

AWARD NUMBER: W81XWH-18-2-0051

TITLE: A Precision Medicine Approach Based on Discrete Time Windows for Predicting Outcomes of Polytrauma Patients

PRINCIPAL INVESTIGATOR: Timothy R. Billiar, MD

CONTRACTING ORGANIZATION: University of Pittsburgh, Pittsburgh, PA

REPORT DATE: October 2022

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; Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE*Form Approved*
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE October 2022		2. REPORT TYPE Annual		3. DATES COVERED 30Sep2021 – 29Sep2022	
4. TITLE AND SUBTITLE A Precision Medicine Approach Based on Discrete Time Windows for Predicting Outcomes of Polytrauma Patients				5a. CONTRACT NUMBER W81XWH-18-2-0051	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Timothy R. Billiar E-Mail: billiartr@upmc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF PITTSBURGH 3520 FIFTH AVE PITTSBURGH PA 15213-3320				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 We propose to leverage Precision Medicine approaches in a three-phase study of military and civilian trauma, incorporating 1) Phase 1- (Narrow-Window Diagnostic): A novel, time window-based trauma patient stratification scheme will be refined with genomic and admission clinical/inflammation biomarkers using both retrospective and prospective data on patients with polytrauma. We will define the admission variables that most accurately prognosticate for these adverse outcome categories. We can report that a unified Master dataset of retrospective data has been created and the Narrow-Window patient stratification model has been initiated. 2) Phase 2- (Wide-Window Diagnostic): The stratification algorithm from Phase 1, which is based on single time point data, will be compared against a wide-window algorithm involving multiple initial readings in the first 24h post-injury, using the dataset obtained in Phase 1. We will test the hypothesis that widening the time window for data acquisition will increase the precision of the prognostication. 3) Phase 3- (Optimized Patient Stratification): a prospective study testing the optimal stratification algorithm in patients with polytrauma ± TBI. In addition, UPITT has begun its recruitment of patients; 109 eligible patients to date					
15. SUBJECT TERMS Precision Medicine, polytrauma, stratification, narrow window					
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	13	19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4-6
4. Impact	6
5. Changes/Problems	7-8
6. Products	8- 10
7. Participants & Other Collaborating Organizations	11-12
8. Special Reporting Requirements	13
9. Appendices	13

1. INTRODUCTION:

This study proposes to deliver, within 3 years, precision medicine methods that will predict each patient's risk for adverse outcomes using patient specific metrics that quantify genetic and demographic signatures combined with individualized injury and injury response signals to accurately stratify expected clinical trajectories

2. KEYWORDS:

Precision medicine, polytrauma, narrow-window, stratification, biomarkers, SNP, WGA, time to recovery, model comparison

3. ACCOMPLISHMENTS:

What were the major goals of the project?

This project is focused on developing a time window-based scheme that could serve as a diagnostic and prognostic platform for early outcome stratification of trauma patients. We will leverage Precision Medicine approaches in a three-phase study of military and civilian trauma to accomplish our goals. An overview of the Major Tasks is below.

Phase I – Narrow-Window Diagnostic

Major Task 1.1 – Administrative Tasks

Milestone 1 – Obtain IRB and HRPO approval for patient enrollment

Milestone 2 – Register with FITBIR

Milestone 3 – All progress reports submitted to CDMRP

Milestone 4 – All data submitted to FITBIR

Major Task 1.2 – Genomic analyses from archival tissues

Milestone 5 – Completion of genomics analyses on archived Narrow Window samples

Major Task 1.3 – Biomarker studies on prospectively recruited polytrauma +/- TBI patients

Major Task 1.4 – Statistical and computational modeling of Narrow-Window data

Phase II – Wide-Window Diagnostic

Major Task 2.1 – Biomarker studies on polytrauma +/- TBI patients prospectively recruited in Phase I

Phase III – Optimized Patient Stratification

What was accomplished under these goals?

Our goals for the third year were to continue to continue recruitment, sample testing, and launch the long-term outcomes collection protocol.

Major Task 1.1 – Administrative Tasks

- Maintenance of IRB and HRPO approval at all sites
- Maintenance of FITBIR DUA
- 5 monthly all-site PI conference calls
- 26 Site 1 weekly internal coordination meetings
- 5 monthly all-site regulatory/clinical coordinators call
- 1 Face to Face / virtual conference held in Pittsburgh on 15 February 2022

Major Task 1.2

- Completed in Y2

Major Task 1.3

- o Completed 70 patients total, each with 3-4 time points per patient and 265 patient/time point permutations total, 46 cytokines/chemokines assayed per sample
- o Completed 3 SNPs assays with 82 samples, isolated 32 DNA samples
- Enrolled 32 at Site 1, 5 at Site 2, and 38 at Site 3 in past year, for a total of 75
- Total enrollment is 109 at Site 1, 14 at Site 2, and 75 at Site 3, for a total of 198

Major Task 1.4

- Identified key predictor and outcome variables for modeling
- Modelers received retrospective and prospective data and are currently developing a Dynamic Profiling Method that will classify new subjects based on the database

Phase III

- Site I and II continues enrolling under Phase III
- Site II continues to enrolling Phase I and II

Data Management

- Redcap database complete, now includes all clinical, physiological and biochemical data for a total of 150 patients
- Modeling database in process to include 121 patients

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

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

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

1. Continue Phase III recruitment at Site 1 and 3
2. Continue Phase I-II recruitment at Site 2
3. Complete enrollment by December 22, 2022
4. Complete 6-month follow up by June of 2023
5. Complete all MSD and SNP of prospectively enrolled patients
6. Validation of Narrow Window modeling
7. Completion of Wide Window predictive modeling
8. Submit all data to FITBUR

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

While COVID-19 restrictions were reduced during the last reporting year, we continued to use a hybrid in-person/remote work protocol. Additionally, due to the slowed recruitment, we plan to keep Site 2 on Phase I-II recruitment, and initiate Phase III at Sites 1 and 3 only.

