AD _____

Award Number: W81XWH-18-1-0196

TITLE: (Enter title of award) Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment

PRINCIPAL INVESTIGATOR: Martin Edelman, M.D.

CONTRACTING ORGANIZATION:

Institute for Cancer Research
Philadelphia, PA 19111

REPORT DATE: August, 2019

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT:

✓ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3 DATES COVERED *(From - To)*
Aug 2019	Annual	15 Jul 2018 - 14 Jul 2019

4. TITLE AND SUBTITLE

Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment

5a. CONTRACT NUMBER

5b. GRANT NUMBER

W81XWH-18-1-0196

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Martin Edelman, M.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Institute for Cancer Research
333 Cottman Avenue
Philadelphia, Pennsylvania 19111
E-Mail: Martin.Edelman@fccc.edu

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel 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

The hypothesis of this study is that Cancer Associated Macrophage Like cells (CAMLs) can enrich for the presence of malignancy in patients with pulmonary nodules.
Specific Aims: 1. Determine the prevalence of CAMLS (+/- CTCs) in patients with indeterminate pulmonary nodules.; 2. Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.; 3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.
Subjects will be drawn from pulmonary nodule and thoracic surgery clinics at the Fox Chase Cancer Center (FCCC) and VA Philadelphia (VA). CAMLs will be evaluated at the time of clinically indicated scans and correlated with the presence or absence of cancer. Patients with biopsy confirmed lung cancer within 12 months of the CAML test will be defined as "diseased"; otherwise, they will deemed as "disease free". Positive and negative predictive value of the test will be determined. Logistic regression will be used to assess the utility of this test after accounting for clinical factors and nodule characteristics. To date, the study has been activated and is accruing patients at FCCC and is undergoing IRB review at the VA.

15. SUBJECT TERMS

Lung cancer, pulmonary nodules, screening

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER
Unclassified	Unlimited	Unclassified		14	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

Principal Investigator: Martin Edelman, M.D.
Institution: Institute for Cancer Research
Grant Number: W81XWH-18-1-0196

INTRODUCTION:

Background and Hypothesis: The National Lung Screening Trial (NLST), for which the PI was a member of the endpoint verification committee, determined that low dose CT screening could decrease lung cancer death by 20%. However, almost 25% of screened subjects were determined to have pulmonary nodules with only 1.5% actually demonstrated to be malignant. This very high false positive rate results in several critical problems including the requirement for further testing (scans, biopsies), the potential of loss to follow-up, the possibility of false negative biopsy and the resultant patient stress and anxiety. Nodules between from .8-3.0 cm have been described as "indeterminate" and represent a management challenge. Recently we published preliminary data on the presence of CAMLs, specialized myeloid polyploid cells transiting the circulation of patients that have engulfed tumor cells or tumor material in a variety of malignancies and their clinical use in tracking cancer progression and evolution in response to therapy. CAMLs are rarely found in healthy controls and are easily identified by filtration methods.

Hypothesis: CAMLs can substantially enrich for the presence of malignancy in the population of patients with pulmonary nodules.

Specific Aims:

1. Determine the prevalence of CAMLS (+/- CTCs) in patients with indeterminate pulmonary nodules.
2. Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.
3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Subjects will be drawn from pulmonary nodule and thoracic surgery clinics at the Fox Chase Cancer Center and VA Philadelphia. CAMLs will be evaluated at the time of clinically indicated scans and correlated with the presence or absence of cancer, as determined by clinically indicated biopsies. The proportion of patients with presence of CAMLs (CAML+), Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity and specificity of CAMLs (along with two-sided 95% confidence intervals (CI)) will be computed. Patients with biopsy confirmed lung cancer within 12 months of the CAML test will be defined as "diseased"; otherwise, they will deemed as "disease free". Logistic regression will be used to assess the utility of this test after accounting for clinical factors and nodule characteristics. We will also explore whether test performance differs among subsets of the population defined by demographic, clinical and nodule characteristics.

KEYWORDS: Lung cancer, pulmonary nodules, screening

ACCOMPLISHMENTS:

What were the major goals of the project?

1. To conduct an observational study of CAMLs in patients with indeterminate pulmonary nodules.

2. To determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.

3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

What was accomplished under these goals?

At this time, we have met the following milestones:

1. Drafting of the clinical trial protocol.

2. IRB (Fox Chase) submission and approval of the protocol.

3. Activation and commencement of accrual to the protocol.

4. Creation of computerized data base for entry of data and future analysis.

5. Submission of the trial to the IRB at the Veterans Administration Hospital of Philadelphia/University of Pennsylvania.

To date there have been 10 subjects accrued to the study. This study was open to enrollment 05/21/2019. The first patient was enrolled on 05/29/2019.

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?

The focus of the next reporting period will be on accruing evaluable subjects to the study and processing samples obtained. We anticipate activation of the VA/UPenn site during the next reporting period.

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.

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

Nothing to report

Changes that had a significant impact on expenditures

Nothing to report

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

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

PRODUCTS:

Nothing to report

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. Nothing to report

Website(s) or other Internet site(s)

N/A

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Martin Edelman, M.D.*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Edelman is the PI of the project and during this period, submitted and gained approval of the study, assembled the study team, designed the case report forms and coordinated all efforts related to the study.*
Funding Support:	

Name:	*Anil Vachani, M.D.*
Project Role:	*Site PI/Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Vachani has submitted the protocol to the VA/UPenn IRB and will begin accruing patients once activated.*
Funding Support:	

Name:	*Elizabeth V Gudesblat*
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Ms. Gudesblat has consented patients identified in the pulmonary clinic and collected and entered appropriate data.*
Funding Support:	

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

Please see attached updated Other Support for key personnel. Changes are marked with a line in the right hand margin.

