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14. ABSTRACT

Despite recent advances in hemorrhage control, traumatic hemorrhage (TH)remains a leading cause of mortality among military and civilian trauma patients. Hemorrhage after trauma is the primary cause of death on the battlefield accounting for 50%. Approximately 90% of battlefield casualties die in the prehospital environment. In addition, hemorrhage is associated with 85% of potentially survivable death in the recent conflicts. Early inflammatory response especially in complement C5 and damage associated molecular patterns represent more generalizable biological principles, which critically regulate systemic inflammatory response syndrome, compensatory anti-inflammatory syndrome, endotheliopathy, and persistent inflammation/immunosuppression and catabolism syndrome, which contribute to multi-organ failure (MOF) and mortality after TH. Therefore, early modulation of these two cascades constitutes a most effective therapeutic principle for the treatment of MOF and the improvement of survival after TH.

This project builds on our previous works and well-established capabilities. The program of trauma immunomodulation has successfully proven that anti-C5 or anti-HMGB1 therapy increases survival, improves metabolism and hemodynamics, reduces resuscitation fluid volumes, modulates systemic and local inflammatory responses, and mitigates MOF in a rat TH model. However, the efficacy of inhibition of C5 and/or HMGB1 therapeutic approaches has not been validated in a large animal trauma model at a prolonged field care (PFC) setting. Therefore, this project is to validate the effectiveness of early administration of nomacopan/Nomacopan (C5 inhibitor) and/or CX-01 (HMGB1 inhibitor) therapies aimed to attenuate morbidity and mortality after TH during PFC and prolonged damage control resuscitation.

15. SUBJECT TERMS
Immunotherapy, hemorrhage control, polytrauma, damage control resuscitation, prolonged field care, prehospital, systemic inflammatory response syndrome, multi-organ dysfunction syndrome

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

Traumatic hemorrhage (**TH**) is a major cause of death on the battlefield as well as for in the civilian world. The causes of battlefield deaths have remained unchanged over the last decade despite recent advances in treatment protocols. TH-involved ischemia/reperfusion injury, and trauma-related therapeutic approaches (blood transfusion, volume resuscitation, instrumentation, surgical damage control, extracorporeal membrane oxygenation, etc.) that play a major role in the systemic inflammatory response syndrome (SIRS), the compensatory anti-inflammatory response syndrome (CARS), endotheliopahty (EPT), and persistent inflammation/immunosuppression and catabolism syndrome (PICS). SIRS and CARS ultimately lead to injury-related multi-organ failure (MOF). MOF represents a leading cause of late mortality following severe trauma. Current prehospital care of the critically ill civilian and military trauma patients is primarily supportive for TH patients and does not address the destructive influence of unchecked inflammation-mediated MOF. Based on these premises, the lack of effective pharmacological solutions for MOF following TH, with potential for prehospital use, is a serious unmet need, which will be particularly important for severely injured patients with TH in future prolonged field care scenarios. This proposal is a **continuation** of our previous DoD funded proposals (C_008_2009_WRAIR, D61_I_10_J6_82, C_004_2011_USAISR, C_001_2009_USAISR, and BA-150310, and builds on our previous works and well-established capabilities at the Water Reed Army Institute of Research (WRAIR), US Army Institute of Surgical Research (USAISR) and the UT Health Science Center at San Antonio (UTHSCSA) [1-20]. Over the past 15 years, utilizing a translational medicine approach (**BBB**, Bedside to Bench and Back again) we have identified innate immunological damage control therapy as an urgent and unmet medical need for the treatment of severe TH, determined the ComC (C5) and damage-associated molecular patterns (HMGB1) as new therapeutic targets [1-22], selected clinical phase III ready **nomacopan** (C5 inhibitor, Akari Therapeutics) [1,14] and **CX-01** (HMGB1 inhibitor, Chemerix Inc.) [4] as lead investigation drugs (**repurposing drugs**), developed/validated clinically-relevant rodent [1,4,5,10,12-14,16,18] and swine [6,15,17,19,20] TH animal models, and proven early treatment with nomacopan [1,14] or CX-01 [4] **creating organ-protective and/or pro-survival phenotype**(s) through modulating systemic and local inflammatory responses, improving endotheliopathy and metabolism, and increasing responsiveness to fluid resuscitation in rat TH models of prolonged damage control resuscitation (**PDCR**, 24h) during prehospital care. However, the pharmacokinetic/pharmacodynamic profile and efficacy of nomacopan and CX-01 have not been examined in swine TH models during prolonged field care (**PFC**) and PDCR (≥24h). The purpose of this DoD project is to establish the effectiveness of the optimal inhibition therapy of nomacopan and CX-01 to improve morbidity and mortality after severe TH during PFC and PDCR. We will perform preclinical swine studies to develop and validate these novel therapies, as a prelude to clinical trials for nomacopan and CX-01 as **innate immunological damage control resuscitation** for early intervention in severe TH during PFC and PDCR (72h).

