Award Number: W81XWH-18-1-0196

TITLE: 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

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Fort Detrick, Maryland 21702-5012

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

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Martin Edelman, M.D.

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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	Unclassified	13	

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

6. Activation and accrual at the University of Pennsylvania. Accrual on hold at the VA due to COVID.

7. As of 6.20.2021, 122 subjects have been enrolled and 119 are evaluable.

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?

We anticipate completion of accrual by July 2022.

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

An analysis of the rate of positive biopsies (over 25%) indicates that we can complete the trial with fewer patients. Of the first 85 subjects entered, 30 were biopsied with 27 positive for malignancy. The study was therefore modified March 2021 to decrease sample size based upon much higher rate of positive biopsies than anticipated. Amendment approved by FCCC and DOD HRPO.

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

Accrual was halted due to COVID. A one year no-cost extension was sought and approved.

Changes that had a significant impact on expenditures

Expenditures on testing may be somewhat decreased due to the decreased sample size.

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

See above. Decreased number of subjects.

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 leads the project at the University of Pennsylvania/VA. He is actively recruiting patients at Penn.*
Funding Support:	

Name:	*Rohit Kumar, M.D.*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*

Contribution to Project:	*Dr. Kumar is a pulmonary physician who leads the accrual effort at Fox Chase.*
Funding Support:	

Name:	*Dana Hagan*
Project Role:	*Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Hagan has consented patients identified in the pulmonary clinic and collected and entered appropriate data. She has also provided valuable assistance in terms of data collection methods and protocol mechanics.*
Funding Support:	

Name:	*Michelle Andronov*
Project Role:	*Research Coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4*
Contribution to Project:	*Ms. Andronov has provided assistance with subject recruitment and regulatory management.*
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 Drs. Edelman and Vachani. Changes are marked with a line in the right hand margin. There has been no change in the Other Support for Drs. Kumar and Anaokar.

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

SL42797 (PI: Fleisher) 6/15/2021 - 6/14/2023 2.0%
Genentech Salary only 0.24 calendar
myChoiceTM Shared Decision Making Study
The primary objective of the study is to assess the perceptions and decision making process related to clinical trials for both Patients (attitudes towards clinical trials) and providers (the decision making process to offer clinical trials and how they communicate their decision making to patients) throughout the course of treatment providing a deeper understanding of the complex factors that impact shared decision making.
Procuring Contracting/Grants Officer: Monica Smith, Sr. Contracts Manager, One DNA Way, S. San Francisco, A 94080, 650-457-9288

(PI: Edelman) 1/1/2020 - 12/31/2021 5.0%
Hope Fdn 0.60 calendar
SWOG Lung-MAP Sub-Study
This project is a subcontract to the SWOG-Clinical Trials Partnership (SWOG-CTP). This project provides support to Dr. Edelman for oversight of the Lung-Map master protocol and substudy activities.
Procuring Contracting/Grants Officer: Johanna Horn, CEO, The Hope Fdn, 24 Frank Lloyd Wright Dr., Ann Arbor, MI 48106, 734-998-6890

U10 CA180868 (PI: Wolmark/Curran/Mannel, NRG Onc) 3/1/2019 - 2/28/2025 5.0%
NIH (Partial Salary) 0.60 calendar
NCI National Clinical Trials Network (NCTN) - Network Group Operations Centers
This project is a subcontract to the NRG Oncology Foundation and provides support to Dr. Edelman as Co-Chair of the Lung Cancer Committee.
Procuring Contracting/Grants Officer: Stephen Shephard, Nova Tower 2, Two Allegheny Ctr, Ste 1200, Pittsburgh, PA 151212, 412-339-5310

W81XWH-18-1-0196 (PI: Edelman) 7/15/2018 - 7/14/2022 5.0%
DOD 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 No 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: Sarah Lee, 9609 Medical Center Dr., BG0609 RM 2W552, Rockville MD 20850, 240-276-6280

OVERLAP

None

OTHER SUPPORT

Dr. Vachani holds a dual appointment at The University of Pennsylvania (UPENN) and the Philadelphia VA Medical Center (VA) (4/8ths). A memorandum of understanding exists between UPENN and VA that allocates Dr. Vachani's time as 30 hours per week at UPENN and 20 hours per week at VA.

VACHANI, ANIL

ACTIVE

5UM1CA221939-03 (Ritzwoller/Vachani) 04/15/18–03/31/23 1.2 CM – Y1-Y2 (Total effort)
NIH/NCI 2.4 CM – Y3-Y5 (Total effort)
Total Award Amount (incl. indirect costs):
Center for Research to Optimize Precision Lung Cancer Screening in Diverse Populations (PROSPR II)
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.