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

1. COVID-19 restrictions caused a decrease in activities that may result in traumatic injuries and facilitate enrollment into the study. Site 1 continued to enroll Phase I-II subjects beyond the originally planned recruitment cap to make up for slowed recruitment at the other sites. In order to make-up for the recruitment slowdown, we are keeping Site 2 on Phase I-II recruitment for the duration of the study.

Changes that had a significant impact on expenditures

Due to both aforementioned events, recruitment, and thus expenditures, were less 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**
Report only the major publication(s) resulting from the work under this award.

Journal publications.

Publications for this reporting period.

1. Zamora, R.; Forsberg, J.; Shah, A.M.; Unselt, D.; Grey, S.; Lisboa, F.A.; Billiar, T.R.; Schobel, S.; Potter, B.K.; Elster, E.*; Vodovotz, Y.* Central role for neurally dysregulated IL-17A in dynamic networks of systemic and local inflammation in combat casualties. Sci. Rep. (Submitted) *Co-first authors.

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

For this reporting period:
None to report

Other publications, conference papers and presentations.

Oral Presentation:

MHSRS 2022 - Title: A Novel, High-Prevalence and -Penetrance Single-Nucleotide Polymorphism Associated with Trauma-Associated Critical Illness - Presenter: Yoram Vodovotz, Ph.D.

MHSRS 2022 - Title: A Combined Predictive Model Comprised of Circulating Biomarkers, Clinical, and Genetic Variables Improve Prognostication of Nosocomial Infection in Polytrauma Patients - Presenter: Henry Robertson, PhD

American College of Surgeons - Title: Genome-wide Analysis Suggests A Differential Interaction Between Genetic Polymorphism and Injury Severity in Driving Outcomes Post-Injury Presenter: Rami Namas, MD

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

Nothing to Report

- **Technologies or techniques**

Nothing to Report

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

Provisional patent as outlined in the previous annual report.

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Timothy Billiar, MD
Project Role: Principal Investigator
Nearest person month worked: 2
Funding Support: This grant

Name: Yoram Vodovotz
Project Role: Co-Principal Investigator
Nearest person month worked: 3
Funding Support: This grant

Name: Rami Namas
Project Role: Co-Investigator
Nearest person month worked: 4
Funding Support: This grant

Name: Derek Barclay
Project Role: Lab Manager
Nearest person month worked: 3
Funding Support: This grant

Name: Jinling Yin
Project Role: Molecular Biologist
Technician
Nearest person month worked: 6
Funding Support: This grant

Name: Michelle Situ
Project Role: Data Extractor
Nearest person month worked: 6
Funding Support: This grant

Name: Zachariah Hoydich
Project Role: Clinical Research
Coordinator
Funding Support: This grant

Name: Lilith Bailey-Kroll
Project Role: Clinical Research
Coordinator
Funding Support: This grant

Name: Dr. David Okonkwo
Project Role: Co-Investigator
Nearest person month worked: 2
Funding Support: This grant

Name: Dr. Ava Puccio
Project Role: Co-Investigator
Nearest person month worked: 2
Funding Support: This grant

Name: Allison Borrasso
Project Role: Clinical Research Coordinator
Nearest person month worked: 4
Funding Support: This grant

Name: Gregory Constantine
Project Role: Professor of Mathematics and
Statistics
Nearest person month worked: 4
Funding Support: This grant

Name: Alexander Limkakeng
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: Institutional

Name: Grace Hall
Project Role: Lead Clinical Research
Coordinator
Nearest person month worked: 6
Funding Support: Institutional

Name: Eric Elster
Project Role: Co-Investigator
Nearest person month worked: 1
Funding Support: Institutional

Name: Seth Schobel-McHugh
Project Role: Bioinformatician
Nearest person month worked: 2
Funding Support: This grant

Name: Kim McLaughlin
Project Role: Bioinformatician
Nearest person month worked: 5
Funding Support: This grant

Name: Henry Robertson
Project Role: Biostatistician
Nearest person month worked: 2
Funding Support: This grant

Name: Richard Sloan
Project Role: Research Associate
Nearest person month worked: 1
Funding Support: This grant

Name: Felipe Lisboa
Project Role: Medical Scientist
Nearest person month worked: 1
Funding Support: This grant

Name: William Patino
Project Role: IT Database Administrator
Nearest person month worked: 3
Funding Support: This grant

Name: Bradley Krivit
Project Role: Research Assistant
Nearest person month worked: 1
Funding Support: This grant

Name: Christopher Joy
Project Role: Research Associate
Nearest person month worked: 1
Funding Support: This grant

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?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: