AWARD NUMBER: W81XWH-21-1-0506

TITLE: Biopsy Guidance of Lung Cancer Using a Novel Electromagnetic and Optical Coherence Tomography Platform

PRINCIPAL INVESTIGATOR: Melissa J. Suter, Ph.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital

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Biopsy Guidance of Lung Cancer Using a Novel Electromagnetic and Optical Coherence Tomography Platform

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6. AUTHOR(S)

Melissa J Suter

E-Mail: msuter@mgh.harvard.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

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

Massachusetts General Hospital
55 Fruit St
Boston MA 02129

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14. ABSTRACT

Early diagnosis of lung cancer is critical to patient survival. Diagnosis must be made on the microscopic level, unfortunately, low-risk bronchoscopy techniques for retrieving biopsy samples are hampered by low diagnostic yields, and trans-thoracic and surgical approaches carry higher intrinsic risk of complications. The objective of this proposal is to develop and test a steerable and electromagnetic optical coherence tomography (EM-OCT) biopsy guidance and diagnosis tool with the goal of dramatically increasing the diagnostic yield of low risk bronchoscopic based diagnosis of lung cancer. The EM-OCT guidance platform will provide large-scale computed tomography (CT), and electromagnetic (EM) guidance as well as microscopic (OCT) guidance ensuring that the catheter is positioned within the target lesion. This will better allow clinicians to target and collect biopsy specimens from tumor tissue, improving the diagnostic yield of the biopsy. We anticipate that when used in combination with CT screening, the EM-OCT guidance tool will significantly increase the early detection, diagnosis, and treatment of lung cancer and will reduce the number of high-risk surgical diagnostic and therapeutic procedures performed.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The objective of this proposal is to develop and test a steerable and electromagnetic optical coherence tomography (EM-OCT) biopsy guidance and diagnosis tool with the goal of dramatically increasing the diagnostic yield of low risk bronchoscopic based diagnosis of lung cancer. The EM-OCT guidance platform will provide large-scale computed tomography (CT), and electromagnetic (EM) guidance as well as microscopic (OCT) guidance ensuring that the catheter is positioned within the target lesion. This will better allow clinicians to target and collect biopsy specimens from tumor tissue, improving the diagnostic yield of the biopsy. We anticipate that when used in combination with CT screening, the EM-OCT guidance tool will significantly increase the early detection, diagnosis, and treatment of lung cancer and will reduce the number of high-risk surgical diagnostic and therapeutic procedures performed.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

OCT, optical coherence tomography, electromagnetic guidance, guided biopsy, lung cancer

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: Develop and Fabricate a steerable EM-OCT catheter to facilitate real-time 3D imaging of, and navigation to, peripheral pulmonary lesions for bronchoscopic biopsy and diagnosis

- Major Task 1: Construct an electro-optical rotary junction
  - Target completion 6 months, 100% complete
- Major Task 2: Design and construct EM-OCT catheters that are compatible with standard TBNA
  - Target completion 9 months, 100% complete
- Major Task 3: Design and develop navigational software to provide real-time tracking of the catheter position within the tracheobronchial tree
  - Target completion 20 months
  - Subtask 1: 100% complete
  - Subtask 2: 100% complete
  - Subtask 3: 30% complete

Specific Aim 2: Conduct a preclinical swine study to demonstrate the safety and feasibility of EM-OCT biopsy guidance of artificial pulmonary nodules in living swine

- Major Task 4: Obtain DoD ACURO approval
  - Target completion 8 months, 0% complete

Remaining Major tasks scheduled to commence in year 2

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

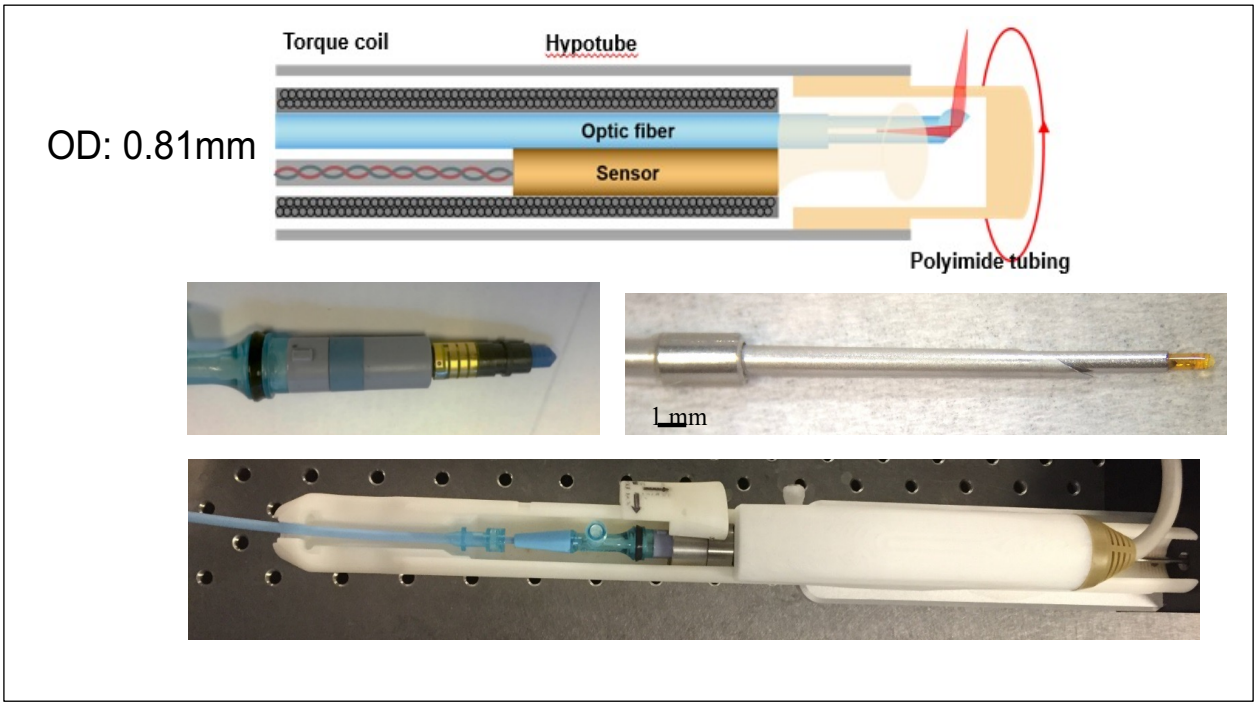
In the first year of this award we have made considerable progress as outlined below.

Specific Aim 1: Develop and fabricate a steerable EM-OCT catheter to facilitate real-time 3D imaging of, and navigation to, peripheral pulmonary lesions for bronchoscopic biopsy and diagnosis.

Major Task 1: Construct an electro-optical rotary junction.

We have successfully fabricated an electro-optic rotary junction that includes a rapid connect/disconnect joint to provide ensure electrical and optical connection is maintained throughout. A photo of the rapid catheter connection is provided below highlighting the 3 electrical slip rings that surround the connector also housing the optical fiber connection.

Major Task 2: Design and construct EM-OCT catheters that are compatible with standard TBNA
We have designed and fabricated EM-OCT catheters that are compatible with 18 gage TBNA needles. The design for the catheters can been seen below including a photo of how the rapid connect catheter secures to the EM-OCT rotary junction..



We additionally assessed the performance of the EM-OCT sensors.

The measurement accuracy provided by NDI Medical is 1.2 mm in spatial position and 0.5° in orientation angle, both were root mean square (RMS) values. The measurement accuracy is better when the sensor is placed close to the center of tabletop field generator. Ferromagnetic materials within the measurement volume can also increase the measurement error. We measured the RMS values by placing the sensor in multiple positions within the measurement volume and recorded at least 300 data points for each position measurement. Our measurement results showed that the best position accuracy is as good as 0.01 mm in position and 0.01° in angle when the sensor is placed close to the field generator at center. The measurement accuracy deteriorates to 1.3 mm in position and 0.1° in angle when sensor was placed close to boundaries at top of the dome.