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

Traumatic hemorrhage, multi-organ failure, mortality, system inflammatory response syndrome, C5 inhibition, HMGB1 inhibition, immunological damage control resuscitation, prolonged field care

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1. Optimize the Nomacopan and CX-01 treatment regimen in a swine TH model	**Timeline (Months)**	**Original aims/tasks for performance at USAISR (not initiated)**	**New aims/tasks for performance at UTHSCSA (initiated)**

Major Task 1. Assess PK and PD profiles of Nomacopan and CX-01	Months	Drs. Li, Cancio, Dubick, Walters, and Yang	
Subtask 1. Local IACUC and ACURO approval	1-3	Drs. Li, Walters, and Yang	
Subtask 2. Determine PK profile in swine TH model	4-10	Drs. Li, Yang, and Dubick	
Subtask 2.1. Characterize PK profile of Nomacopan in swine TH model	4-7	Drs. Li and Yang	
Subtask 2.2. Characterize PK profile of CX-01 in swine TH model	6-10	Drs. Li and Yang	
Subtask 3. Determine PD profile in swine TH model	5-11	Drs. Li, Yang, Cancio, Dubick, Walters	
Subtask 3.1. Characterize PD profile of Nomacopan in swine TH model	5-8	Drs. Li and Yang	
Subtask 3.2. Characterize PD profile of CX-01 in swine TH model	7-11	Drs. Li and Yang	
Subtask 3. Determine drug-related immunotoxicity in swine TH model	4-12	Drs. Li, Dubick and Yang	
Subtask 3.1. Evaluate Nomacopan immunotoxicity in swine TH model	4-9	Drs. Li and Yang	
Subtask 3.2. Assess CX-01 immunotoxicity in swine TH model	6-12	Drs. Li and Yang	
Milestone(s) Achieved. 1) IACUC protocol/ ACURO approval; and 2) 3 optimal treatment regimens identified	*12*	Drs. Li, Cancio, Dubick, Walters, and Yang	
Specific Aim 2. Validate the efficacy of the 3 regimens in a swine TH model with fresh whole blood transfusion			
Major Task 2. Test the efficacy of the 3 regimens in a swine TH model with fresh whole blood transfusion		Drs. Li, Cancio, Dubick, Walters, and Yang	
Subtask 1. Perform animal study to test the efficacy of the Nomacopan optimal regimen	13-24	Drs. Li and Yang	
Subtask 2. Perform animal study to test the efficacy of the CX-01 optimal regimen	13-24	Drs. Li and Yang	
Subtask 3. Perform animal study to test the efficacy of the Nomacopan+CX-01 optimal regimen	13-24	Drs. Li and Yang	
Milestone(s) Achieved: 1) 1 lead treatment regimen identified; and 2) Submission of full IND application	24	Drs. Li, Cancio, Dubick, Walters, and Yang	
Specific Aim 3. Validate the efficacy of the 3 regimens in a swine TH model with Hex resuscitation			
Major Task 3. Evaluate the efficacy of the 3		Drs. Li, Cancio,	