What other organizations were involved as partners?

Organization Name: VA Philadelphia (University of Pennsylvania)

Location of Organization: Philadelphia, PA

Partner's contribution to the project *(identify one or more)*

Financial support: N/A

In-kind support: N/A

Facilities: The VA pulmonary clinic facilities (and possibly U Penn) will serve as the sites for evaluation and recruitment of patients.

Collaboration: See above.

Personnel exchanges: N/A

Other: N/A

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable.

QUAD CHARTS: Not applicable.

APPENDICES: Award Chart is attached.

Other Support

Edelman, Martin J.

Remaining salary support from clinical activities.

CURRENT

W81XWH-18-1-0196 (PI: Edelman) 7/15/2018 - 7/14/2021 5.0%
DOD $149,605 0.60 calendar
Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment
The major goals of this project are to: 1) Determine the prevalence of CAMLS in patients with pulmonary nodules; 2) Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy; and 3) Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

P30 CA006927 (PI: Fisher) 8/12/2016 - 7/31/2021 15.0%
NIH Partial Salary 1.80 calendar
Comprehensive Cancer Center Program at Fox Chase
The major goal of this Cancer Center Support Grant is to provide partial salary support for professional personnel, including senior and program leadership, administration, planning and evaluation, and developmental funds, as well as support for 5 established peer-reviewed Research Programs, 12 Shared Research Resources and 2 Support Elements.

Procuring Contracting/Grants Officer: Candace Cofie, 9609 Medical Center Dr., Bethesda, MD 20892, 240-276-6317

OVERLAP

None

COMPLETED

U10 CA180868

Other Support

Anaokar, Jordan

Salary support from institutional sources.

CURRENT

W81XWH-18-1-0196 (PI: Edelman) 7/15/2018 - 7/14/2021 5.0%
DOD Salary only 0.60 calendar
Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment
The major goals of this project are to: 1) Determine the prevalence of CAMLS in patients with pulmonary nodules; 2) Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy; and 3) Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

OVERLAP

None

Other Support

Kumar, Rohit

Remaining salary support from clinical activities.

CURRENT

W81XWH-18-1-0196 (PI: Edelman) 7/15/2018 - 7/14/2021 8.3%
DOD Salary only 1.00 calendar
Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment
The major goals of this project are to: 1) Determine the prevalence of CAMLS in patients with pulmonary nodules; 2) Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy; and 3) Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

OVERLAP

None

OTHER SUPPORT

Vachani, Anil

ACTIVE

W81XWH-18-1-0196 (Edelman) 07/15/2018-07/14/2021 0.6 calendar
Fox Chase Cancer Center/DOD $189,237
Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment
This project is a subcontract to Fox Chase Cancer Center. The major goals of this project are to: 1) Determine the prevalence of CAMLS in patients with pulmonary nodules; 2) Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy; and 3) Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Pragmatic Trials Program, #18-06240 (Halpern) 03/01/19-05/31/22 1.2 calendar
PCORI $1,800,000
Comparing Smoking Cessation Interventions Among Underserved Patients Referred for Lung Cancer Screening: A Randomized Pragmatic Trial
Pragmatic randomized trial comparing approaches to tobacco dependence treatment among patients undergoing lung cancer screening.

UM1 CA221936 (Ritzwoller/Vachani) 04/1/18 – 03/31/23 1.2 calendar
NIH/NCI $2,397,803
Center for Research to Optimize Precision Lung Cancer Screening in Diverse Populations
The goal of this Center is to build a comprehensive data ecosystem of the entire lung cancer screening process and to assess associated multilevel factors to conduct high impact multilevel studies including interventions to address gaps in care that may lead to lung cancer health disparities in the PROSPR initiative

P30 ES013508 (Penning) 04/01/15-03/31/2020 1.2 calendar
NIH/NIEHS $175,000
Center of Excellence in Environmental Toxicology
The IHSFC transdisciplinary services including study design, enrollment of research subjects, human exposure measurement, and biostatistical analyses to environmental health investigators.

Pragmatic Studies Program (Gould) 07/01/15-06/30/22 0.6 calendar
PCORI $100,000
Lung Nodule Surveillance Trial (LNST)
Pragmatic trial of more versus less intensive strategies for active surveillance of patients with small pulmonary nodules

Lung Cancer Early Detection Clinical Consortium (Bilatos) 09/30/11-09/29/19 0.12 calendar
Department of Defense/Johnson & Johnson $67,850
Detection of Early Lung Cancer Among Military Personnel
Multi-center study on lung cancer biomarker discovery and validation; study coordinated by Boston University.

COMPLETED
R21 CA198558
P42 ES023720

Other Support

Walia, Rohit

Dr. Walia has left our Institution. His efforts have been replaced by Dr. Anaokar.

LC170215: Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment

PI: Martin Edelman, M.D., Institute for Cancer Research, PA **Budget:** $672,969

Topic Area: Lung Cancer **Mechanism:** Translation Research Partnership Award

Research Area(s): 0701 – Clinical Biomarkers **Award Status:** 07/15/2018 – 07/14/2021

Study Goals: Cancer Associated Macrophage Like (CAML) cells are a recently discovered immune cell that appears early in the course of malignancy. Indeterminate pulmonary nodules are commonly seen and present a clinical problem regarding the timing and intensity of evaluation for malignancy. Our hypothesis is that CAMLs can substantially enrich for the presence of malignancy in the population of patients with pulmonary nodules and allow for earlier diagnosis in malignancy. Conversely, the absence of CAMLs would predict for absence of malignancy and prevent unnecessary procedures.

Specific Aims:

1. To conduct an observational study of CAMLs in patients with indeterminate pulmonary nodules.
2. To determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.
3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date