We also measured the position accuracy while moving the bare sensor with translational stage (Newport 423 series). The translational stage was ferromagnetic and was placed outside of field generator and sensor was mounted on an aluminum post for movement. The minimal movement step on the translational stage was 0.01 mm. We moved the sensor along X, Y, and Z axis separately and did the measurement accordingly. For each axis, we placed the sensor at two different spatial positions, and then moved the sensor in steps of 0.01, 0.05, 0.1 and 0.5 mm respectively. For each position, more than 300 data points were recorded for calculation. Table 1 shows the moving steps we set and the corresponding measured moving distances. We did manual adjustment on the translational stage, the error between the ideal set moving step and the measured movement is up to 0.021 mm.

Table 1. Characterization of spatial positions

Move with X(mm)			Move with Y(mm)			Move with Z(mm)		
Set	x=18.81, y=-43.69, z=-150.55	x=183.05, y=-43.25, z=-149.15	Set	x=9.91, y=-12.66, z=-150.34	x=10.92, y=-281.09, z=-147.37	Set	x=-19.05, y=-33.67, z=-155.92	x=-19.61, y=-36.18, z=-303.57
0.01	0.009 ±0.008	0.007 ±0.012	0.01	0.01 ±0.006	0.011 ±0.013	0.01	0.010 ±0.008	0.010 ±0.037
0.05	0.050 ±0.007	0.049 ±0.011	0.05	0.047 ±0.006	0.045 ±0.014	0.05	0.053 ±0.008	0.054 ±0.041
0.1	0.104 ±0.007	0.100 ±0.011	0.1	0.097 ±0.006	0.094 ±0.007	0.1	0.102 ±0.009	0.100 ±0.037
0.5	0.504 ±0.007	0.499 ±0.011	0.5	0.495 ±0.006	NA	0.5	0.521 ±0.009	0.516 ±0.036

The angle accuracy was calculated by measuring relative rotation angle. An angle rotation mount (Thorlabs CRM1) was used to mount a bare sensor, the minimal rotation angle step on the rotator was 2°. We rotated the mount with step rotation of 2° and 10° respectively, the sensor was placed close to position x = -55.41 mm, y = -48.08 mm, z = -228.37 mm. The rotation angle was calculated as the relative angle difference between measured angle and angle at initial position. The measured results are shown in table 2. The error between set rotation angle and the measured rotation is up to 0.21° including the error caused by manually moving the rotation mount.

Table 2. Characterization of orientation angle in XY plane

Set rotation (degree)	***Measured (degree)***	***Set rotation (degree)***	***Measured (degree)***
2	*1.91 ± 0.004*	*10*	*10.02 ± 0.002*
4	*3.88 ± 0.003*	*20*	*20.02 ± 0.002*
6	*5.94 ± 0.003*	*30*	*30.05 ± 0.003*
8	*7.92 ± 0.004*	*40*	*40.13 ± 0.003*
10	*9.80 ± 0.004*	*50*	*50.17 ± 0.003*
12	*11.79 ± 0.003*	*60*	*59.81 ± 0.003*
14	*14.00 ± 0.003*	*70*	*69.83 ± 0.003*
16	*15.90 ± 0.004*	*80*	*79.87 ± 0.002*

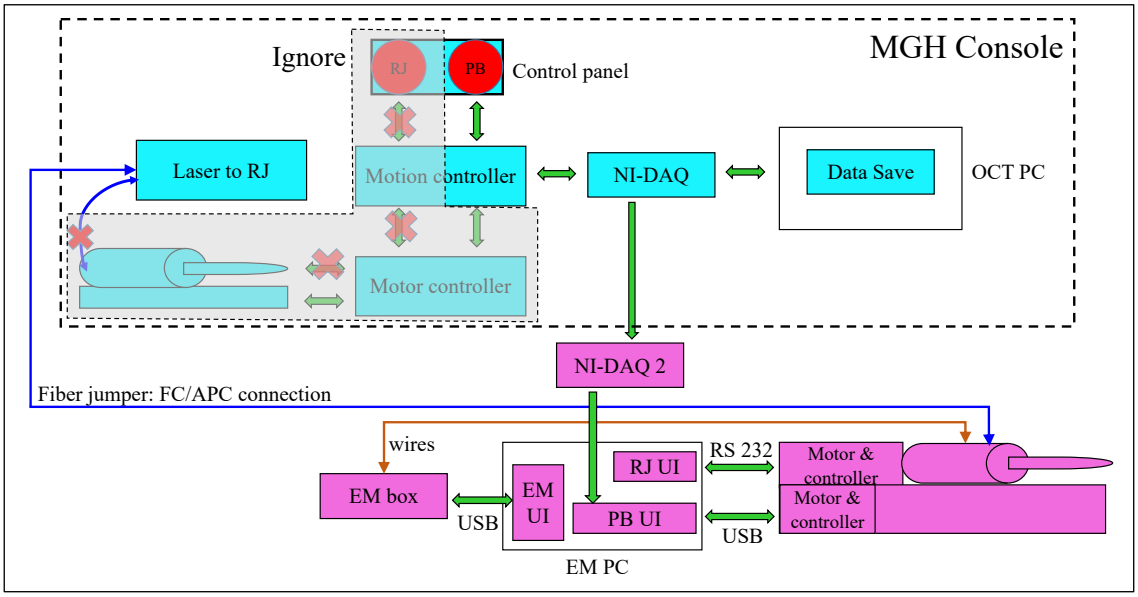
We also measured the accuracy after assembling the sensor into the catheter, and compared the measurement accuracy while placing the EM-OCT probe at multiple steady positions, and compared with a bare sensor used as above. Table 3 shows the measurement error of a bare sensor and EM-OCT probes close to spatial position of x = 15.3 mm, y = 121.1 mm, and z = 184.8 mm. We found assembling the sensor into the catheter and connecting the catheter to hybrid rotary junction did not influence the measurement accuracy. The measured accuracy in position and angle by EM-OCT probe is comparable to a bare sensor.

Table 3. Measurement error of EM-OCT probes compared to a bare sensor

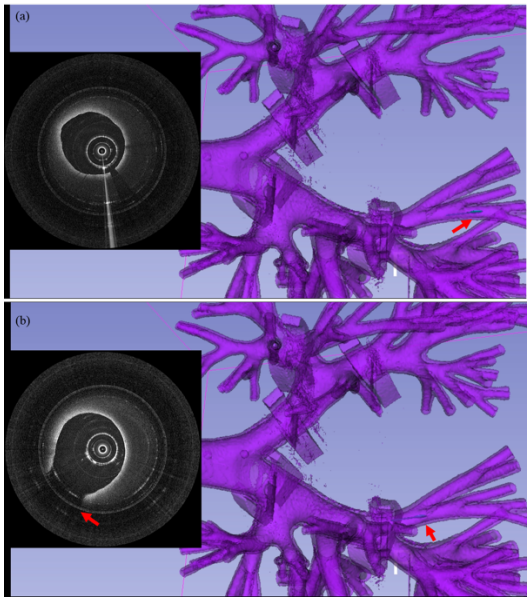
	Bare sensor	*EM-OCT probe (non-spinning)*	*EM-OCT probe (spinning)*	*EM-OCT needle probe (non-spinning)*
X	*0.006*	*0.012*	*0.016*	*0.011*
Y	*0.007*	*0.012*	*0.021*	*0.012*
Z	*0.012*	*0.017*	*0.026*	*0.026*
Pitch	*0.007*	*0.008*	*0.008*	*0.008*
Yaw	*0.005*	*0.005*	*0.013*	*0.013*

Major Task 3: Design and develop navigational software to provide real-time tracking of the catheter position within the tracheobronchial tree

We have successfully modified an existing OCT system to simultaneously record the catheter positional data associated with each OCT image axial depth profile. The diagram below outlines the design of this system modification.



