionally, the proposed experiments are focused on the 5' and the 3' UTRs and do not consider the possibility that regulation could occur by N protein binding in the coding region, for example, just downstream of the AUG. The application implies that the investigator will examine 58 genes for N protein effects; this appears to be a very lofty goal.

5. Environment:

Strengths

- The environment seems well equipped and supportive of the proposed research. The institution is supportive of the investigator.

Weaknesses.

- There was no mention of journal clubs, student-sponsored seminar speakers, etc.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

- The precautions, training and safety protocols are appropriate.

Resubmission:

- The investigator addressed the previous reviewers' concerns.

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Unacceptable

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:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R15 AI126395-01A1; PI Name: Mir, Mohammad Ayoub

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
AREA applications in Infectious Diseases and Microbiology
ZRG1 IDM-S (81)
11/07/2016

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