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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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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

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TABLE OF CONTENTS

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 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)[1-17] 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 as new therapeutic targets (C5, C1, etc.,)[1-17], selected clinical phase III ready **nomacopan** (C5 inhibitor, Akari Therapeutics)[1] and marked recombinant human C1 inhibitor (**rhC1INH**, Pharming Group NV)[10,14] as lead investigation drugs (**repurposing drugs**), developed/validated clinically-relevant rat[1,4,6,7,8,9,12,14] and swine[10,13,15,16] TH animal models, and proven early treatment with nomacopan[1,9] or rhC1INH[10,15] **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 model of prolonged damage control resuscitation (**PDCR**, 24h) and in porcine models of hemorrhage or TH during prehospital care (≤6h). However, the pharmacokinetic/pharmacodynamic profile and efficacy of nomacopan and rhC1INH 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 rhC1INH 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 rhC1INH as **innate immunological damage control resuscitation** for early intervention in severe TH during PFC and PDCR (24h).

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2. KEYWORDS:

Trauma, hemorrhage, multi-organ failure, mortality, complement cascade, multi-system inflammatory syndrome, thromboinflammation, immunological damage control resuscitation, prolonged field care

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Evaluate the efficacy of nomacopan or C1-INH in a clinically relevant porcine trauma hemorrhage during a short-term PFC (15 pigs).	Timeline Months	Original aim & task for performance at USAISR	New Aim & Task for performance at UTHSCSA
Major Task 1: Determine the efficacy of nomacopan or C1-INH in a clinically relevant porcine trauma hemorrhage during a short-term PFC.			
Subtask 1. Obtain an approval of animal protocol by local IACUC/ACURO protocol	1-3	Drs. Li, Cancio, Dubic, Yang	
Subtask 2. Renew CRADAs between Akari/Pharming and USAISR, and obtain investigational drugs (nomacopan and C1-INH)	1-8	Drs. Li, Nunn, Doorten, Cancio	
Subtask 3. Characterize and validate new shock tube performance	4-10	Drs. Li, rule, Edsall, Yang, Simovic, Ms. Fraker	
Subtask 4. Prepare and conduct model development and characterization of blast injury and hemorrhage (Total # of swine needed: 15)	10-23	Drs. Li, Cancio, Corina, Edsall, Yang, Simovic, Ms. Fraker	
Subtask 5. Characterize and assess systemic ComC activation and inflammatory response by ELISA, CBC, and CH50 after blast injury and hemorrhage	12-24	Drs. Li, Yang, Simovic, Ms. Fraker	

(whole blood samples = 15 pigs x 6 timepoints = 90; plasma samples = 15 pigs x 6 timepoints = 90; serum samples = 15 pigs x 6 timepoints = 90)			
Subtask 6. Characterize and measure MOF and mortality by biochemistry, survival rate, ELISA and i-Stat after blast injury and hemorrhage (whole blood samples = 15 pigs x 6 timepoints = 90; plasma samples = 15 pigs x 6 timepoints = 90; serum samples = 15 pigs x 6 timepoints = 90)	12-24	Drs. Li, Corina, Yang, Simovic, Ms. Fraker	
Subtask 7. Characterize and assess hemodynamic and metabolic using non-invasive hemodynamic monitor and i-stat after blast injury and hemorrhage (whole blood samples = 15 pigs x 6 timepoints = 90)	11-23	Drs. Li, Corina, Yang, Simovic, Ms. Fraker	
Subtask 8. Characterize and evaluate tissue/organ damage by histopathology and CT scan imaging after blast injury and hemorrhage (tissue/organ samples = 15 pigs x 7 organs = 105; CT scans = 15 pigs x 2 timepoints = 30)	12-24	Drs. Li, Corina, Yang, Simovic, Ms. Fraker	
Subtask 9. Characterize and assess changes of coagulation and biochemicals by i-Stat and biochemistry after blast injury and hemorrhage (whole blood samples = 15 pigs x 6 timepoints = 90; plasma samples = 15 pigs x 6 timepoints = 90)	11-23	Drs. Li, Corina, Yang, Simovic, Ms. Fraker	
Milestone(s) Achieved. 1) approval of the IACUC/ACURO protocol, 2) renewal of the CRADAs, 3) acquisition of the investigational drugs, 4) completion of the shock tube characterization/validation, and 5) completion of the model development and characterization.	24	Drs. Li, Cancio, Corina, Yang, Edsall, Rule, Nunn, Doorten, Simovic	
Specific Aim 2: Develop a clinically relevant porcine model of polytrauma hemorrhage and evaluate PK/PD and toxicity in this model during a 24hr-PFC (Total # of swine needed: 30)			
Major Task 2: Perform a mini model development, and determine PK/PD and toxicity of nomacopan or C1-INH in a clinically relevant porcine trauma hemorrhage			
Subtask 1. Prepare/submit/revise a package for changing performance site	25-36		Dr. Li, Ms. Norton
Subtask 2. Establish a CRADA between UTHSCSA and Geneva Foundation	25-28		Drs. Li, Nicholson, Ms. Norton
Subtask 3. Obtain an approval of animal protocol by local IACUC/ACURO protocol	29-35		Drs. Li, Simovic, Cancio, Nunn, Hacker, Elliott, Nicholson, Batchinsky, Doorten
Subtask 4. Establish new MTAs between Akari, Pharming, and Geneva Foundation	25-35		Drs. Li, Nunn, Doorten, Ms. Norton