We have additionally developed a simple software program that facilitates visualization of the real-time catheter position within a previously rendered 3D image of a phantom. This software needs some more refinement but will be critical in real-time biopsy guidance navigation within the tracheobronchial tree (red arrow points to imaging catheter tip.



Specific Aim 2: Conduct a preclinical swine study to demonstrate the safety and feasibility of EM-OCT biopsy guidance of artificial pulmonary nodules in living swine (n=6).

Major Task 4: Obtain DoD and ACURO approval.

While we have not obtained ACURO approval for this protocol, we are actively working on obtaining MGH approval of separate standalone protocols to cover the work in this proposal as is required by the DoD. We anticipate we will apply for ACURO approval in the coming months.

Major Task 5 and 6: Scheduled to commence in year 2.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Through the conduct of this project a research technician and a postdoctoral fellow have received training on OCT imaging, catheter design and fabrication through direct mentorship.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

In next reporting period we will continue work on the Specific Aims as outlined in the Statement of Work. This will include completing the multimodality imaging synchronization, obtaining approval for our animal research, conducting an ex vivo validation study, and subsequently a preclinical swine study to demonstrate the feasibility of EM-OCT transbronchial biopsy guidance and to assess the diagnostic yield.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We had some turnover of staff during this period and therefore the application for ACURO approval was delayed. We are currently working to remedy this.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

We experience difficulties in hiring new staff during the pandemic. We recently hired a new postdoctoral fellow and are currently searching for a new research technician.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Not applicable

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding,

prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Melissa Suter
Role: PI
Research Identifier: msuter
Nearest person month worked: 2
Contribution to project: Dr. Suter planned and executed the design, development and coordinated all aspects of this project. She worked on the design and fabrication of the new EB-OCT systems and catheters as well as data analysis.

Name: David Adams
Role: Co-Investigator
Research Identifier: dcadams
Nearest person month worked: 1
Contribution to project: Together with Dr Suter, Dr Adams has worked on both the design and development of the EM-OCT system and catheters. He additionally has worked on catheter and system testing.

Name: Lida Hariri
Role: Co-Investigator
Research Identifier: lhariri
Nearest person month worked: 1
Contribution to project: Dr Hariri has been involved in providing design and testing feedback for the EM-OCT catheters. As a board certified pathologist she will be responsible for assessing all the histology slides and will serve as a blinded reviewer for the OCT image interpretation in Aim 2.

Name: Colleen Keyes
Role: Co-Investigator
Research Identifier: ckeyes@bu.edu
Nearest person month worked: 1
Contribution to project: Dr Keyes is the Medical Co-Director of the Interventional Pulmonary Program at MGH. She has worked closely with Dr Suter to provide feedback on the design and functionality of the EM-OCT catheter design including iterative testing of the design. Dr Keyes will conduct the preclinical studies in Aim 2 as well as ex vivo assessments.

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Suter, Melissa J

Previous/Current/Pending Support

PREVIOUS

Title: Increasing the diagnostic yield of low-risk bronchial biopsy in the evaluation of lung cancer
Effort: 4.8 CM
Funding Agency & Award Number: NCI, **5R01CA167827-05**
Grants Officer: Cornice Young Performance Period: 04/19/13 – 03/31/19 Funding Amount:

Project Goals: we will develop and translate polarization-sensitive optical frequency domain imaging (PS-OFDI) systems, and novel catheters for conducting PS-OFDI of the airways and peripheral lung. We will develop and validate diagnostic criteria for evaluating the PS-OFDI Images of lung cancer pathology, and we will conduct clinical studies to demonstrate the improvement in biopsy yield over conventional approaches.
Specific Aims: Aim 1: Design and construct pulmonary PS-OFDI imaging workstations and bronchoscope compatible catheters. Aim 2: Develop, test, and disseminate PS-OFDI interpretation criteria for the detection of lung cancer. Aim 3: Conduct translational studies to demonstrate the potential for EB and TBOFDI guided biopsy for increasing the diagnostic yield of low-risk biopsy.
Overlap: None

Title: A Portable Multimodal System for in-field Airway Injury Assessment and Compliance Measurement
Effort: 1.2 CM
Funding Agency & Award Number: DoD-CDMRP: Subcontract with Radiation Monitoring Devices, **H2-0276**
Grants Officer: N/A
Performance Period: 4/24/19 – 9/30/20
The goal of this research program is to develop a portable multimodality X-ray and OCT imaging system for the evaluation of combat related lung injury.
Overlap: None

Title: Optical Imaging for early lung cancer diagnosis
Effort: 1.2 CM
Funding Agency & Award Number: LUNGevity, **2016-02 Career Development Award**

Grants Officer: Margery Jacobson Performance Period: 08/01/16 – 07/31/19 Funding Amount:
Project Goals: The goal of this study is to use optical imaging to significantly improve yield and enhance diagnostic capabilities on standard biopsy and needle aspiration from lung modules.
Specific Aims: Aim1: assess the use of optical imaging for 1) real-time intraprocedural evaluation of diagnostic biopsy yield, and 2) post-procedural large volume "optical biopsy" to accompany and complement physical tissue biopsies for final pathology diagnosis.
Overlap: None

Title: Increasing the diagnostic yield of low-risk bronchial biopsy in the evaluation of lung cancer

Effort: 1.92 CM
Funding Agency & Award Number: NCI, **5 R01 CA167827-05**
Grants Officer: Tawana McKeither Performance Period: 04/19/13 – 03/31/19 Funding Amount:
Project Goals: We will develop and translate polarization-sensitive optical frequency domain imaging (PSOFDI) systems, and novel catheters for conducting PS-OFDI of the airways and peripheral lung. We will develop and validate diagnostic criteria for evaluating the PS-OFDI Images of lung cancer pathology, and we will conduct clinical studies to demonstrate the improvement in biopsy yield over conventional approaches.
Specific Aims: Aim 1: Design and construct pulmonary PS-OFDI imaging workstations and bronchoscope compatible catheters. Aim 2: Develop, test, and disseminate PS-OFDI interpretation criteria for the detection of lung cancer. Aim 3: Conduct translational studies to demonstrate the potential for EB and TBOFDI guided biopsy for increasing the diagnostic yield of low-risk biopsy.
Overlap: None

Title: Polarization-Sensitive Optical Coherence Tomography for Detection and Monitoring of Skin Fibrosis

Effort: 2 CM
Funding Agency & Award Number: Biogen, **A223737**
Grants Officer: Sheila Violette Performance Period: 04/13/15 – 04/12/17 Funding Amount:
Project Goals: The goal of this proposal is to develop and validate the ability of polarization sensitiveoptical coherence tomography (PS-OCT) to detect and monitor the extent of dermal fibrosis that develops in mouse models of skin fibrosis.
Specific Aims: Aim 1. Assess the development of dermal fibrosis with PS-OCT. Aim 2. Assess the regression of dermal fibrosis with PS-OCT.
Overlap: None

(NEWLY COMPLETED)

Title: Detection and diagnosis of lung cancer using high-resolution endoscopic optical imaging

Effort: 0.36 CM
Funding Agency & Award Number: U.S. Army Medical Research Acquisition Activity, **W81XWH2010300**
Grants Officer: Shortall, Jamie
Performance Period: 06/01/2020 - 06/30/2021 Funding Amount:
Project Goals: 1) to develop a miniature endoscopic imaging-biopsy catheter that can image and

biopsy airways in the lung periphery and 2) evaluate the utility of this imaging-biopsy catheter in accurate diagnosis of lung cancer.
Specific Aims: Aim1. Development and test of 10 miniature endoscopic imaging-biopsy catheters.
Aim 2 – Preliminary evaluation of the utility of the proposed catheters ex vivo
Overlap: None

