

AWARD NUMBER: W81XWH-19-2-0040

TITLE: Anti-complement Therapy to Improve Mortality and Morbidity for Traumatic hemorrhage during Prolonged Field Care and Prolonged Damage Control Resuscitation

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REPORT DATE: October 2021

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE			<i>Form Approved</i> <i>OMB No. 0704-0188</i>		
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1. REPORT DATE October 2021		2. REPORT TYPE Annual		3. DATES COVERED 15Sep2020-14Sep2021	
4. TITLE AND SUBTITLE Anti-complement Therapy to Improve Mortality and Morbidity for Traumatic hemorrhage during Prolonged Field Care and Prolonged Damage Control Resuscitation			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W81XWH-19-2-0040		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Dr. Yansong Li E-Mail: yli@genevausa.org			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Geneva Foundation 917 Pacific Ave. Ste 600 Tacoma, WA 98402			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 Bleeding (hemorrhage) after trauma remains a leading cause of death. Traumatic hemorrhage (TH) causes early innate immune response and clotting disorders. An inappropriate innate immune response after TH leads to an abnormal release of inflammatory mediators that contribute to early inflammation-mediated multi-organ failure (MOF) and death. Complement cascade (ComC) as a "first line defense" and a master alarm system of the innate immunity, represents a key mechanism to prime overzealous cytokine storm and thromboinflammation that contribute to multi-system inflammatory syndrome (MSIS)-mediated MOF after TH. The purpose of this study is to develop and validate anti-ComC therapies aimed at mitigating the MSIS-induced MOF and increasing survival, thereby improving outcomes during prolonged field care and/or prehospital scenario for TH patients.					
15. SUBJECT TERMS Trauma, hemorrhage, multi-organ failure, mortality, complement cascade, multi-system inflammatory syndrome, thromboinflammation, complement inhibition, prolonged field care					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	11	19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION:

Traumatic hemorrhage (TH) is a significant global burden in civilians and military service members. Current prehospital/hospital care of the critically ill trauma patients remains primarily supportive and fails to address the destructive influence of unchecked inflammation-mediated multi-organ failure (MOF). Complement cascade (ComC) as an important part of innate immune system represents a key mechanism to prime overzealous cytokine storm and thromboinflammation that contribute to multi-system inflammatory syndrome (MSIS)-mediated MOF after TH. This DoD project is to develop and validate new anti-ComC as an effective therapy for the critically ill trauma patients to improve the poor outcomes of MSIS-induced MOF and mortality.

2. KEYWORDS:

Trauma, hemorrhage, multi-organ failure, mortality, complement cascade, multi-system inflammatory syndrome, thromboinflammation, complement inhibition, prolonged field care.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Evaluate the efficacy of Coversin or C1-INH in a clinically relevant porcine trauma hemorrhage during a short-term PFC (10 hrs).	Timeline Months	Project Status
Major Task 1: Determine the efficacy of Coversin or C1-INH in a clinically relevant porcine trauma hemorrhage during a short-term PFC (10 hrs).		In progress
Subtask 1. Local IACUC and ACURO approval	9/15/2019 - 12/14/2019	Completed
Subtask 2. Conduct model development and characterization of blast injury and hemorrhage (Total # of swine needed: 15)	12/15/2019 - 3/14/2020	Underway (70% completed)
Subtask 3. Characterize and assess ComC activation, inflammatory response, MOF, and survival after blast injury and hemorrhage (Total # of swine needed: 15)	12/15/2019 - 4/14/2020	Underway (70% completed)
Subtask 4: Perform animal study to test the efficacy of Covesin or C1-INH in the developed swine model (Total # of swine needed: 50)	5/15/2020 - 12/14/2020	Not initiated
Subtask 5: Assess the PK and PD profiles of Covesin and C1-INH 1 (Total # of swine needed: 50)	6/15/2020 - 1/14/2021	Not initiated
Subtask 6: Assess the efficacy of Covesin or C1-INH on inflammation, MOF, and mortality in the developed swine model (Total # of swine needed: 50)	6/15/2020 - 3/14/2021	Not initiated
Subtask 7: Assess the efficacy of Coversin or C1-INH on ComC, CoaC, KinC, and FibC (Total # of swine needed: 50)	6/15/2020 - 3/14/2021	Not initiated
Subtask 8: Assess the efficacy of Coversin or C1-INH on DAMPs, endotheliopathy, and oxidative stress (Total # of swine needed: 50)	7/15/2020 - 1/14/2021	Not initiated
Milestone(s) Achieved. 1. IACUC protocol approval; and 2) Submission of full IND application	3/14/2021	Underway (60% completed)
Specific Aim 2: Evaluate efficacy of selected optimal anti-ComC regiments from Specific Aim 1 in a clinically relevant porcine model		

