AWARD NUMBER: W81XWH-18-1-0368

TITLE: Antiviral Drug Discovery Targeting Zika Virus Protease

PRINCIPAL INVESTIGATOR: Yongcheng Song, PhD

CONTRACTING ORGANIZATION: Baylor College of Medicine

REPORT DATE: AUGUST 2022

TYPE OF REPORT: Annual Progress Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
AUGUST 2022	Annual	7/15/2021-7/14/2022

4. TITLE AND SUBTITLE

Antiviral Drug Discovery Targeting Zika Virus Protease

5a. CONTRACT NUMBER
W81XWH-18-1-0368

5b. GRANT NUMBER
W81XWH-18-1-0368

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Yongcheng Song

E-Mail: ysong@bcm.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Zika virus, transmitted primarily by mosquitos, could become endemic in the tropical and subtropical regions including the southern states and territories of the United States. It could cause catastrophic consequences to the public health, such as microcephaly (small brain/head) of newborns. However, there are no antiviral drugs or vaccines for Zika infection. Zika virus protease (ZVpro) is a viral protein that is essential for viral replication. ZVpro is therefore a drug target. The overall goal of this project is to use a combination of rational inhibitor design, medicinal chemistry, X-ray crystallography and antiviral activity testing to discover small-molecule inhibitors of ZVpro, which are potential drug candidates for Zika infection. During this funding period, although the overall progress has been delayed due to the COVID-19 pandemic, we have produced good results showing our potent ZVpro inhibitors are non-cytotoxic and have strong anti-ZIKV activity. A total of 7 research articles and 1 patent application have been published or filed. We will perform the experiments in accordance with the approved SOW to achieve the goals of the project in the next funding period.

15. SUBJECT TERMS
Zika virus, Antiviral, NS2B-NS3 protease, Small-molecule inhibitor, Medicinal chemistry

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	17	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Zika virus (ZIKV), transmitted primarily by mosquitos, could become endemic in the tropical and subtropical regions including the southern states and territories of the United States. It could cause catastrophic consequences to the public health, including microcephaly (small brain/head) of newborns and Guillain-Barre syndrome. However, there have been no antiviral drugs or vaccines for the prevention and treatment of ZIKV infection. Zika virus protease (ZVpro) is a viral protein that is essential for viral replication. ZVpro is therefore a drug target for ZIKV infection. The overall goal of this project is to use a combination of rational inhibitor design, medicinal chemistry, X-ray crystallography and antiviral activity testing to discover and develop potent and selective small-molecule inhibitors of ZVpro. These compounds are potential drug candidates to treat and prevent Zika infections.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Zika virus, Antiviral, NS2B-NS3 protease, Small-molecule inhibitor, Medicinal chemistry

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

There are 4 major goals/tasks of the projects:
The major Task 1 is to use medicinal chemistry to develop potent ZVpro inhibitors, with the milestones (at Month 60) being ~85% accomplished.
The major Task 2 is to use biochemical and X-ray crystallographic methods to characterize ZVpro inhibitors synthesized in Task 1, with milestones (at Month 60) being ~90% accomplished.
The major Task 3 is to test cellular anti-ZIKV activity as well as cytotoxicity of selected ZVpro inhibitors identified in Task 2, with milestones (at Month 60) being ~90% accomplished.
The major Task 4 is to perform pharmacokinetics, toxicity and in vivo antiviral activity studies, with milestones (at Month 60) being ~80% accomplished

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results

achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Task 1: Medicinal Chemistry development of ZVpro inhibitors. The objective of this Task is to use rational inhibitor design, medicinal chemistry and structure activity relationship (SAR) studies to find potent small-molecule inhibitors of ZVpro.

Subtask 1: Structure activity relationship (SAR)-guided medicinal chemistry. During Year-4, a new chemo-type of small-molecule ZVpro inhibitors have been discovered and developed. Indole-3-carboxamide compounds with *para-tert*-butylphenyl substituent were found to be inhibitors of ZVpro with IC_{50} values of 4.5 and 11 μM. Medicinal chemistry based on these new lead compounds were performed and ~70 new analogous or derivative compounds were synthesized successfully. Most of these compounds were synthesized using a general synthetic route. Methyl indole-3-carboxylate compound was brominated, hydrolyzed and subjected to an amide-formation reaction to produce the indole intermediate. The target compounds were obtained by a Suzuki coupling reaction and deprotection of the *tert*-butyloxycarbonyl (Boc) group. Detailed synthesis as well as that for other compounds can be found in our recent publication (*Eur. J. Med. Chem.* **2021**, *225*, 113767), which is included in the Appendix of this progress report.