Subtask 5. Prepare and complete in-process and a kick-off meeting with Drs. Nicholson and Hacker at UTHSCSA	25-29		Drs. Li, Simovic, Cancio, Batchinsky, Ms. Fraker, Ms. Norton
Subtask 6. Participate and complete animal-based training at UTHSCSA	26-29		Drs. Li, Simovic, Cancio, Batchinsky, Ms. Fraker
Subtask 7. Prepare and setup a laboratory at UTHSCSA	29-36		Drs. Li, Simovic, Ms. Fraker
Subtask 8. Preparing SOPs, manuscripts, conference abstracts, oral/poster presentations, proposals, press release, etc.,	25-36		Drs. Li, Cancio, Simovic, Le, Nicholson, Batchinsky, Ms. Fraker
Subtask 9. Building a new research team	28-36		Drs. Li, Simovic, Ms. Norton
Subtask 11. Obtaining investigational drugs (nomacopan and C1-INH)	33-36		Drs. Li, Nunn, Doorten
Subtask 12. Develop and characterize swine trauma and hemorrhage model (Total # of swine needed: 12)	37-39		Drs. Li, Simovic, Cancio, Batchinsky, Nicholson, Hacker
Subtask 12.1. Conduct model development	37-38		Drs. Li, Simovic, Cancio, Batchinsky, Nicholson, Hacker
Subtask 12.2. Characterize and assess ComC activation, inflammatory response, MOF, and survival after trauma and hemorrhage by ELISA, CH50, biochemistry, IHC, and histopathology (whole blood samples = 12 pigs x 8 timepoints = 96; serum samples = 12 pigs x 8 timepoints = 96; plasma samples = 12 pigs x 8 timepoints = 96; tissue samples = 12 pigs x 9 organs = 108)	37-39		Drs. Li, Simovic, Ms. Fraker
Subtask 13. Determine PK/PD profiles and toxicity of nomacopan or C1-INH in the developed swine model (Total # of swine needed: 18)	39-41		Drs. Nunn, Li, Dr. Doorten, Simovic, Ms. Fraker
Subtask 13.1. Assess PK profile of nomacopan and C1-INH using HPLC/mass spectrum and ELISA (plasma samples = 18 pigs x 10 timepoints = 180; tissue samples = 18 pigs x 9 organs = 99)	39-40		Drs. Li, Nunn, Doorten, Simovic, Ms. Fraker
Subtask 13.2. Assess PD profile of nomacopan or C1-INH using ELISA, IHC, and histopathology (plasma samples = 18 pigs x 10 timepoints = 180; tissue samples = 18 pigs x 9 organs = 99)	39-41		Drs. Li, Simovic, Ms. Fraker
Subtask 13.3. Assess toxicity of nomacopan or C1-INH by ELISA, IHC, biochemistry, and histopathology (plasma samples = 18 pigs x 10 timepoints = 180; tissue samples = 18 pigs x 9 organs = 99)	39-41		Drs. Li, Nunn, Doorten, Simovic, Ms. Fraker
Milestone(s) Achieved. 1) approval of the IACUC/ACURO protocol, CRADA and MTAs, 2) approval of the package of changing performance	41		Drs. Li, Cancio, Nunn, Nicholson, Batchinsky,