regimens in a swine TH model with Hex resuscitation		Dubick, Walters, and Yang	
Subtask 1. Conduct animal study to test the efficacy of the Nomacopan optimal regimen	25-36	Drs. Li and Yang	
Subtask 2. Conduct animal study to test the efficacy of the CX-01 optimal regimen	25-36	Drs. Li and Yang	
Subtask 3. Conduct animal study to test the efficacy of the Nomacopan+CX-01 optimal regimen	25-36	Drs. Li and Yang	
Milestone(s) Achieved: 1) 1 lead treatment regimen identified; and 2) Submission of full IND application	36	Drs. Li, Cancio, Dubick, Walters, and Yang	
Specific Aim 1. Optimize the Nomacopan and CX-01 treatment regimen in a swine TH model			
Major Task 1. Assess PK and PD profiles of Nomacopan and CX-01 ***[pigs needed = [3 (per group) x 4 (doses) + 3 (per group) x 2 (dose windows) + 3 (per group) x 2 (dose frequencies)] x 2 (drugs) + replacement = 49]***			Drs. Li, Cancio, Simovic, Nunn (Akari), Elliott, Batchinsky, Bynum, Nicholson, and Colton (Chimerix)
Subtask 1. Prepare/submit a package for changing performance site	13-18		Dr. Li and Ms. Norton
Subtask 2. Establish a CRADA between UTHSCSA and Geneva Foundation	13-16		Drs. Li/Nicholson/Hacker and Ms. Norton
Subtask 3. Obtain an approval of animal protocol by local IACUC/ACURO protocol	18-24		Drs. Li, Elliott, Simovic, Nunn, Cancio, Batchinsky, Colton, and Nicholson
Subtask 4. Establish new MTAs between Akari/ Chimerix and Geneva Foundation	13-23		Drs. Li, Nunn, Colton, and Ms. Norton
Subtask 5. Prepare and complete in-process and a kick-off meeting with Drs. Nicholson and Hacker at UTHSCSA	13-21		Drs. Li, Simovic, Nicholson, Hacker, Elliott, and Ms. Fraker
Subtask 6. Participate and complete animal-based training at UTHSCSA	13-16		Drs. Li, Simovic, Hacker, Elliott, Nicholson, and Ms. Fraker
Subtask 7. Prepare and setup animal/wet laboratories at UTHSCSA	13-27		Drs. Li, Cancio, Simovic, Elliott, Nunn, Bynum, Nicholson, and Ms. Fraker
Subtask 8. Preparing SOPs, manuscripts, conference abstracts, oral/poster presentations, proposals, press release, etc.,	13-27		Drs. Li, Simovic, Elliott, and Ms. Fraker
Subtask 9. Building a new research team	24-27		Drs. Li, Simovic,

			Bynum, and Mr. Tusa
Subtask 11. Obtaining investigational drugs (nomacopan and CX-01)	24-27		Drs. Li, Nunn, and Colton
Subtask 12. Determine PK profile in swine TH model	25-27		Drs. Li, Nunn, Colton, and Bynum
Subtask 12.1. Characterize PK profile of Nomacopan in swine TH model	25-26		Drs. Li, Nunn, and Bynum
Subtask 12.2. Characterize PK profile of CX-01 in swine TH model	26-27		Drs. Li, Colton, and Bynum
Subtask 13. Determine PD profile in swine TH model	25-27		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nunn, Colton, and Nicholson
Subtask 13.1. Characterize PD profile of Nomacopan in swine TH model	25-26		Drs. Li, Cancio, Simovic, Elliott, Nunn, Bynum, Batchinsky, and Nicholson
Subtask 13.2. Characterize PD profile of CX-01 in swine TH model	26-28		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Colton, and Nicholson
Subtask 14. Determine drug-related immunotoxicity in swine TH model	26-28		Drs. Li, Nunn, Colton, Simovic, Elliott, and Bynum
Subtask 14.1. Evaluate Nomacopan immunotoxicity in swine TH model	26-28		Drs. Li, Nunn, Simovic, Elliott, and Bynum
Subtask 14.2. Assess CX-01 immunotoxicity in swine TH model	26-28		Drs. Li, Colton, Simovic, Elliott, and Bynum
Milestone(s) Achieved. 1) IACUC protocol/ ACURO approval; and 2) 3 optimal treatment regimens identified	28		Drs. Li, Cancio, Simovic, Nunn, Elliott, Bynum, Batchinsky, Nicholson, and Colton
Specific Aim 2. Validate the efficacy of the 3 regimens in a swine TH model with fresh whole blood transfusion			
Major Task 2. Test the efficacy of the 3 regimens in a swine TH model with fresh whole blood transfusion *[pigs needed = 15 (per group) x 4 (treatments) + 5 (non-injury/time control) + 5 replacement = 70]*	28-33		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, Nunn, and Colton
Subtask 1. Perform animal study to test the efficacy	28-32		Drs. Li, Cancio,