Subtask 3: Structure-activity relationship (SAR) studies. Inhibitory activity against Zika NS2B-NS3 protease (ZVpro) and Zika virus replication of these synthesized compounds have been tested using the methods described in the Year-1 progress report. Activities of a total of 73 di-substituted indole and related compounds were analyzed and detailed structure activity relationships can be found in our recently published article (*Eur. J. Med. Chem.* **2021**, *225*, 113767). Collectively, a novel series of 2,6-disubstituted indole-containing compounds were found to be potent, allosteric inhibitors of Zika virus protease (ZVpro) with IC_{50} values as low as 320 nM.

The overall progress for Task 1 has been delayed due to unusually high personnel changes as well as significant delays in hiring new personnel caused by the COVID-19 pandemic. Despite this, we have produced good results for the project. We have designed and synthesized ~310 compounds (as compared to 300 compounds proposed for the project) during the 4 years of performance. The goal and milestone for the Task have not been fully met. A no-cost-extension for 1 year has been requested and approved.

Major Task 2: Biochemical and X-ray crystallographic characterization of ZVpro inhibitors. The objective of this Task is to perform enzyme inhibition, X-ray crystallographic and other biochemical studies to characterize compounds made in Task 1, which will be used for rational design and SAR studies in Task 1 to find compounds with improved potency.

Subtask 1: Expression and inhibition of ZVpro. Expression, purification of recombinant ZVpro as well as the biochemical assay to determine the activity and inhibition of ZVpro have been described in the Year-1 progress report. Several new batches of recombinant ZVpro were expressed and purified. Compounds synthesized in Task 1 were tested for their inhibitory activities against ZVpro, among which potent small-molecule inhibitors were identified with IC_{50} as low as 320 nM. Detailed activity data can be found in our published article (*Eur. J. Med. Chem.* **2021**, *225*, 113767).

Following similar methods, we expressed and obtained recombinant NS2B-NS3 proteases of closely related dengue serotype-2 and West Nile viruses in the Flavivirus family, which are also important human pathogens. Activity of selected compounds against these viral proteases were tested and results are shown in Table 1. These ZVpro inhibitors also inhibit the activity of DV2pro and WVpro, but with considerably reduced potency.

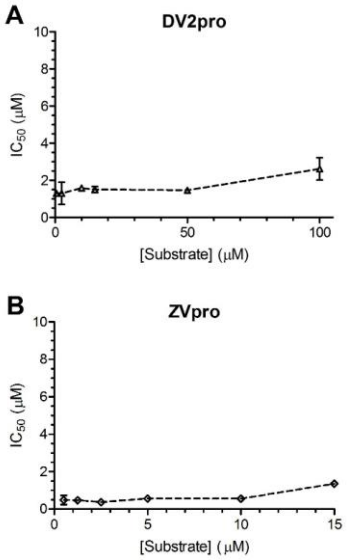
Table 1. Inhibitory activity IC_{50} (μM) against Flavivirus proteases ZVpro, DV2pro and WVpro.

Cpd #	ZVpro	DV2pro	WVpro
66	0.32	1.6	5.7
67	0.37	3.1	3.7
72	0.45	9.2	8.6
64	0.99	10.3	3.5
30	1.0	10.0	10.5
50	1.0	10.6	20.1
8	1.3	15.0	21.8
56	1.6	6.5	6.6
26	3.1	49.7	32.0
51	3.2	10.7	16.0
7	5.0	30.4	35.1
32	5.7	48.3	42.0
40	11.4	40.2	31.0
24	21.8	12.0	50.5
45	40.2	>50	>50
22	48.9	>50	>50

Subtask 2: Enzyme selectivity for ZVpro. As high selectivity is required for these compounds to be less toxic or interfering to normal physiology, three selected potent ZVpro inhibitors were tested against 5 selected human proteases at 10 μM. None of these compounds had significant inhibitory activities, showing a high selectivity.