of trauma hemorrhage during a long-term PFC (24 hrs).		
Major Task 2: Determine the efficacy of selected optimal anti-ComC regiments from Specific Aim 1 in a clinically relevant porcine model of trauma hemorrhage during a long-term PFC (24 hrs).		
Subtask 1: Perform animal study to test the efficacy of Covessin or C1-INH in the developed swine model (Total # of swine needed: 50)	4/15/2021 - 3/14/2022	
Subtask 2: Assess PK and PD profiles of Coversin and C1-INH (Total # of swine needed: 50)	4/15/2021 - 4/14/2022	
Subtask 3: Assess the efficacy of Covessin or C1-INH on inflammation, MOF, and mortality in the developed swine model (Total # of swine needed: 50)	4/15/2021- 6/14/2022	
Subtask 4: Assess the efficacy of Coversin or C1-INH on ComC, CoaC, KinC, and FibC (Total # of swine needed: 50)	4/15/2021 - 6/14/2022	
Subtask 5: Assess the efficacy of Coversin or C1-INH on DAMPs, endotheliopathy, and oxidative stress (Total # of swine needed: 50)	7/15/2021 - 6/14/2022 22-33	
Milestone(s) Achieved: Submission of full IND application	6/15/2022 - 9/14/2022	

What was accomplished under these goals?

- **Objective:** To develop and characterize a clinically relevant swine model of blast injury (BI) and hemorrhage (H).
- **Major research activity:** During the year 2, we have performed 12-pig experiment for the model development. We have achieved following outcomes:
- **Significant results/key outcomes:**
 1. 1. Animal studies (For details, For details, please see below Appendices: attachment #1):
 - 1) In order to determine optimal conditions of BI and H, we conducted the 1st round-animal study (4 pigs). In this study, we determined the blast injury (BI) conditions (orientation: side-on; animal location: z = 91-94cm; blast intensity: BOP=338.4±10.1 kPa, t+=2.1±0.1ms, I=230.9±13.2kPa-ms); BI + 45% H resulted in multi-organ damage (brain, lung, liver, and jejunum), early complement activation, hypovolemic shock, and metabolic acidosis; and there were inconsistent responses of hemodynamics, metabolism, and complement activation to BI + 45% H, which may be due to individual animal heterogeneity to the injury.
 - 2) To develop/characterize a clinically relevant swine model of BI + H, we performed the 2nd round-animal experiment (4 animals) based on the conditions defined in the 1st round-study. Our data in this study demonstrated that a) BI and 45% H resulted in 20% mortality rate; b) The USAISR shock tube was able to produce consistent open field blast wave parameters and wave forms; c) The combination of BI + 45% H led to mild-moderate multiple-organ damage including lung, heart, brain, small intestine, liver, and kidney as evident by histopathological changes; d) The combination of BI + 45% H elevated blood levels of organ function parameters including troponin I, myoglobin, bilirubin and AST; e) The injury triggered mild-moderate systemic complement activation; f) BI + 45% H led to remarkably high blood levels of C3a in and HMGB1, and severe inflammation-induced brain/heart injury, which may contribute to the animal early death; g) BI + 45% H resulted in a transient increase in WBCs and neutrophils, and decrease in lymphocytes and monocytes; h) A combined injury showed a transient shock/hemodilution, metabolic acidosis, and mild hypocoagulopathy; and i) The animals received a large amount of anesthetic drugs and only 2 animals required plasmalyte A fluid resuscitation, which may interfere on hemorrhagic shock and fluid resuscitation requirement, and with measurement matrix and therapeutic drugs.