of the Nomacopan optimal regimen			Simovic, Elliott, Bynum, Batchinsky, Nicholson, and Nunn
Subtask 2. Perform animal study to test the efficacy of the CX-01 optimal regimen	28-32		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, and Colton
Subtask 3. Perform animal study to test the efficacy of the Nomacopan+CX-01 optimal regimen	29-33		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, Nunn, and Colton
Milestone(s) Achieved: 1) 1 lead treatment regimen identified; and 2) Submission of full IND application	33		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, Nunn, and Colton
Specific Aim 3. Validate the efficacy of the 3 regimens in a swine TH model with Hex resuscitation			
Major Task 3. Evaluate the efficacy of the 3 regimens in a swine TH model with Hex resuscitation *[pigs needed = 15 (per group) x 4 (treatments) + 5 (non-injury/time control) + 5 replacement = 70]*	30-36		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, Nunn, and Colton
Subtask 1. Conduct animal study to test the efficacy of the Nomacopan optimal regimen	30-35		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, and Nunn
Subtask 2. Conduct animal study to test the efficacy of the CX-01 optimal regimen	30-35		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, and Colton
Subtask 3. Conduct animal study to test the efficacy of the Nomacopan+CX-01 optimal regimen	31-36		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, Nunn, and Colton
Milestone(s) Achieved: 1) 1 lead treatment regimen identified; and 2) Submission of full IND application	36		Drs. Li, Cancio, Simovic, Elliott, Bynum, Batchinsky, Nicholson, Nunn, and Colton

Performance sites of project aims tasks: Original aim & task for performance at USAISR highlighted in light blue and revised aim &task for performance at UTHSCSA highlighted in yellow.

Project status: completed in green, initiated in blue, and not initiated in purple.

Notes: Akari Therapeutics and Chimerix Inc will provide the investigational drugs: nomacopan/coversin (a C5 inhibitor) and CX-01 (a HMGB1 inhibitor) respectively via a CRADA/MTA between the Geneva Foundation and the pharmaceutical companies. The pharmaceutical companies will offer us PK/PD/toxicological support.

Abbreviations: ACURO, Animal Care and Use Review Office; CRADA, cooperative research & development agreement; IACUC, institutional animal care and use committee; IND, Investigational New Drug; MTA, material transfer agreement; PD, pharmacodynamics; PK, pharmacokinetics; SOP, standard operating procedure; TH, traumatic hemorrhage; UTHSCSA, UT Health Science Center at San Antonio.

What was accomplished under these 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 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 will be best suited for our research program applying a translational BBB approach (Bedside to Bench and Back).

- **Objective:** 1) to obtain an approval of the package for changing performance site; 2) to establish new collaboration with the UTHSCSA, Akari, and Chimerix; and 3) to obtain an approval of IACUC protocol.

- **Major research activity:** During the year 2, we have presented two posters in terms of the model development data in two scientific conferences, established CRADA/MTAs with the UTHSCSA, Akari Therapeutics and Chimerix, and obtained an approval of animal research protocol by IACUC and ACURO. We have achieved following key outcomes:

- **Significant results/key outcomes:**
  1. We have established a CRADA between Geneva Foundation and UTHSCSA that allows us to perform this project at the UTHSCSA (For details, please see the Appendices: attachment #1).
  2. We have established a new MTA between Geneva Foundation and Akari Therapeutics to obtain nomacopan (For details, please see the Appendices: attachment #2).
  3. We have established a new MTA between Geneva Foundation and Chimerix to obtain CX-01 (For details, please see the Appendices: attachment #2).
  4. We are going to receive the investigational drugs next month (Nov 2022).
  5. We have prepared and submitted an animal research protocol.
  6. We have obtained an approval of the animal research protocol by the UTHSCSA IACUC and DoD ACURO (For details, please see the Appendices: attachment #3).
  7. We have completed the animal-related training at the UTHSCSA.
  8. We have obtained the UTHSCSA badge and computer access.
  9. We have submitted the package for changing performance site.
  10. We have set up our animal lab and are setting up our wet lab at the UTHSCSA.
  11. We are interviewing technician candidates to hire a lab technician.
  12. We have routinely discussed experimental data/design, current challenges and future plans with the co-Investigators (biweekly), group members (daily), and the Geneva Foundation's grant/contracts manager (weekly).
  13. We have prepared and submitted 8 manuscripts (4 published and 2 in press, for details, please see the Appendices: attachment #4) and 6 proposals.
  14. We have attended 4 conferences and had 5 oral and 2 poster presentations (For details, please see the Appendices: attachment #5).
  15. To keep our knowledge and skills current, we have searched/read scientific articles, attended virtual scientific meetings, and took online training courses.