site, 3) 1 press release and 2 posters, 4) completion of the model development and characterization, 5) completion of the PK/PD studies, and 6) acquisition of the investigational drugs			Doorten, Simovic
Specific Aim 3: Evaluate efficacy of anti-ComC regiments in a clinically relevant porcine model of polytrauma hemorrhage during a 24hr-PFC at UTHSCSA (Total # of swine needed: 50)			
Major Task 3: Determine the efficacy of anti-ComC regiments in a clinically relevant porcine model of trauma and hemorrhage			
Subtask 1. Obtain an approval of animal protocol by local IACUC/ACURO protocol	29-35		Drs. Li, Simovic, Cancio, Nunn, Hacker, Elliott, Nicholson, Batchinsky, Doorten
Subtask 2. Perform animal study to test efficacy of nomacopan or C1-INH on survival and hemodynamic changes using a non-invasive hemodynamic monitor in the developed swine model (Total # of swine needed: 50)	41-47		Drs. Li, Simovic, Cancio, Hacker, Elliott, Nicholson, Batchinsky, Ms. Fraker
Subtask 3. Assess efficacy of nomacopan and C1-INH on metabolism and gut microbiome by i-stat, Oroboros oxygraph-2k system, and 16S metagenomics (whole blood samples = 50 pigs x 8 timepoints = 400; plasma samples = 50 pigs x 8 timepoints = 400; tissue samples = 50 pigs x 9 organs = 450; rectal swab samples = 50 x 5 timepoints = 250)	42-47		Drs. Nicholson, Li, Simovic, Cancio, Hacker, Elliott, Batchinsky, Ms. Fraker
Subtask 4. Assess efficacy of nomacopan or C1-INH on inflammation and MOF in the developed swine model using ELISA, IHC and PCR (plasma samples = 50 pigs x 8 timepoints = 400; tissue samples = 50 pigs x 9 organs = 450)	43-48		Drs. Li, Simovic, Cancio, Hacker, Elliott, Nicholson, Batchinsky, Ms. Fraker
Subtask 5. Assess efficacy of nomacopan or C1-INH on ComC, CoaC, KinC, and FibC by ROTEM, ELISA, CH50, IHC, and PCR (serum samples = 50 pigs x 8 timepoints = 400; plasma samples = 50 pigs x 8 timepoints = 400; tissue samples = 50 pigs x 9 organs = 450)	41-48		Drs. Li, Simovic, Cancio, Hacker, Elliott, Nicholson, Batchinsky, Ms. Fraker
Subtask 6. Assess efficacy of nomacopan or C1-INH on DAMPs, endotheliopathy, and oxidative stress by ELISA, biochemistry, IHC, and PCR (plasma samples = 50 pigs x 8 timepoints = 400; tissue samples = 50 pigs x 9 organs = 450)	45-48		Drs. Li, Simovic, Cancio, Hacker, Elliott, Nicholson, Batchinsky, Ms. Fraker
Subtask 7. Evaluate efficacy of nomacopan or C1-INH on organ damage by histopathology (organ/tissue samples = 50 pigs x 9 organs = 450)	45-48		Drs. Li, Simovic, Cancio, Hacker, Elliott, Nicholson, Batchinsky, Ms. Fraker

Milestone(s) Achieved: Submission of a full IND application	48		Drs. Li, Cancio, Nunn, Nicholson, Batchinsky, Doorten, Simovic

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 Pharming Group NV will provide the investigational drugs: nomacopan/coversin (a C5 inhibitor) and C1-INH (a C1 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; C1-INH, C1 inhibitor; CH50, 50% hemolytic complement activity assay; CoaC, coagulation cascade; ComC, complement cascade; CT, computed tomography; DAMPs, damage-associated molecular patterns; ELISA, enzyme-linked immunosorbent assay; FibC, fibrinolytic cascade; HPLC, I High-performance liquid chromatography; IACUC, institutional animal care and use committee; IHC, immunohistochemistry; IND, Investigational New Drug; KinC, kinin cascade; MOF, multiple-organ failure; PCR, Polymerase chain reaction; PD, pharmacodynamics; PDCR, prolonged damage control resuscitation; PFC, prolonged field care; PK, pharmacokinetics; ROTEM, Rotational Thromboelastogram.

