A. OVERALL COVER PAGE

Project Title: Cooperative Research Agreements Related to the World Trade Center Health Program (U01)	
Grant Number: 5U01OH011933-02	**Project/Grant Period:** 01/01/2019 - 06/30/2020
Reporting Period: 07/01/2019 - 06/30/2020	**Requested Budget Period:** 07/01/2019 - 06/30/2020
Report Term Frequency: Annual	**Date Submitted:** 11/01/2021
Program Director/Principal Investigator Information: AMIT K VERMA , MD **Phone Number:** 718-430-8761 **Email:** amit.verma@einsteinmed.org	**Recipient Organization:** ALBERT EINSTEIN COLLEGE OF MEDICINE 1300 MORRIS PARK AVE BRONX, NY 104611900 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: DHANONJOY C SAHA 1300 Morris Park Avenue Bronx, NY 10461 **Phone number:** 7184303642 **Email:** dhanonjoy.saha@einsteinmed.org	**Signing Official:** DHANONJOY C SAHA 1300 Morris Park Avenue Bronx, NY 10461 **Phone number:** 7184303642 **Email:** dhanonjoy.saha@einsteinmed.org
Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Specific Aim 1: To determine the prevalence of myeloma and its precursor state, monoclonal gammopathy of unknown significance
(MGUS) by use of serum proteomic analyses. Our preliminary data reveals a significantly higher rate of MGUS in WTC-exposed firefighters. In the proposed studies we will conduct sensitive immunophenotyping to detect MGUS and myeloma in our cohort.
Specifically, samples will be examined for presence of light chain MGUS/myeloma that is particularly higher in our preliminary studies
and is associated with chronic immune stimulation.
Specific Aim 2: To determine the prevalence of chronic lymphocytic leukemia (CLL) and its precursor lesions in this cohort. CLL is
associated with environmental exposures and we have shown that CLL is preceded by a monoclonal B-cell lymphocytosis that can be
detected by flow cytometry (Landgren et al, NEJM, 2009)(2). We have cryopreserved mononuclear cells from WTC exposed firefighters
and will examine these for presence of monoclonal B-cell lymphocytosis and subsequent immunoglobulin chain rearrangements.
Specific Aim 3: To determine the prevalence of myelodysplasia by evaluation of mutations using next generation sequencing. Myelodysplasia is a pre leukemic neoplasm that is associated with genotoxic exposures. Based on our preliminary data demonstrating
increased genomic instability and leukemia associated nucleotide variants in WTC–exposed firefighter samples, we propose to conduct
deep sequencing to detect MDS/leukemia associated mutations in a cohort of firefighter and control samples.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

B.2 (B2 accomplishments.pdf)

B.2 What was accomplished under these goals?

We continue to prospectively follow the entire FDNY cohort of firefighters for cancer incidence and have built a biorepository of samples consisting of fractionated blood components and serum from 3000+ WTC exposed FDNY subjects. We aimed to first characterize WTC-exposed firefighters diagnosed with multiple myeloma. Secondly, we aimed to conduct a screening study for MGUS and light-chain-MGUS. Sixteen WTC-exposed firefighters were diagnosed with multiple myeloma post-9/11; median age at diagnosis was 57 years (IQR 50-68 years). Serum/urine monoclonal protein isotype/free light-chain data were available for 14 cases; 7 (50%) had light-chain-multiple myeloma. In a subset of 7 patients, myeloma cells were assessed for CD20 expression; 5 (71%) were CD20 positive. In the screening study, we assayed peripheral blood from 781 WTC exposed firefighters. The age standardized prevalence rate of MGUS and light-chain-MGUS combined was 7.63 per 100 persons (95% CI: 5.45-9.81), 1.8-fold higher than rates from the Olmsted County, MN reference population (RR=1.76; 95% CI, 1.34, 2.29). The age standardized prevalence rate of light-chain-MGUS was more than three-fold higher than the same reference population (RR=3.13; 95% CI: 1.99-4.93).
Conclusions and Relevance: Environmental exposure to the WTC-disaster site is associated with myeloma precursor disease (MGUS and light-chain-MGUS), and may be a risk factor for the development of multiple myeloma at an earlier age, particularly the light-chain sub-type. and non WTC exposed firefighter controls.