Subtask 3: X-ray crystallography of ZVpro in complex with selected inhibitors. Methods for crystallization, data collection and structure determination and refinement have been described in the Year-1 progress report. We continued working on this subtask for our newly synthesized inhibitors, but due to COVID-19 and personnel changes, no new X-ray structures of ZVpro/DV2pro-inhibitor complexes were obtained.

Subtask 4: Other biochemical/biophysical characterization of selected ZVpro inhibitors. Steady-state enzyme kinetic studies for the most potent compound **66** were performed to find its mode of inhibition against ZVpro and DV2pro. Initial velocities were determined in the presence of increasing concentrations of the inhibitor and substrate. IC_{50} values of compound **66** were then calculated and plotted against the substrate concentrations. As shown in the Figure below, the IC_{50} values against DV2pro were found to be almost unchanged when the substrate concentration was increased from 0.5 to 50 μM (~0.05-5×K_m) and do not linearly increase according to the Cheng-Prusoff equation ($IC_{50} = K_i + K_i/K_m \times [S]$). These results show compound **66** is not a competitive inhibitor and more likely adopts a non-competitive mode of inhibition. Similarly, the IC_{50} values of **66** against ZVpro remain almost unchanged when the substrate concentration was increased from 0.5 to 10 μM (~0.03-0.7×K_m). The results for ZVpro do not exclude a competitive mode of action. However, given the very high similarity between ZVpro and DV2pro in both sequence and structure, it is postulated that compound **66** inhibits ZVpro with the same mode of action.



The overall progress for Task 2 has been delayed due to the COVID-19 pandemic. Despite this, significant progress has been achieved including obtaining potent and selective inhibitors of Zika and dengue virus proteases with IC_{50} as low as 320 nM. The goal and milestone for the Task have not been fully met.

Major Task 3: To test cellular anti-ZIKV activity and cytotoxicity of selected potent ZVpro inhibitors. The objective of this Aim is to perform cell-based assays to determine cytotoxicity and anti-ZIKV activity of potent ZVpro inhibitors.

Subtask 1: Perform cytotoxicity testing of selected inhibitors. Cytotoxicity assays against mammalian cells Vero and U87 have been described in the Year-1 progress report. We selected ~20 ZVpro inhibitors and tested their cytotoxicity. Most of these compounds do not significantly inhibit proliferation of these cells with EC_{50}s of more than 10 μM.

Subtask 2: Perform cellular antiviral activity testing of selected inhibitors. The assays for evaluating antiviral activity of our compounds have been described in the Year-1 progress report. We tested anti-ZIKV activity of ~20 ZVpro inhibitors without significant cytotoxicity. The most potent ZVpro inhibitor **66** was able to inhibit ZIKV replication in U87 cells by 68% (i.e., half-log reduction) at 1 μM in two independent experiments. Compound **67** with a comparable enzyme activity exhibited a reduced anti-ZIKV activity with an EC_{68} of 3 μM. In addition, as compared to compound **66**, compounds **72**, **30** and **31** with slightly to moderately reduced activity against ZVpro (IC_{50} = 0.45-1 μM) showed considerably reduced anti-ZIKV activity (EC_{68} = 10 μM). Compounds **73** and **64** did not inhibit ZIKV replication by 68% at 10 μM. These variable antiviral activities might be due to different cellular permeability of these compounds. Compound **56** with an enzyme IC_{50} of 1.6 μM exhibited a strong anti-ZIKV activity with an EC_{68} of 2.5 μM, which might be due to improved cellular uptake or off-target effects. Less potent inhibitors **26**, **54**, **51** and **25** (IC_{50} = 3.1-4.2 μM) did not show antiviral activity at 10 μM.

Table 2. Antiviral EC_{68} (μM) against ZIKV-FLR in U87 cells.