CURRENT

(THIS AWARD)

Title: Biopsy Guidance of Lung Cancer using a Novel Electromagnetic and Optical Coherence Tomography Platform
Effort: 1.80 CM
Funding Agency & Award Number: Department of Defense-Congressionally Directed Medical Research Programs, **W81XWH-21-1-0506**
Grants Officer: Shortall, Jamie
Performance Period: 06/15/2021 - 06/14/2023 Funding Amount:
Project Goals: The objective of this proposal is to develop and test a steerable and electromagnetic optical coherence tomography (EM-OCT) biopsy guidance and diagnosis tool with the goal of dramatically increasing the diagnostic yield of low risk bronchoscopic based diagnosis of lung cancer.
Specific Aims: Aim 1: Develop and fabricate a steerable EM-OCT catheter to facilitate real-time 3D imaging of, and navigation to, peripheral pulmonary lesions for bronchoscopic biopsy and diagnosis.
Aim 2: Conduct a preclinical swine study to demonstrate the safety feasibility of EM-OCT biopsy guidance of artificial pulmonary nodules in living swine
Overlap: None

Title: Early Detection and Diagnosis of Lung Cancer with Endomicroscopy
Effort: 6.40 CM
Funding Agency & Award Number: NIH, **1R01CA255326-01**
Grants Officer: Daly, Chelsea Simone Performance Period: 01/01/2021 - 12/31/2025 Funding Amount:
Project Goals: to develop a powerful optical bronchoscopy tool to increase the diagnostic yield of low risk approaches by 1) guiding biopsy site selection, and 2) by providing in vivo optical diagnosis that will allow for immediate treatment of the target tissue within the single clinical procedure.
Specific Aims: Aim 1: Develop an EB-OCT platform that will provide intra-procedural visualization of the tumor microenvironment with unprecedented resolution and contrast for biopsy guidance and diagnosis
Aim 2: In vivo EB-OCT biopsy guidance for increasing the diagnostic accuracy and tumor yield in lung cancer. Aim 3: Conduct a study to evaluate the accuracy of EB-OCT diagnosis of lung cancer in human subjects.
Overlap: None

(NEW)

Title: Defining small airways disease as a therapeutic target in Post-Acute Sequela of COVID 19 (PASC)

Effort: 0.30 CM
Funding Agency & Award Number: Department of Defense **PR211232PI**
Grants Officer: N/A
Performance Period: 09/01/2022 - 08/31/2026 Funding Amount:
Project Goals: to use a novel combination of advanced physiologic testing, optical microscopy imaging, and cellular/molecular characterization to comprehensively assess the airways of patients with PASC and identify appropriate, personalized therapies to treat their symptoms in a way not currently achievable with standard of care techniques.
Specific Aims: Aim 1: To determine whether microscopic small airway disease is the primary cause of dyspnea in a subset of long COVID patients.
Aim 2: To profile distinct cellular and molecular changes associated with small airway disease in long COVID in order to identify targets for new treatments.
Overlap: There is scientific overlap between the DoD award under consideration and the NIH R01 proposals R01HL162372 and R01HL165701. Should more than one of these proposals be funded, the budgets will be adjusted appropriately in conjunction with agency staff.
Overlap: None

Title: In vivo endobronchial OCT for IPF diagnosis and therapy response assessment

Effort: 1.20 CM
Supporting Agency: NIH-National Institutes of Health, **1R01HL152075-01**
Grants Officer: Vuga, Louis
Performance Period: 06/01/2020 - 05/31/2025 Funding Amount:
Project Goals: The major goals of this project are to validate low-risk, minimally-invasive endobronchial OCT for microscopic IPF diagnosis and monitoring of therapy response in early disease stages in a multi-center study
Specific Aims:
Aim 1. Conduct a histologic correlative study to determine the accuracy of EB-OCT for IPF diagnosis and auto- mated IPF feature quantification ex vivo. Using our existing library of matched EB-OCT and histology from ex- cised lung tissue from ILD patients (n=50), we will: Aim 1.1: Determine sensitivity and specificity for IPF diagnosis ex vivo with multiple, independent pathologist readers in a blinded fashion; Aim 1.2: Validate automated methods to quantify individual IPF features, including subpleural fibrosis and microscopic honeycombing that are known indicators of disease progression, as compared with matched histology.

Aim 2. Conduct a prospective clinical study to determine the accuracy of EB-OCT for microscopic IPF diagnosis and therapeutic efficacy assessment. In this multicenter study (MGH and Rhode Island Hospital), we will perform EB-OCT in ILD patients (n=96) with non-diagnostic CT undergoing SLBX. Aim 2.1: Pathologists from Aim 1.1 will interpret EB-OCT, and we will determine sensitivity and specificity for IPF diagnosis as compared with SLBX. Aim 2.2: We hypothesize that improved lung function and survival in patients on anti-fibrotic therapy originate from changes in disease microstructure. Patients from Aim 2.1 diagnosed with IPF (n=48) will undergo repeat EB-OCT 6 months later, using anatomic mapping to access the same locations. We will quantify EB-OCT fea- tures at each time point using the automated methods validated in Aim 1.2 and compare changes amongst patients on and off therapy, as well as against changes in PFTs and overall survival.
Overlap: None

Title: Phenotyping Asthma for Bronchial Thermoplasty: Airway Smooth Muscle Structure and Function

Effort: 0.13 CM
Funding Agency & Award Number: NIH-National Institutes of Health, **5R01HL133664-05**
Grants Officer: Noel, Patricia
Performance Period: 07/01/17 – 06/30/23 (NCE) Funding Amount:
Project Goals: The goal of this research proposal is to develop a novel optical imaging platform to quantitatively assess airway smooth muscle in vivo. We anticipate that the developed imaging system may help to increase our current understanding of asthma by linking structural changes in the airway wall to physiologic function.
Specific Aims:
Specific Aim 1: Develop a novel catheter-based optical imaging platform to enable the assessment of airway structure and function relationships in vivo.
Specific Aim 2: Linking changes in airway wall structure with physiologic function. Specific Aim 3: *Phenotyping Asthma and Predicting Response to Bronchial Thermoplasty.*
Overlap: None

(NEW)
Title: Airway Epithelial Basal Cells Determine the Asthma Phenotype in Allergic Subjects

Effort: 0.12 CM
Funding Agency & Award Number: Sanofi US Services Inc. Grants Officer: N/A
Performance Period: 06/2022 - 06/2024 Funding Amount:
Project Goals: The goal of the project is to define the AEC epigenetic profile in allergic asthmatics and compare the profile to AEC from AC and other asthma endotypes including asthma-COPD overlap.
Specific Aims: Aim 1: Identify regulatory signatures in AEC from asthmatics by profiling in parallel the transcrip- tome and epigenome of AEC at baseline and after allergic stimuli, compared to AC.
Aim 2: Identify transcriptional and regulatory signatures in AEC in other airway diseases such as severe asthma, non-type 2 asthma, and asthma-COPD overlap.
Overlap: None

PENDING

Title: Non-rotating nano-optic endoscope for 360 degree in vivo imaging

Effort: 0.60 CM
Funding Agency & Award Number: NIH, **R21EB034798**
Grants Officer: Ruthann McAndrew Performance Period: 09/2023 - 08/2026 Funding Amount:
Project Goals: to develop a novel optical endoscope that does not need to be rotated to perform 360 degree imaging
Specific Aims: Aim 1. Development of Optical Scanning Metasurface.
Aim 2. Development, Testing, and Validation of the Optical Scanning Endoscope. Overlap: None

Title: Title: Microscopic EB-OCT imaging to predict progression in interstitial lung abnormalities

Effort: 3.60 CM
Funding Agency & Award Number: NIH, **R01HL169225**
Grants Officer: Nina Hall Performance Period: 07/2023 - 06/2028 Funding Amount:

Project Goals: to validate a low-risk, minimally-invasive, microscopic optical bronchoscopy tool to accurately detect early PF at the presymptomatic stages, before significant lung destruction has occurred, which would allow for early treatment and improve patient outcomes.