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

This project has provided a great opportunity to train 1 Scientist and 1 Technician with regard to histopathological evaluation, data entry, analysis and summary, poster preparation and presentation, MTA/CRADA preparation, manuscript/proposal/IACUC protocol writing/preparation, and SOP writing/preparation.

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 professional conferences (For details, please see the Appendices: attachment #5) and a press release (For details, please see the Appendices: attachment #6).

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

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 expertise at swine models of trauma-induced multi-organ failure), **Dr. James Bynum** (a research scientist with expertise at trauma-induced coagulopathy and mitochondrial dysfunction), and **Dr. Simovic** (a senior trauma physiologist with expertise at swine TH models).
2. We are revising the package for changing performance site/no cost extension and expect an approval on December 2022.
3. We are arranging the shipment of the investigational drugs and anticipate to receive them on November 2022.
4. We are proactively searching and purchasing equipment, reagents, and supplies.
5. We are setting up the new wet laboratory at the UTHSCSA.
6. We are interviewing candidates and going to hire a new postdoc.
7. We are exploring new cross-team/organization collaborations at the UTHSCSA.
8. We are planning to initiate the animal study on February 2023.
9. We are preparing/writing new SOPs for our animal/laboratory experiments.
10. We are preparing/writing 5 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 the UTHSCSA (see above).
2. We are planning to keep good communication with the grans/contract manager and science officer to speed up the package approval process.
3. We are continuing to communicate with the grans/contract manager and science officer, and share how the crisis is affecting our work and how we plan to keep making progress.
4. We are planning to keep good communication with our Co-Is, team members and animal facility to keeping the research going.
5. 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.
6. We will keep searching/reading research articles to gain new knowledge.
7. We will take on webinar/online courses/conferences to gain insights and build skills.
8. We are preparing and writing SOPs for the research project.
9. We are searching and purchasing reagents and equipment 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 performing animal study and personnel hiring 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

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

1. Yang Z, Nunn MA, Le TD, Simovic MO, Edsall PR, Liu B, Barr JL, Lund BJ, Hill-Pryor CD, Wade CE, Pusateri AE, Cancio LC, and Li Y. Immunopathology of Terminal Complement Activation and Complement C5 Blockade Creating a Pro-survival and Organ-protective Phenotype in Trauma. Br J Pharmacol. Bime C, Casanova NG, Camp SM, Oita RC, Ndukum J, Hernon VR, Oh DK, Li Y, Greer PJ, Whitcomb DC, Papachristou GI, Garcia JGN. Circulating eNAMPT as a biomarker in the critically ill: acute pancreatitis, sepsis, trauma, and acute respiratory distress syndrome. BMC Anesthesiol. 2022 Jun 15;22(1):182 (in press).
2. Yang Z, Le TD, Simovic MO, Liu B, Fraker TL, Cap AP, Wade CE, DalleLucca JJ, Li Y. Traumatized Triad of Complementopathy, Endotheliopathy and Coagulopathy - Impact on Clinical Outcomes in Severe Polytrauma Patients. Frontiers in Immunology. 2022 (in press).
3. Bime C, Casanova NG, Camp SM, Oita RC, Ndukum J, Hernon VR, Oh DK, Li Y, Greer PJ, Whitcomb DC, Papachristou GI, Garcia JGN. Circulating eNAMPT as a biomarker in the critically ill: acute pancreatitis, sepsis, trauma, and acute respiratory distress syndrome. BMC Anesthesiol. 2022 Jun 15;22(1):182.
4. Yang Z, Dubick MA, Burgess MB, Cancio LC, DalleLucca JJ, Li Y. Indices of Complement Activation and Coagulation Changes in Trauma Patients. TSACO. 2022; 7(1):e000927.
5. Yang Z, Simovic MO, Edsall PR, Liu B, Cancio TS, Batchinsky AI, Cancio LC and Li Y. HMGB1 inhibition to ameliorate organ failure and increase survival in trauma. Biomolecules. 2022; 12:101.
6. Bermudez T, Sammani S, Song JH, Hernon VR, Kempf CL, Garcia AN, Burt J, Hufford M, Camp SM, Cress AE, Desai AA, Natarajan V, Jacobson JR, Dudek SM, Cancio LC, Alvarez J, Rafikov R, Li Y, Zhang DD, Casanova NG, Bime C, Garcia JGN. eNAMPT neutralization reduces preclinical ARDS severity via rectified NFkB and Akt/mTORC2 signaling. Sci Rep. 2022 Jan 13;12(1):696.