PUBLICATIONS:
Landgren O, Zeig-Owens R, Giricz O, Goldfarb D, Murata K, Thoren K, Ramanathan L, Hultcrantz M, Dogan A, Nwankwo G, Steidl U, Pradhan K, Hall CB, Cohen HW, Jaber N, Schwartz T, Crowley L, Crane M, Irby S, Webber MP, Verma A, Prezant DJ. Multiple Myeloma and Its Precursor Disease Among Firefighters Exposed to the World Trade Center Disaster. JAMA Oncol. 2018 Jun 1;4(6):821-827. doi: 10.1001/jamaoncol.2018.0509. PMID: 29710195; PMCID: PMC6145680.

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Landgren O, Zeig-Owens R, Giricz O, Goldfarb D, Murata K, Thoren K, Ramanathan L, Hultcrantz M, Dogan A, Nwankwo G, Steidl U, Pradhan K, Hall CB, Cohen HW, Jaber N, Schwartz T, Crowley L, Crane M, Irby S, Webber MP, Verma A, Prezant DJ. Multiple Myeloma and Its Precursor Disease Among Firefighters Exposed to the World Trade Center Disaster. JAMA oncology. 2018 June 1;4(6):821-827. PubMed PMID: 29710195; PubMed Central PMCID: PMC6145680; DOI: 10.1001/jamaoncol.2018.0509.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
AMIT72	Y	Verma, Amit K.	MD	PD/PI	2.0	0.0	0.0			NA
RZEIGOWENS	N	Zeig-Owens, Rachel	DPH,MPH	Co-Investigator	1.0	0.0	0.0			NA
DPREZANT	N	PREZANT, DAVID J	MD,BS,MD,BA	PD/PI	1.0	0.0	0.0			NA
	N	Bhattacharyya, Sanchari		Associate	9.0	0.0	0.0			NA
	N	Pradhan, Kith		Biostatistician	1.2	0.0	0.0			NA
	Y	Hall, Charles		Co-Investigator	0.6	0.0	0.0			NA
	N	Bhagat, Tushar		Associate	3.5	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

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G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

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G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES Not Applicable
G.9 FOREIGN COMPONENT No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE Not Applicable
G.11 PROGRAM INCOME Not Applicable
G.12 F&A COSTS Not Applicable

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: Cooperative Research Agreements Related to the World Trade Center Health Program (U01)

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native										0
Asian										0
Native Hawaiian or Other Pacific Islander										0
Black or African American										0
White		781								781
More Than One Race										0
Unknown or Not Reported										0
Total	**0**	**781**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**781**

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

We continue to prospectively follow the entire FDNY cohort of firefighters for cancer incidence and have built a biorepository of samples consisting of fractionated blood components and serum from 2000+ WTC-exposed firefighters and non-WTC-exposed firefighter controls. Using this cohort, we have conducted preliminary studies in 781 WTC-exposed firefighters that demonstrate a significantly higher prevalence of monoclonal gammopathy of undetermined significance (MGUS), a precursor for multiple myeloma.

Furthermore, we have conducted deep targeted genome sequencing of a pilot cohort of WTC-exposed firefighters (N=481) and non-WTC-exposed age matched firefighter controls (N=52). We observed a high incidence of Clonal hematopoiesis (CH) and leukemia associated mutations (48/481; 10%) in WTC-exposed firefighters. The rate of mutations in controls was significantly less and is comparable to age matched controls in published studies . Clonal hematopoiesis (CH) is acquisition of leukemia associated somatic mutations that carry increase risk of hematologic cancer as well as all-cause mortality. The mutations seen in WTC-exposed firefighters affected DNMT3A, TET2, TP53, Splicing and other commonly recurrently mutated genes. These mutations suggest a high rate of CH, and CH in other cohorts has been shown to be associated with risk for development of myeloid neoplasms, inflammatory conditions and heart diseases.