Specific Aims: Aim 1. Determine the accuracy of EB-OCT to detect high-risk microscopic features and predict disease progression in smokers with ILA undergoing nodule resection.
Aim 2. Determine the accuracy of EB-OCT to predict disease progression in subjects with ILA and family history of PPF.
Overlap: None

Previous\Current\Pending Support

Adams, David

Previous
(NEWLY COMPLETED)
Title: Phenotyping Asthma for Bronchial Thermoplasty: Airway Smooth Muscle Structure and Function
Effort: 6.00 CM
Funding Agency & Award Number: NIH-National Institutes of Health, **5R01HL133664-05**
Grants Officer: Noel, Patricia
Performance Period: 07/01/17 – 06/30/23 (NCE) Funding Amount:
Project Goals: The goal of this research proposal is to develop a novel optical imaging platform to quantitatively assess airway smooth muscle in vivo. We anticipate that the developed imaging system may help to increase our current understanding of asthma by linking structural changes in the airway wall to physiologic function.
Specific Aims:
Specific Aim 1: Develop a novel catheter-based optical imaging platform to enable the assessment of airway structure and function relationships in vivo.
Specific Aim 2: Linking changes in airway wall structure with physiologic function. Specific Aim 3: *Phenotyping Asthma and Predicting Response to Bronchial Thermoplasty.* Overlap: None

Current

(THIS AWARD)
Title: Biopsy Guidance of Lung Cancer using a Novel Electromagnetic and Optical Coherence Tomography Platform
Effort: 1.2 CM
Funding Agency & Award Number: DoD, **LC200392**
Grants Officer: N/A
Period of Performance: 06/15/2021 - 06/14/2023 Funding Amount:
Project Goals: The objective of this is to develop and test a steerable and electromagnetic optical coherence tomography (EM-OCT) biopsy guidance and diagnosis tool with the goal of dramatically increasing the diagnostic yield of low bronchoscopic based diagnosis of lung cancer.
Aim 1: Develop EM-OCT catheter and imaging system.
Aim 2: Conduct a preclinical swine study to demonstrate safety and feasibility.
Overlap: None

(NEW)
Title: In vivo endobronchial OCT for IPF diagnosis and therapy response assessment
Effort: 0.60 CM

Supporting Agency: NIH-National Institutes of Health, **1R01HL152075-01**
Grants Officer: Vuga, Louis
Performance Period: 06/01/2020 - 05/31/2025 Funding Amount:
Project Goals: The major goals of this project are to validate low-risk, minimally-invasive endobronchial OCT for microscopic IPF diagnosis and monitoring of therapy response in early disease stages in a multi-center study
Specific Aims:
Aim 1. Conduct a histologic correlative study to determine the accuracy of EB-OCT for IPF diagnosis and auto- mated IPF feature quantification ex vivo. Using our existing library of matched EB-OCT and histology from ex- cised lung tissue from ILD patients (n=50), we will: Aim 1.1: Determine sensitivity and specificity for IPF diagnosis ex vivo with multiple, independent pathologist readers in a blinded fashion; Aim 1.2: Validate automated methods to quantify individual IPF features, including subpleural fibrosis and microscopic honeycombing that are known indicators of disease progression, as compared with matched histology.

Aim 2. Conduct a prospective clinical study to determine the accuracy of EB-OCT for microscopic IPF diagnosis and therapeutic efficacy assessment. In this multicenter study (MGH and Rhode Island Hospital), we will perform EB-OCT in ILD patients (n=96) with non-diagnostic CT undergoing SLBX. Aim 2.1: Pathologists from Aim 1.1 will interpret EB-OCT, and we will determine sensitivity and specificity for IPF diagnosis as compared with SLBX. Aim 2.2: We hypothesize that improved lung function and survival in patients on anti-fibrotic therapy originate from changes in disease microstructure. Patients from Aim 2.1 diagnosed with IPF (n=48) will undergo repeat EB-OCT 6 months later, using anatomic mapping to access the same locations. We will quantify EB-OCT fea- tures at each time point using the automated methods validated in Aim 1.2 and compare changes amongst patients on and off therapy, as well as against changes in PFTs and overall survival.
Overlap: None

Title: Assessing Airway Smooth Muscle Tone in Asthma with Endobronchial Optical Coherence Tomography

Effort: 9 CM
Funding Agency & Award Number: NIH/NHLBI, **K25HL145120**
Grants Officer: Nina Hall
Performance Period: 01/08/19 – 07/31/24 Funding Amount:
Project Goals: The goals of this study are to develop, validate, and investigate in a clinical setting a novel approach for assessing airway smooth muscle tone in vivo using endobronchial PS-OCT.
Specific Aims: Aim 1: Validate our approach to identifying the axis of force transmission with PS-OCT. Aim 2: Establish a mathematical relationship for quantifying ASM tone in vivo. Aim 3: Investigate differences in ASM function in asthmatics and non-asthmatics in a pilot clinical study.
Overlap: None

Title: Early Detection and Diagnosis of Lung Cancer with Endomicroscopy

Effort: 1.2 CM
Funding Agency & Award Number: NIH/NCI, **R01CA255326**
Grants Officer: Guillermo Marquez
Performance Period: 01/01/21 – 12/31/25 Funding Amount:
Project Goals: The major goal of this proposal is to develop a powerful optical bronchoscopy tool to increase the diagnostic yield of low risk approaches by 1) guiding biopsy site selection, and 2) by providing in vivo optical diagnosis that will allow for immediate treatment of the target tissue within the single clinical procedure. Specific Aim 1: Develop an EB-OCT platform that will provide intra-procedural visualization of the tumor microenvironment with unprecedented resolution and

contrast for biopsy guidance and diagnosis. Specific Aim 2: In vivo EB-OCT biopsy guidance for increasing the diagnostic accuracy and tumor yield in lung cancer. Aim 3: Conduct a study to evaluate the accuracy of EB-OCT diagnosis of lung cancer in human
Overlap: None

Pending

Title: Non-rotating nano-optic endoscope for 360 degree in vivo imaging
Effort: 2.40 CM
Funding Agency & Award Number: NIH, **R21EB034798**
Grants Officer: Ruthann McAndrew
Performance Period: 09/2023 - 08/2026 Funding Amount:
Project Goals: to develop a novel optical endoscope that does not need to be rotated to perform 360 degree imaging
Specific Aims: Aim 1. Development of Optical Scanning Metasurface.
Aim 2. Development, Testing, and Validation of the Optical Scanning Endoscope.
Overlap: If funded, Dr. Adams will work with sponsors to adjust effort to maintain commitment below 12 CM.