5P30ES013508-16 (Penning) 04/01/20-03/31/25 1.2 CM – Y1-Y5 (Total effort)
NIH/NIEHS
Total Award Amount (incl. indirect costs):
Center of Excellence in Environmental Toxicology
The CEET's mission is to elucidate the mechanistic links between environmental exposures and human disease and translate its findings into action to improve the health of vulnerable individuals, and local, national and global communities. This is accomplished through thematic areas of research, facility cores, community outreach and engagement and through the funding of pilot projects. The Integrated Health Science Facilities Core provides transdisciplinary services including study design, population exposure measurement, human exposure laboratories, access to biorepositories, and biostatistical analyses for center investigators.

PCS-2018C1-11326 (Halpern) 03/01/19-02/28/24 1.2 CM – Y1-Y5 (Total effort)
PCORI
Total Award Amount (incl indirect costs):
Comparing Ways to Promote Quitting Smoking for People Referred for Lung Cancer Screenings
Pragmatic randomized trial comparing approaches to tobacco dependence treatment among patients undergoing lung cancer screening.

99908 (Vachani/Rendle) 10/26/20-04/25/22 0.9 CM – Y1-Y2 (Total effort)
Gordon and Betty Moore Foundation
Total Award Amount (incl indirect costs):
Improving Diagnostic Quality and Safety in Lung Cancer Screening
Multicenter study that will utilize qualitative and quantitative methods to develop and test quality metrics for lung cancer screening.

PCS-1403-12653 (Gould) 07/01/15-06/30/22 0.6 CM – Y1-Y7 (Total effort)
PCORI
Total Award Amount (incl indirect costs):
Watch the Spot Trial: Pragmatic Trial of More versus Less Intensive Strategies for Active Surveillance of Patients with Small Pulmonary Nodules
Pragmatic trial of more versus less intensive strategies for active surveillance of patients with small pulmonary nodules.

N/A – Penn ACC (Vachani/Rendle, et al.) 04/01/18 – 03/31/22 0.12 CM – Y1-Y3 (Total effort)
Total Award Amount (incl indirect costs):

Abramson Cancer Center, University of Pennsylvania
Penn Center of Excellence in Population Science: Catchment Area Precision Lung Cancer Screening
This internal grant supports three projects: 1) Characterize a cohort of patients at the University of Pennsylvania Health System that are eligible for lung cancer screening; 2) conduct community exposomics as a predictor of lung cancer risk; and 3) evaluate the use of circulating and imaging biomarkers for the early detection of lung cancer.

W81XWH-18-1-0196 (Edelman) 07/15/18-07/14/21 0.12 CM – Y1-Y3 (Total effort)
Fox Chase Cancer Center/DOD
Total Award Amount (incl indirect costs): (sub only)
Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early-Stage Lung Cancer and Relapse after Definitive Treatment
Prospective study to determine the diagnostic accuracy of CAML cells for the diagnosis of early-stage lung cancer.

10057723 – CTA (Vachani) 7/1/16-12/31/22 0.12 CM – Y1-Y6 (Total effort)
MagArray, Inc.
Total Award Amount (incl indirect costs):
Validation of a plasma biomarker for the detection of lung cancer
Investigator initiated study to develop and validate a multiplex protein assay for lung cancer diagnosis using a case-control study design.

10081653 – CTA (Vachani) 12/16/20-12/15/22 0.12 CM – Y1-Y2 (Total effort)
Precyte, Inc.
Total Award Amount (incl indirect costs):
Development of an Indicator Cell Assay for Blood-based Diagnosis of Lung Cancer
Investigator initiated study to validate an indicator cell assay for lung cancer diagnosis using a case-control study design.

K08 CA234335 (Thompson) 09/01/18-08/31/23 0.12 CM – Y1-5 (Total effort)
NIH/NCI
Total Award Amount (incl indirect costs):
A multimodal approach to develop molecular markers to predict response to immune targeted agents in non-small cell lung cancer.
The major goal of this work is to develop both tissue and blood-based biomarkers to predict response to immunotherapy in patients with NSCLC.

COMPLETED
DOD/Johnson & Johnson: Lung Cancer Early Detection Clinical Consoritum

OVERLAP
There are no scientific or budgetary overlap among the currently active or pending grants.

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 – 07/14/2022

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