- 3) To develop an optimal model, we carried out the 3rd round-animal study by increasing H volume from 45% to 55% and titrating anesthetic drugs. This experiment showed that a) All animals (4/4) survived 24hrs after BI and 55% H; b) Compared to BI + 45% H, BI + 55% H led to predominant alternative complement pathway activation; c) There were no differences in hemodynamics, metabolism and biochemistry between BI + 45% H and BI + 55% H; d) Titrated TIVA and isoflurane reduced the requirements of propofol and midazolam, but no effects on Plasmalyte A requirements and urine outputs; and e) There is no significantly increased organ damage in BI + 55% H.
2. We have built a professional research team with 3 Research Scientists and 2 technicians.
3. We routinely discussed experimental data, current challenges and future plans with the Co-Investigators (weekly), group members (daily), department leaders (weekly) and the Geneva Foundation's grant/contracts manager (weekly).
4. Proposal submission: Development of a novel NLRP3 inflammasome-targeted therapeutic to treat traumatic hemorrhage-induced multiple-organ failure during prolonged field care (PI, PRMRP-IIRA)
5. To keep our knowledge and skills current, we have searched/read scientific articles, attended virtual scientific meetings and participated in online training courses.

What opportunities for training and professional development has the project provided?

This project has provided a great opportunity to train 3 Scientist and 4 Technicians with regard to blast injury, animal ICU, anesthesia, animal handling, surgery, blood sample collection/processing and analysis, blast injury, hemorrhagic shock, vital sign monitoring and recording, data entry and organization, necropsy, functional complement assays, and reagent/supply purchase.

How were the results disseminated to communities of interest?

The generated results and important findings in this project have been disseminated and shared with the civilian/military trauma research communities in the forms of oral/poster presentation in 2021 MHSRS (Kissimmee, FL), 2021 Military City USA Trauma Collaborative Research Conference (San Antonio TX), and a joint press release (New York and London, March 04, 2021 Globe Newswire, <https://www.globenewswire.com/en/news-release/2021/03/04/2187148/0/en/Akari-Therapeutics-Announces-a-Cooperative-Research-and-Development-Agreement-CRADA-with-the-U-S-Army-Institute-of-Surgical-Research-USASIR-for-Nomacopan-in-Trauma.html>).

What do you plan to do during the next reporting period to accomplish the goals?

Due to USAISR's limited research capacity caused by the COVID-19 pandemic, the USAISR is no longer to support this project. To achieve the project milestones/goals, we are planning to perform this project in the Division of Trauma Research at the UT Health Science Center at San Antonio (UTHSCSA). The UTHSCSA has distinguished animal facilities and animal care system, clinical trauma research experts, laboratory support, and a world-class research core facilities/services as well as an excellent research environment, where is best suited for our research program applying a translational **BBB** approach (**B**edside to **B**ench and **B**ack). Our detailed plans are as follows:

1. We have assembled a new exceptional multidisciplinary team consisting of team members: Dr. Li (PI, a senior trauma immunologist), and Co-Is: COL (ret.)/Dr. Cancio (a physician-scientist with his expertise at critical care), Dr. Susannah Nicholson (a physician-scientist with expertise at trauma-induced multi-organ failure), Dr. Batchinsky (a senior research scientist with his expertise at swine models of trauma-induced multi-organ failure), and Dr. Simovic (a senior trauma physiologist).
2. We are preparing a package of documents for changing performance site and are going to submit it to USAMRDC for an approval.
3. We are preparing a new IACUC protocol and doing online/in-person trainings of animal research, ethics, and compliance.
4. We are proactively setting up the new animal surgical room and wet laboratory at the UTHSCSA.

5. We are planning to hire a new postdoctor and a new technician.
6. We are exploring new cross-team/organization collaborations at the UTHSCSA.
7. We are planning to initiate the animal study on December 2021.
8. We are preparing/writing new SOPs for our animal/laboratory experiments.
9. We are preparing/writing two manuscripts.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Amid continuous problematic COVID-19 pandemic and limited research capacity at USAISR that have significantly upended our research plans and nixed research activities. To keep this project on track, we have developed strategic plans as follows:

1. We are planning to change the performance site from the USAISR to UTHSCSA (see above).
2. We are planning to keep good communication with our team members and animal facility to keeping the research going.
3. We are continuing to communicate with the grants/contract manager, department chief and science officer, and share how the crisis is affecting our work and how we plan to keep making progress.
4. We are going to cross-train staff to reduce the likelihood of institutional skill/knowledge being locked up with one person and to maximize shared research resources at UTHSCSA.

5. We will keep searching/reading research articles to gain new knowledge.
6. We will take on webinar/online courses/conferences to gain insights and build skills.
7. We are preparing and writing SOPs for the research project.