Hariri, Lida P

Previous/Current/Pending Support PREVIOUS

Title: Phenotyping Asthma for Bronchial Thermoplasty: Airway Smooth Muscle Structure and Function
Effort: 1.20 CM
Funding Agency & Award Number: NIH-National Institutes of Health, **5R01HL133664-05**
Grants Officer: Noel, Patricia Performance Period: 07/01/17 – 06/30/22 Funding Amount:

Project Goals: The goal of this research proposal is to develop a novel optical imaging platform to quantitatively assess airway smooth muscle in vivo. We anticipate that the developed imaging system may help to increase our current understanding of asthma by linking structural changes in the airway wall to physiologic function.
Specific Aims:
Specific Aim 1: Develop a novel catheter-based optical imaging platform to enable the assessment of airway structure and function relationships in vivo.
Specific Aim 2: Linking changes in airway wall structure with physiologic function. Specific Aim 3: *Phenotyping Asthma and Predicting Response to Bronchial Thermoplasty.* Overlap: None

Title: Optical imaging for early lung cancer diagnosis

Effort: 2.4 CM
Funding Agency & Award Number: **LUNGevity Foundation 2016-02**
Grants Officer: N/A
Performance Period: 09/01/16 – 07/31/19 Funding Amount:
Project Goals: In this project, we aimed to dramatically improve lung cancer diagnosis on low-risk biopsy using cutting-edge optical imaging tools in combination with navigation techniques to provide: 1) real-time, intra- procedural assessment of biopsy site locations to ensure adequate

tissue sampling, and 2) large volume "virtual optical biopsy" of nodules for diagnosis as a complement to tissue biopsy.
Specific Aims:
Aim 1. To assess if in vivo OCT VIPER biopsy assessment increases tumor yield on bronchoscopic biopsy Aim 2. To assess diagnostic accuracy of large volume in vivo OCT optical biopsy in lung nodules.
Overlap: None

Title: PET Imaging of Pulmonary Fibrosis

Effort: 0.6 CM
Funding Agency & Award Number: NIH-NHLBI, **R01HL131907**
Grants Officer: N/A
Performance Period: 04/15/2016 – 12/30/2020 Funding Amount:
Project Goals: The major goals of this study are to translate Type I collagen-targeted PET imaging to patient with idiopathic pulmonary fibrosis (IPF) from animal models of pulmonary fibrosis in which we have demonstrated it to visualize recently synthesized collagen with high sensitivity and specificity. This project will include IND-enabling studies for the Type I collagen-targeted probe, determining correlations of PET imaging with this probe to histology of resected lung specimens, and determining correlations with disease activity in IPF.
Overlap: None.

(NEWLY COMPLETED)

Title: Low risk in vivo diagnosis of IPF with optical imaging

Effort: 9.00 CM
Supporting Agency: NIH-NHLBI, **5K23HL132120-05**
Grants Officer: Colombini-Hatch, Sandra
PI: Hariri, Lida P
Performance Period: 09/01/2016 - 9/30/2021 NCE Funding Amount:
Project Goals: The major goal of this study is to develop a low-risk, minimally-invasive OCT optical bronchoscopy tool to diagnose idiopathic pulmonary fibrosis (IPF) without surgery or tissue removal. We will develop and validate OCT imaging criteria to detect microscopic features of IPF, including honeycombing, and conduct a pilot clinical study to test the translation of bronchoscopic OCT to diagnose IPF *in vivo*.
Specific Aims:
Aim 1. To develop and validate OCT criteria to diagnose IPF, including microscopic honeycombing. Diagnostic OCT criteria relevant to IPF will be developed, tested and validated for use in subsequent clinical studies. We will create a library of endobronchial OCT images correlated with precisely matched histology from excised lung specimens of patients with suspected IIP (n=110, ~50% IPF and 50% other IIPs). We hypothesize that OCT features of IPF will mimic low-power microscopy, including microscopic honeycombing, dense peripheral fibrosis, and spatial heterogeneity, and demonstrate high sensitivity and specificity for IPF.
Aim 1.1: To develop OCT criteria to distinguish IPF from other IIPs, and train pathologists on these criteria. *Aim 1.2:* To validate OCT criteria in a blinded assessment, and determine sensitivity and specificity for IPF. Aim 2. To translate bronchoscopic OCT to *in vivo* diagnosis of IPF in a pilot clinical study.
We will enroll patients with suspected IIP (n=30) and non-diagnostic CTs who will be undergoing bronchoscopy prior to surgical lung biopsy. We will perform bronchoscopic OCT in these patients to test the diagnostic criteria developed in Aim 1. We hypothesize that in this pilot study, bronchoscopic OCT will achieve diagnostic accuracy equivalent to lung biopsy in identifying microscopic honeycombing and diagnosing IPF.

Overlap: None

(NEWLY COMPLETED)

Title: Evaluating Pulmonary Fibrosis with Optical Coherence Tomography: Pilot Study

Effort: 0.1 CM
Supporting Agency: Boehringer Ingelheim Grants Officer: N/A;
PI: Hariri, Lida P.
Performance Period: 11/18/2018 – 10/31/2020
Funding Amount:
Project Goals: The major goal of this project is to conduct pilot studies to determine whether bronchoscopic optical coherence tomography (OCT) can be used to: 1) identify microscopic features of idiopathic pulmonary fibrosis (IPF) at the time of diagnosis and 2) assess changes occurring over disease progression, on or off therapy, in IPF patients with macroscopic established disease visible on high-resolution CT.
Specific Aims:
Aim 1. In vivo OCT for microscopic IPF diagnosis. We will perform endobronchial OCT in consented ILD patients (n=24) with non-diagnostic HRCTs undergoing bronchoscopy and diagnostic lung biopsy. We will apply OCT diagnostic criteria for UIP/IPF and determine preliminary sensitivity and specificity of OCT against final pathology diagnosis in a blinded study. OCT will also be compared against concurrent and follow-up HRCTs to determine if OCT detects features of UIP/IPF, including microscopic honeycombing, at an earlier stage than HRCT.
Aim 2: Microscopic monitoring of disease progression over time with OCT. Patients (n=10) with an established diagnosis of UIP/IPF by HRCT will be consented, and undergo research bronchoscopy with endobronchial OCT imaging at two timepoints, spaced at 6-month time intervals. For each patient, OCT imaging will be performed at the same anatomic locations at each timepoint. Patients will undergo concurrent PFTs and HRCTs at each OCT imaging timepoint, as well as follow-up PFTs and HRCTs for clinical monitoring purposes at 12 months. We will assess endobronchial OCT microscopic features, including amount of fibrosis, honeycombing, and traction bronchiectasis, at each time point, and determine changes occurring over the two timepoints for each patient. We will compare OCT feature changes against percent change in FVC and DLCO, and qualitative HRCT changes, over 6 and 12 months. We will also determine the relationship between endobronchial OCT features, progression-free survival, and overall survival.
Overlap: None

CURRENT

(THIS AWARD)

Title: Biopsy Guidance of Lung Cancer using a Novel Electromagnetic and Optical Coherence Tomography Platform

Effort: 0.60 CM
Funding Agency & Award Number: Department of Defense-Congressionally Directed Medical Research Programs, **W81XWH-21-1-0506**
Grants Officer: Shortall, Jamie
Period of Performance: 06/15/2021 - 06/14/2023
Funding Amount:
Project Goals: The objective of this proposal is to develop and test a steerable and electromagnetic optical coherence tomography (EM-OCT) biopsy guidance and diagnosis tool with the goal of dramatically increasing the diagnostic yield of low risk bronchoscopic based diagnosis of lung cancer.

Specific Aims: Aim 1: Develop and fabricate a steerable EM-OCT catheter to facilitate real-time 3D imaging of, and navigation to, peripheral pulmonary lesions for bronchoscopic biopsy and diagnosis.
Aim 2: Conduct a preclinical swine study to demonstrate the safety feasibility of EM-OCT biopsy guidance of artificial pulmonary nodules in living swine
Overlap: None

(NEW)

Title: Defining small airways disease as a therapeutic target in Post-Acute Sequela of COVID 19 (PASC)

Effort: 0.89 CM
Funding Agency & Award Number: Department of Defense **PR211232PI**
Grants Officer: N/A
Performance Period: 09/01/2022 - 08/31/2026
Funding Amount:
Project Goals: to use a novel combination of advanced physiologic testing, optical microscopy imaging, and cellular/molecular characterization to comprehensively assess the airways of patients with PASC and identify appropriate, personalized therapies to treat their symptoms in a way not currently achievable with standard of care techniques.
Specific Aims: Aim 1: To determine whether microscopic small airway disease is the primary cause of dyspnea in a subset of long COVID patients.
Aim 2: To profile distinct cellular and molecular changes associated with small airway disease in long COVID in order to identify targets for new treatments.
Overlap: There is scientific overlap between the DoD award under consideration and the NIH R01 proposals R01HL162372 and R01HL165701. Should more than one of these proposals be funded, the budgets will be adjusted appropriately in conjunction with agency staff.