	ZVpro IC_{50} (μM)	ZIKV-FLR EC_{68} (μM)	U87 Cytotoxicity CC_{50} (μM)
66	0.32	1.0	>10
67	0.37	3.0	>10
72	0.45	10.0	>10
73	0.60	>10	>10
31	0.63	10.0	>10
64	0.99	>10	>10
30	1.0	10.0	>10
56	1.6	2.5	>10
26	3.1	10.0	>10
54	3.1	>10	>10
51	3.2	>10	>10
25	4.2	>10	>10

The most potent compound **66** also showed dose-dependent anti-ZIKV activity. It was able to inhibit ZIKV (FLR strain) replication in U87 cells by 68%, 90% and 99% (0.5, 1 and 2 log reduction) at the concentration of 1, 3 and 10 μM, respectively, in two independent experiments. These results suggest the potent ZVpro inhibitor **66** is a promising antiviral agent against ZIKV infection.

Although the progress for the Task 3 has been delayed due to the COVID-19 pandemic, our results are satisfactory, showing our potent ZVpro inhibitors are non-cytotoxic and have potent anti-ZIKV activity. The goal and milestone for the Task have not been fully met.

Major Task 4: To test PK/Tox and in vivo anti-ZIKV activity of selected potent ZVpro inhibitors. The objective of this Aim is to perform a series of in vitro and in vivo PK/Tox testing to select good drug candidates and test their in vivo antiviral activity in a mouse model of ZIKV infection.

Subtask 1: PK/Tox and brain distribution testing of selected inhibitors. Due to the COVID-19 pandemic, we will perform this task for qualified compounds in the next NCE period.

Subtask 2: To test in vivo anti-ZIKV activity of selected ZVpro inhibitors. Due to the COVID-19 pandemic, we will perform this task for qualified compounds in the next NCE period.

The overall progress for the Task 4 involving mouse studies has been delayed due to the COVID-19 pandemic. We will perform this task for qualified compounds in the next funding period. The goal and milestone for the Task have not been fully met.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars,

study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next no-cost-extension (NCE) period, we will perform the experiments we proposed in accordance with the approved SOW (NCE period) to achieve the goals of the project, using a combination of rational inhibitor design, synthetic medicinal chemistry, biochemistry, X-ray crystallography and in vitro and in vivo testing of biological activities and toxicities of potent ZVpro inhibitors.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and

research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Due to unusually high personnel changes as well as significant delays in hiring new personnel caused by the COVID-19 pandemic, our overall progress has been delayed. Despite this, our results have been satisfactory as described in the Accomplishment section. With the approval of the NCE, we expect there would be no negative impact to our overall accomplishment of this project.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nie, S.; Zhao, J.; Wu, X.; Yao, Y.; Wu, F.; Lin, Y.-L.; Li, X.; Kneubehl, A. R.; Vogt, M. B.; Rico-Hesse, R.; Song, Y.* Synthesis, Structure-Activity Relationship and Antiviral Activity of Indole-Containing Inhibitors of Flavivirus NS2B-NS3 protease. *Eur. J. Med. Chem.* **2021**, *225*, 113767. (Published and acknowledged this DoD grant award). A copy of reprint is attached.

Nie, S.; Wu, F.; Wu, J.; Li, X.; Zhou, C.; Yao, Y.; Song, Y.* Structure-Activity Relationship and Antitumor Activity of 1,4-Pyrazine-Containing Inhibitors of Histone Acetyltransferases P300/CBP. *Eur. J. Med. Chem.* **2022**, *237*, 114407. (Published and acknowledged this DoD grant award). A copy of reprint is attached.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name: Song, Yongcheng
Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-2611-2476
Person Months: 3
Contribution to Project: As PI, Dr. Song is responsible for all aspects of the studies proposed, including experimental design, data analysis, postdoc training and manuscript preparation.
Funding Support:

Name: Abdullaha, Mohd
Role: Postdoc
Researcher Identifier (e.g. ORCID ID): 0000-0003-4875-7080
Person Months: 5
Contribution to Project: Dr. Abdullaha performed molecular modeling and organic synthesis of novel inhibitors of ZIKV protease.
Funding Support:

Name: Mishra, Chandra
Role: Postdoc
Researcher Identifier (e.g. ORCID ID): 0000-0001-9274-5912
Person Months: 4
Contribution to Project: Dr. Mishra performed molecular modeling and organic synthesis of novel inhibitors of ZIKV protease.
Funding Support:

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

See attached updated Other Support forms (with changes noted) for the PI. These changes have no impact on the funded project.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

1. A copy of the published articles.
2. Other Support forms for the PI.