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 develop and characterize a clinically relevant swine model of blast injury (BI) and hemorrhage (H); 2) to obtain an approval of the package for changing performance site; 3) to establish new collaboration with the UTHSCSA, Akari, and Pharming; and 4) to obtain an approval of IACUC protocol.

- **Major research activity:** During the year 3, 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 Pharming Group NV, 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 analyzed, summarized, and presented the swine model development data in 2 scientific conferences (For details, please see the Appendices: attachment #1).
  2. 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 #2).
  3. We have established a new MTA between Geneva Foundation and Akari Therapeutics to obtain nomacopan (For details, please see the Appendices: attachment #3).
  4. We have established a new MTA between Geneva Foundation and Pharming Group NV to obtain rhC1INH (For details, please see the Appendices: attachment #3).
  5. We are going to receive the investigational drugs next month (Nov 2022).
  6. We have prepared and submitted an animal research protocol.
  7. We have obtained an approval of the animal research protocol/addendum by the UTHSCSA IACUC and DoD ACURO (For details, please see the Appendices: attachment #4).
  8. We have completed the animal-related training at the UTHSCSA.
  9. We have obtained the UTHSCSA badge and computer access.
  10. We have submitted the package for changing performance site with a no cost extension.
  11. We have set up our animal lab and are setting up our wet lab at the UTHSCSA.
  12. We are interviewing postdoc candidates to hire a postdoc.
  13. 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).

14. We have prepared and submitted 7 manuscripts (3 published and 2 in press) and 6 proposals.
15. 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 2 Scientists and 2 Technicians with regard to blast injury, hemorrhagic shock, animal ICU, necropsy, biosampling, ComC assays (CH50, ComC screening, C3a/C5a ELISA, etc.,), histopathological evaluation, data entry, analysis and summary, poster preparation and presentation, MTA/CRADA preparation, manuscript/proposal/IACUC protocol writing/preparation, and SOP

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 abstracts/poster presentations in 2021 Military City USA Trauma Collaborative Research Conference (San Antonio, TX) and 2022 MHSRS (Kissimmee, FL), and a press release (Apr 2021, Geneva Foundation website). The detailed information is described in the 6. Product/attachment #1 and the Appendices: attachment #5.

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 November 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 December 2022.
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 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)
6. Addendum #5: Change burn injury to TBI and lung contusion/injury (approved on June 17, 2022, please see attachment#4)

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

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

Journal publications.

Nothing to Report

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

Nothing to Report

Other publications, conference papers and presentations.

1. 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). For details, please see below Appendices (Attachment #1).
2. 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 #1).

- **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 #5).

- **Technologies or techniques**

Nothing to Report

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

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

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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/addendum, 3) establishment of collaboration with the UTHSCSA for changing performance site, 4) preparation MTAs between Geneva and Akari Therapeutics Plc. (London, UK) and the Pharming Technologies B.V. (Leiden, Netherlands) 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: W81XWH1920040

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: W81XWH1920040

Name: **Tamara Fraker** (Geneva Foundation)
Project role: Research Technician
Research identifier:
Nearest person month worked: 6
Contribution to project: Participated in 1) data analysis, 2) poster preparation/presentation, 3) SOP preparation, 4) animal-related training, 5) equipment/reagent/supply search and order, and 6) manuscript/proposal edition.
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: **Sander Hacker** (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: **Yolanda Ponstein-Simarro Doorten** (Pharming Group B.V.)
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 experimental 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 MTA and discuss our data/experimental plans and gain insightful inputs.
2. We routinely shared our data/plans and discuss the new MTA and experimental design with the Pharming Technologies B.V.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: Attached.

9. APPENDICES:

1) Attachment #1: Conference abstracts/posters
2) Attachment #2: CRADA_Geneva-UTHSCSA
3) Attachment #3: MTAs_Geneva-Akari/Pharming
4) Attachment #4: Approved IACUC protocol/addendum
5) Attachment #5: Press release