(NEW)

Title: Early Detection and Diagnosis of Lung Cancer with Endomicroscopy

Effort: 2.30 CM
Funding Agency & Award Number: NIH, **1R01CA255326-01**
Grants Officer: Daly, Chelsea Simone
Performance Period: 01/01/2021 - 12/31/2025 Funding Amount:
Project Goals: To develop a powerful optical bronchoscopy tool to increase the diagnostic yield of low risk approaches by 1) guiding biopsy site selection, and 2) by providing in vivo optical diagnosis that will allow for immediate treatment of the target tissue within the single clinical procedure.
Specific Aims: Aim 1: Develop an EB-OCT platform that will provide intra-procedural visualization of the tumor microenvironment with unprecedented resolution and contrast for biopsy guidance and diagnosis
Aim 2: In vivo EB-OCT biopsy guidance for increasing the diagnostic accuracy and tumor yield in lung cancer.
Aim 3: Conduct a study to evaluate the accuracy of EB-OCT diagnosis of lung cancer in human subjects.
Overlap: None

Title: In vivo endobronchial OCT for IPF diagnosis and therapy response assessment

Effort: 4.8 CM

Supporting Agency: NIH-National Institutes of Health, **1R01HL152075**
Grants Officer: Vuga, Louis
Performance Period: 06/01/2020 - 05/31/2025
Funding Amount:
Project Goals: The major goals of this project are to validate low-risk, minimally-invasive endobronchial OCT for microscopic IPF diagnosis and monitoring of therapy response in early disease stages in a multi-center study
Specific Aims:
Aim 1. Conduct a histologic correlative study to determine the accuracy of EB-OCT for IPF diagnosis and automated IPF feature quantification ex vivo. Using our existing library of matched EB-OCT and histology from excised lung tissue from ILD patients (n=50), we will: Aim 1.1: Determine sensitivity and specificity for IPF diagnosis ex vivo with multiple, independent pathologist readers in a blinded fashion; Aim 1.2: Validate automated methods to quantify individual IPF features, including subpleural fibrosis and microscopic honeycombing that are known indicators of disease progression, as compared with matched histology.

Aim 2. Conduct a prospective clinical study to determine the accuracy of EB-OCT for microscopic IPF diagnosis and therapeutic efficacy assessment. In this multicenter study (MGH and Rhode Island Hospital), we will perform EB-OCT in ILD patients (n=96) with non-diagnostic CT undergoing SLBX. Aim 2.1: Pathologists from Aim 1.1 will interpret EB-OCT, and we will determine sensitivity and specificity for IPF diagnosis as compared with SLBX. Aim 2.2: We hypothesize that improved lung function and survival in patients on anti-fibrotic therapy originate from changes in disease microstructure. Patients from Aim 2.1 diagnosed with IPF (n=48) will undergo repeat EB-OCT 6 months later, using anatomic mapping to access the same locations. We will quantify EB-OCT features at each time point using the automated methods validated in Aim 1.2 and compare changes amongst patients on and off therapy, as well as against changes in PFTs and overall survival.
Overlap: None

Title: Optimization of PET probe for imaging lung fibrogenesis

Effort: 0.60 CM
Funding Agency & Award Number: NIH, **1R33HL154125-01**
Grants Officer: Matt Craig matt.craig@nih.gov
Performance Period: 08/15/2020 - 07/31/2022
Funding Amount:
Project Goals: To optimize and validate a PET probe for imaging lung fibrogenesis
Specific Aims: Aim 1: To prepare focused libraries of hydrophilic allysine-targeted PET tracers.
Aim 2: To characterize the in vitro and in vivo affinity and reactivity of the probes to allysine, and to assess their distribution, metabolism, and pharmacokinetic (DMPK) properties.
Aim 3: To validate the optimized DC in multiple disease and treatment models.
Overlap: None

Title: HSV1 oncolysis-immune checkpoint inhibition therapy for breast cancer meningeal metastases

Effort: 0.48 CM
Supporting Agency: Department of Defense-Congressionally; Directed Medical Research Programs, W81XWH2010421
Grants Officer: N/A;
Performance Period: 06/2020 - 05/2023 Funding Amount:
Project Goals: The major goals of this project are to investigate a novel form of treatment with oncolytic virus and immune checkpoint inhibitor for breast cancer meningeal metastases

Specific Aims:
Our syngeneic animal model of meningeal metastases that mimics human disease will serve as the platform for this investigation. Investigate the therapeutic effect of combined oncolytic HSV1 and anti-PD-1 immune checkpoint inhibition.
a) Study tumor growth response to combination therapy (with Gd-MRI and tumor Ki67 IHC)
b) Define inflammatory gene signatures expressed during combination therapy (with Nanostring)
c) Correlate gene signatures with imaging scans and immune checkpoint and inflammatory markers (PD-L1, PD-1, CD8+, CD4, and IFNɣ) in ex vivo brains.
1. Investigate the therapeutic effect of repetitive oncolytic HSV1.
a) Determine tumor response to multiple virus injections (with Gd-MRI)
b) Study the kinetics of virus replication over multiple doses (with Fluc bioluminescence)
c) Correlate in vivo scans with in vitro data from ex vivo brains (by IHC for tumor and virus)
Overlap: None

Title: PET-MR Imaging of pulmonary fibrosis
Effort: 0.60 CM
Funding Agency & Award Number: NIH, **1R01HL153606-01A1**
Grants Officer: N/A
Performance Period: 07/01/2021 - 06/30/2026 Funding Amount:
Project Goals: This proposal aims to apply PET-MR imaging to quantify molecular abnormalities in the lungs of IPF patients and determine if such measures can predict the pace of disease progression and determine whether the patient is responding to anti-fibrotic therapy.
Specific Aims: Aim 1: Implement a free-breathing lung MR-assisted PET data optimization pipeline
Aim 2: Demonstrate the robustness of 68Ga-CBP8 PET data and the added value of data optimization
Aim 3: Apply the bi-modal quantitative PET/MR protocol using both optimized static 68Ga-CBP8 PET and DCE-MRI to assess disease activity and treatment response in IPF subjects
Overlap: None

Industry Sponsored Clinical Trials Aggregated Effort 0.12 CM
Each of these individual projects has a varying need of effort depending on the type of activity currently in progress: protocol development, start-up, patient recruitment, enrollment, follow-up, monitoring, data analysis, publication, and closeout. Faculty determines each project's need and adjust their effort between projects within the total aggregated effort assigned to the clinical projects. Effort is reviewed and confirmed by the department based on the activity of each project.