Changes that had a significant impact on expenditures

The COVID-19 crisis and USAISR's limited capacity have upended our research activities including hiring staff and performing animal study that significantly impact on the expenditures at less cost than anticipated.

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

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

1. Addendum #1: change stain and instrumentation, and carotid artery catheter (approved on October 17, 2018).
2. Addendum #2: Change Principal Investigator (approved on September 13, 2019).
3. Addendum #3: Change animal weight, DSI placement and method development request (approved on March 2, 2020).
4. Additional model development animals (approved on December 4, 2020)
5. Addendum #4: Addition of a pilot study and changes in anesthesia regimen (approved on May 26, 2021)

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

• Publications, conference papers, and presentations

Journal publications.

1. A joint press release entitled "Study of porcine model of blast injury and haemorrhagic shock underway with USAISR as part of the development of a clinical path for the use of Nomacopan (Coversin) to treat trauma" (New York and London, March 04, 2021 Globe Newswire, <https://www.globenewswire.com/en/news-release/2021/03/04/2187148/0/en/Akari-Therapeutics-Announces-a-Cooperative-Research-and-Development-Agreement-CRADA-with-the-U-S-Army-Institute-of-Surgical-Research-USAISR-for-Nomacopan-in-Trauma.html>).
2. Li Y, Yang Z, Barr JL, Gremmer BJ, Lucas ML, Necsoiu C, Jordan BS, Batchinsky AI, Cancio LC. Distal organ inflammation and injury after resuscitative endovascular balloon occlusion of the aorta in swine severe hemorrhagic shock. PLoS One. 2020 Nov 17; 15(11):e0242450
3. Bermudez T, Sammani S, Song JH, Quijada H, Valera DG, Hernon VR, Kempf CL, Garcia AN, Burt J, Camp SM, Hufford M, Cress AE, Desai AA, Natarajan V, Jacobson JR, Dudek SM, Cancio LC, Alvarez J, Rafikov R, Li Y, Zhang DD, Casanova N, Bime C, Garcia JGN. An eNAMPT-neutralizing mAb reduces rat and porcine lung injury severity in preclinical ARDS/VILI models (JEM, submitted).

4. Yang Z, Le TD, Simovic MO, Liu B, Fraker TL, Cap AP, Wade CE, DalleLucca JJ, Li Y. Intercommunication of tri-opathies: Complementopathy, endotheliopathy and coagulopathy, and their impacts on clinical outcomes in severe poly-trauma patients (Front Immunol, submitted).
5. Yang Z, Nunn MA, Le TD, Simovic MO, Edsall PR, Liu B, Barr JL, Lund BJ, Hill-Pryor CD, Pusateri AE, Cancio LC, Li Y. Terminal complement activation in military casualties and the potential of complement C5 inhibition to improve organ function and survival in trauma. (Sci Transl Med, submitted).

For details, please see below Appendices (Attachment #2).

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

1. Yang Z, Cap AP, Simovic MO, Cancio LC, Wade CE, Li Y. Intercommunication of tri-opathies: Complementopathy, endotheliopathy and coagulopathy, and their impacts on clinical outcomes in severe polytrauma patients [oral presentation, 2021 MHSRS (Kissimmee, FL) and 2021 Military City USA Trauma Collaborative Research Conference (San Antonio TX)].
2. Tamara L. Fraker, MS, Zhangsheng Yang, PhD, Bryan S. Jordan, RN, Michael L. Lucas, MS, Tomas S. Cancio, BS, Milomir O. Simovic, PhD, MD, Corina Necsoiu, MD, Thomas J. Walters, PhD, COL Andrew P. Cap, MD, PhD, Yansong Li, MD, and COL (Ret.) Leopoldo C. Cancio, MD. Development of a porcine model of blast injury and hemorrhagic shock: systemic activation of complement pathways, HMGB1 release and coagulation profile [poster presentation, 2021 MHSRS 2021 MHSRS (Kissimmee, FL) and 2021 Military City USA Trauma Collaborative Research Conference (San Antonio TX)].
3. Corina Necsoiu, MD, Zhangsheng Yang, PhD, Tamara L. Fraker, MS, Bryan S. Jordan, RN, Michael L. Lucas, MS, Tomas S. Cancio, BS, Milomir O. Simovic, PhD, MD, Thomas J. Walters, PhD, COL Andrew P. Cap, MD, PhD, COL (Ret.) Leopoldo C. Cancio, MD, and Yansong Li, MD. Indices of organ damage in a swine model of blast injury and hemorrhage [poster presentation, 2021 MHSRS 2021 MHSRS (Kissimmee, FL) and 2021 Military City USA Trauma Collaborative Research Conference (San Antonio TX)].