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. 2021 Military City USA Trauma Collaborative Research Conference (San Antonio TX, oral presentation, OCT 2021).
2. Li Y, Nunn MA, Le TD, Simovic MO, Edsall PR, Liu B, Barr JL, Lund BJ, Hill-Pryor CD, Pusateri AE, Cancio LC. Immunopathology of terminal complement activation and complement C5 blockade creating a pro-survival and organ-protective phenotype for trauma/hemorrhage prolonged damage control resuscitation. MHSRS (Kissimmee, FL, oral presentation, Sep 2022).
3. Yang Z, Le TD, Simovic MO, Liu B, Fraker TL, Cap AP, Wade CE, DalleLucca JJ, Li Y. Triad of Complementopathy, Endotheliopathy and Coagulopathy – Impacts on Clinical Outcomes in Severe Polytrauma Patients. MHSRS (Kissimmee, FL, oral presentation, Sep 2022).
4. Simovic MO, Yang Z, Cancio LC, Li Y. Neutralization of extracellular nicotinamide phosphoribosyltransferase ameliorates blast/ventilator-induced acute lung injury in rats. MHSRS (Kissimmee, FL, oral presentation, Sep 2022).
5. Li Y, Yang Z, Nunn MA, Le TD, Simovic MO, Edsall PR, Liu B, Barr JL, Lund BJ, Hill-Pryor CD, Pusateri AE, Cancio LC. Pathobiology of terminal complement activation and inhibition of complement C5 creating a pro-survival and organ-protective phenotype in a rat model of blast injury and hemorrhage. 6th International Forum on Blast Injury Countermeasures (Vienna, VA, oral presentation, May 2022)
6. Fraker TL, Yang Z, Jordan BS, Lucas ML, Cancio TS, Simovic MO, Necsoiu C, Walters TJ, Cap AP, Li Y, Cancio LC. Development of a porcine model of blast injury and hemorrhagic shock: systemic activation of complement pathways, HMGB1 release and coagulation profile. Poster presentation at the Military City USA Trauma Collaborative Research Conference (San Antonio, TX, Oct 2021).
7. Fraker TL, Necsoiu C, Yang Z, Jordan BS, Lucas ML, Cancio TS, Simovic MO, Cancio LC, Li Y. Pathophysiological indices after blast injury and hemorrhage in a swine model of prolonged damage control resuscitation. Poster presentation at the MHSRS (Kissimmee, FL, Sep 2022).

For details, please see below Appendices (Attachment #5).

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

1. Press release: Research Insights: “Promising Treatment Using Tick Saliva Targets the Body’s Immune System to Treat Trauma and TBI” (the Geneva Foundation website, Apr 2022). For details, please see below Appendices (Attachment #6)

Nothing to Report

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

1. Li Y, Cancio LC, Pusateri AE, Nunn Miles, and Yang Z. Nomacopan for the use to create pro-survival and organ-protective phenotype (s) after trauma and hemorrhagic shock (invention disclosure, in preparation).
2. Li Y, Cancio LC, Pusateri AE, Nunn Miles, and Yang Z. CX-01 for the use to create pro-survival and organ-protective phenotype (s) after trauma and hemorrhagic shock (invention disclosure, in preparation).