For details, please see below Appendices (Attachment #3).

• **Website(s) or other Internet site(s)**

1. Akari Therapeutics announces a Cooperative Research and Development Agreement (CRADA) with the U.S. Army Institute of Surgical Research (USAISR) for Nomacopan (Coversin) in Trauma: Study of porcine model of blast injury and haemorrhagic shock underway with USAISR as part of the development of a clinical path for the use of Nomacopan (Coversin) to treat trauma (Joint press release, New York and London, March 04, 2021 Globe Newswire, <https://www.globenewswire.com/en/news-release/2021/03/04/2187148/0/en/Akari-Therapeutics-Announces-a-Cooperative-Research-and-Development-Agreement-CRADA-with-the-U-S-Army-Institute-of-Surgical-Research-USAISR-for-Nomacopan-in-Trauma.html>).

For details, please see below Appendices (Attachment #3).

• **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

1. Li Y, Cancio LC, Pusateri AE, Nunn Miles, Yang Z, Dubick MA, Walters TJ, and Cap AP. Coversin for the use to reduce mortality and protect organ injury after trauma and hemorrhagic shock (invention disclosure, in preparation).

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Yansong Li

Project role: PI

Research identifier: 60318

Nearest person month worked: 6

Contribution to project: Participated in 1) IACUC protocol addendum writing and submission, 2) an establishment of collaboration with the Akari Therapeutics Plc. (London, UK) and the Pharming Technologies B.V. (Leiden, Netherlands) for providing Coversin and C1 inhibitor respectively, 3) animal BI + H and necropsy; 4) histopathological evaluation, 5) data analysis and interpretation; 6) personnel hiring/training and team building, 7) project design and strategic plan, 8) writing and submitting manuscripts, abstracts, and proposals; and 9) preparing/submitting press release and invention disclosure.

Funding support: W81XWH1920040

Name: Leopoldo Cancio

Project role: Co-I

Research identifier:

Nearest person month worked: 1

Contribution to project: Participated in 1) project design and strategic plan, 2) data analysis and interpretation; 3) personnel hiring/training and team building, 4) revising and submitting manuscripts, abstracts, and proposals; 5) preparing/submitting press release and invention disclosure, and 6) searching/identifying the alternative performance site.

Funding support: Dr. Cancio's salary is paid by the federal government.

Name: Zhangsheng Yang

Project role: Co-I

Research identifier: 48088

Nearest person month worked: 12

Contribution to project: Participated in 1) performing animal surgery, 2) animal BI + H; 3) necropsy, 4) sample/data analysis; 5) data summary and interpretation, and 6) writing manuscripts, abstracts, and proposals.

Funding support: W81XWH1920040

Name: Corina Necsoiu

Project role: Co-I

Research identifier:

Nearest person month worked: 3.0

Contribution to project: Participated in 1) IACUC protocol addendum preparation and submission, 2) animal BI + H, 3) project design, plan and preparation, and 4) animal ICU monitoring.

Funding support: W81XWH1920040

Name: Milomir Simovic

Project role: Co-I

Research identifier:

Nearest person month worked: 4

Contribution to project: Participated in 1) performing animal surgery, 2) animal BI + H; 3) necropsy, 4) sample/data analysis; 5) data summary and interpretation, and 6) writing manuscripts, abstracts, and proposals.

Funding support: W81XWH1920040

Name: Tamara Fraker

Project role: Research Technician

Research identifier:

Nearest person month worked: 6

Contribution to project: Participated in 1) recording surgical support, 2) blood sampling, 3) necropsy, 4) tissue/blood samples process, 5) data recording, 6) sample analysis, 7) searching/ordering reagents/equipment, and 8) revising/editing manuscripts and proposals.

Funding support: W81XWH1920040

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

1. We had monthly phone conference with the Akari Therapeutics Plc. to discuss our data/experimental plans and gain insightful inputs.
2. We routinely shared and discuss our data with the Pharming Technologies B.V..

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: Attached.

9. APPENDICES:

- 1) Attachment #1: Data summary of animal model development
- 2) Attachment #2: Publications
- 3) Attachment #3: Conference presentations