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: **Yansong Li** (Geneva Foundation)
Project role: PI
Research identifier: 60318
Nearest person month worked: 6
Contribution to project: Participated in 1) preparation of the package for changing performance site/no cost extension, 2) preparation/submission of IACUC protocol, 3) establishment of collaboration with the UTHSCSA for changing performance site, 4) preparation MTAs between Geneva and Akari Therapeutics Plc. (London, UK) and the Chimerix Inc (Durham, NC, USA) for obtaining nomacopan and rhC1INH respectively, 5) data analysis, summary and interpretation, 6) revising abstracts/posters/SOPs, 7) preparation/submission of manuscripts/proposals, 8) personnel hiring/training and team building, 9) project design and strategic plan, 10) preparation/submission of press release and invention disclosure, and 11) animal-related training.
Funding support: W81XWH2020040

Name: **Milomir Simovic** (Geneva Foundation)
Project role: Co-I
Research identifier:
Nearest person month worked: 6
Contribution to project: Participated in 1) data analysis, summary and interpretation, 2) IACUC protocol preparation, 3) presentation preparation, 4) manuscript preparation/revision, 5) proposal preparation/revision, and 6) animal-related training.
Funding support: W81XWH2020040

Name: **Tamara Fraker**
Project role: Research Technician
Research identifier:
Nearest person month worked: 6
Contribution to project: Participated in 1) searching/ordering reagents/devices, 2) attending online/in-person trainings, 3) data analysis/summary, 4) revising/editing manuscripts and proposals, and 5) preparing/submitting abstract/poster.
Funding support: W81XWH1920040

Name: **Leopoldo Cancio** (USAISR Burn Center)
Project role: Co-I
Research identifier:
Nearest person month worked: 0.5
Contribution to project: Participated in 1) project design and strategic plan, 2) data analysis and interpretation, new collaboration establishment, and 4) manuscript/proposal/presentation revision.
Funding support: N/A

Name: **Andriy Batchinsky** (Geneva Foundation)
Project role: Co-I
Research identifier: N/A
Nearest person month worked: 0.1
Contribution to project: Participated in 1) IACUC protocol revision, 2) project plans, and 3) manuscript revision.
Funding support: N/A

Name: **Zhangsheng Yang** (USAISR)
Project role: Co-I
Research identifier: 48088
Nearest person month worked: 1
Contribution to project: Participated in 1) data analysis, summary and interpretation, 2) writing manuscripts/abstracts, and 3) presentation at profession meeting.
Funding support: N/A.

Name: **James Elliott** (UTHSCSA)
Project role: Co-I
Research identifier: N/A
Nearest person month worked: 0.2
Contribution to project: Participated in 1) Animal model discussion; 2) IACUC preparation/revision; and 3) animal-based research trainings.
Funding support: N/A

Name: **Miles Nunn** (Akari Pharmaceutics)
Project role: Collaborator/consultant
Research identifier: N/A
Nearest person month worked: 0.1
Contribution to project: Participated in 1) MTA/CRADA preparation/revision, 2) a joint meeting with TBICoE/Akari/Geneva to discuss a potential support for translating nomacopan to a clinical TBI trial, 3) experiment PK/PD design/discussion, 4) experimental plan, 5) arranging experimental drug shipment, and 6) manuscript revision.
Funding support: N/A

Name: **Heidi Colton** (Chimerix Inc.)
Project role: Collaborator/consultant
Research identifier: N/A
Nearest person month worked: 0.2
Contribution to project: Participated in 1) MTA/CRADA preparation/revision, 2) experiment PK/PD design/discussion, 3) experimental plan, and 4) arranging CX-01 drug shipment.
Funding support: N/A

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 prepare the new MAT and discuss our study progress and experimental plans, and gain insightful comments.
2. We routinely to shared project plan/status and discuss the new MTA and our experimental design with the Chimerix Inc.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: Attached

9. APPENDICES:

1) Attachment #1: CRADA_Geneva-UTHSCSA
2) Attachment #2: MTAs_Geneva-Akari/Chimerix
3) Attachment #3: Approved IACUC protocol
4) Attachment #4: Publications
5) Attachment #5: Conference abstracts and oral/poster presentations
6) Attachment #6: Press release