Title: Endobronchial OCT for In Vivo Microscopic Diagnosis and Monitoring of Therapy Response in IPF
Effort: N/A
Funding Agency & Award Number: Boehringer Ingelheim Pharmaceuticals, **IIS2017-10686**
Grants Officer: N/A
Performance Period: 11/01/2018 - 10/31/2023 Funding Amount:
Project Goals: We aim to meet an essential need in IPF, and develop a novel, low-risk, non-surgical paradigm for microscopic diagnosis and disease monitoring with endobronchial optical imaging.
Specific Aims: Aim 1: In vivo validation of OCT for microscopic IPF diagnosis
Aim 2: Microscopic monitoring of response to nintedanib therapy over time with OCT Overlap:

None

Title: Early detection of progressive fibrosis in patients with interstitial lung abnormalities

Effort: N/A
Funding Agency & Award Number: Boehringer Ingelheim Pharmaceuticals, **1199-0437**
Grants Officer: N/A
Performance Period: 01/13/2021 - 01/12/2026 Funding Amount:
Project Goals: We aim to 1) investigate EB-OCT as a rapid, low-risk, minimally-invasive method for microscopic assessment of ILA and 2) investigate genomic expression profiles in ILA patients using single-cell sequencing of tissue and BAL.
Specific Aims: Aim 1. EB-OCT and genomic expression assessment of ILA in lung cancer resection patients. Aim 2. EB-OCT and genomic expression assessment of ILA in patients with rheumatoid arthritis
Overlap: None

(NEW)

Title: High resolution, minimally invasive, longitudinal imaging of pulmonary disease in post-COVID patients

Effort: N/A
Funding Agency & Award Number: Boehringer Ingelheim Pharmaceuticals, **IIS2021-2696**
Grants Officer: N/A
Performance Period: 05/2022 - 05/2027 Funding Amount:
Project Goals: to provide the necessary means for targeted, personalized therapy to treat dyspnea in PASC patients
Specific Aims: Aim 1. To investigate EB-OCT as a rapid, low-risk, minimally-invasive method for fibrosis detection. Aim 2. Microscopic assessment of disease activity over time in patients with post-COVID lung disease and determine the cellular and transcriptional profiles of airway cells in patients with post-COVID lung disease.
Overlap: None PENDING

Title: Title: Microscopic EB-OCT imaging to predict progression in interstitial lung abnormalities

Effort: 3.60 CM
Funding Agency & Award Number: NIH, **R01HL169225**
Grants Officer: Nina Hall Performance Period: 07/2023 - 06/2028 Funding Amount: Project Goals: to validate a low-risk, minimally-invasive, microscopic optical bronchoscopy tool to accurately detect early PF at the presymptomatic stages, before significant lung destruction has occurred, which would allow for early treatment and improve patient outcomes.
Specific Aims: Aim 1. Determine the accuracy of EB-OCT to detect high-risk microscopic features and predict disease progression in smokers with ILA undergoing nodule resection.
Aim 2. Determine the accuracy of EB-OCT to predict disease progression in subjects with ILA and family history of PPF.
Overlap: None

Title: Loss of Endothelial S1PR1 Drives Post-Influenza Pulmonary Fibrosis

Effort: 0.60 CM
Funding Agency & Award Number: NIH-NHLBI, **R01HL168138**

Grants Officer: Nina Hall Performance Period: 04/2023 -03/2028 Funding Amount: Project Goals: Endothelial S1PR1 Contributions to Influenza Viral Infection Induced Pulmonary Fibrosis Specific Aims: Aim 1: To determine whether sustained reduction in EC S1PR1 expression is due to a disruption of homeostatic S1PR1 recycling.
Aim 2: To determine whether downregulation of EC S1PR1 drives post-viral pulmonary fibrosis through alterations to EC-fibroblast cross talk.
Aim 3: To validate the efficacy of S1PR1 agonism as an anti-fibrotic therapeutic strategy. Overlap: None

Title: Collaborative Comprehensive measurements of the chemical composition and biological effects of vaping aerosols

Effort: 0.24 CM
Funding Agency & Award Number: Aerodyne Research, Inc. Grants Officer: N/A
Performance Period: 01/05/2022 - 01/04/2023 Funding Amount:
Project Goals: Dr. Benjamin Medoff will help design and execute studies on the effects of e-cigarette vaping components on primary human airway epithelial cells. These cells are purchased from a commerical source. He will provide cultures and expose them to components provided by Aerodyne and aid in the analysis and interpretation of the data.
Specific Aims: N/A Overlap: None

Previous\Current\Pending Support

Keyes, Colleen Previous

None

Current

(THIS AWARD)

Title: Biopsy Guidance of Lung Cancer using a Novel Electromagnetic and Optical Coherence Tomography Platform

Effort: 0.5 CM
Funding Agency & Award Number: DoD, **LC200392**
Grants Officer: N/A
Period of Performance: 06/15/2021 - 06/14/2023 Funding Amount:
Project Goals: The objective of this is to develop and test a steerable and electromagnetic optical coherence tomography (EM-OCT) biopsy guidance and diagnosis tool with the goal of dramatically increasing the diagnostic yield of low bronchoscopic based diagnosis of lung cancer.
Aim 1: Develop EM-OCT catheter and imaging system.
Aim 2: Conduct a preclinical swine study to demonstrate safety and feasibility. Overlap: None

Title: Early Detection and Diagnosis of Lung Cancer with Endomicroscopy

Effort: 1.2 CM
Funding Agency & Award Number: NIH/NCI, **R01CA255326**
Grants Officer: Guillermo Marquez Performance Period: 01/01/21 – 12/31/25 Funding Amount:
Project Goals: The major goal of this proposal is to develop a powerful optical bronchoscopy tool to increase the diagnostic yield of low risk approaches by 1) guiding biopsy site selection, and 2) by providing in vivo optical diagnosis that will allow for immediate treatment of the target tissue within the single clinical procedure. Specific Aim 1: Develop an EB-OCT platform that will provide

intra-procedural visualization of the tumor microenvironment with unprecedented resolution and contrast for biopsy guidance and diagnosis. Specific Aim 2: In vivo EB-OCT biopsy guidance for increasing the diagnostic accuracy and tumor yield in lung cancer. Aim 3: Conduct a study to evaluate the accuracy of EB-OCT diagnosis of lung cancer in human
Overlap: None

(NEW)

Title: High resolution, minimally invasive, longitudinal imaging of pulmonary disease in post-COVID patients

Effort: 0.12 CM
Funding Agency & Award Number: Boehringer Ingelheim Pharmaceuticals, **IIS2021-2696**
Grants Officer: N/A
Performance Period: 05/2022 - 05/2027 Funding Amount:
Project Goals: to provide the necessary means for targeted, personalized therapy to treat dyspnea in PASC patients
Specific Aims: Aim 1. To investigate EB-OCT as a rapid, low-risk, minimally-invasive method for fibrosis detection. Aim 2. Microscopic assessment of disease activity over time in patients with post-COVID lung disease and determine the cellular and transcriptional profiles of airway cells in patients with post-COVID lung disease.
Overlap: None

(NEW)

Title: A Phase 2 randomized, placebo-controlled, double-blind, dose-ranging study evaluating LTI-01 (single-chain urokinase plasminogen activator, scuPA) in patients with infected, non-draining pleural effusions

Effort: 0.12 CM
Funding Agency & Award Number: Lung Therapeutics, Inc., **LTI-01-2001**
Grants Officer: N/A
Performance Period: 10/2020 - 10/2025 Funding Amount:
Project Goals: To identify an effective dose with a favorable benefit-risk profile to support Phase 3 dosing of LTI-01 administered intrapleurally in patients with infected, non-draining pleural effusions
Specific Aims: Aim 1: To identify an effective dose with a favorable benefit-risk profile to support Phase 3 dosing of LTI-01 administered intrapleurally in patients with infected, non-draining pleural effusions.
Aim 2: To assess safety, tolerability, and efficacy, and evaluate the pharmacokinetic and pharmacodynamic parameters of LTI-01.
Overlap: None

Pending

Title: Title: Microscopic EB-OCT imaging to predict progression in interstitial lung abnormalities

Effort: 1.20 CM
Funding Agency & Award Number: NIH, **R01HL169225**
Grants Officer: Nina Hall Performance Period: 07/2023 - 06/2028 Funding Amount: Project Goals: to validate a low-risk, minimally-invasive, microscopic optical bronchoscopy tool to accurately detect early PF at the presymptomatic stages, before significant lung destruction has

occurred, which would allow for early treatment and improve patient outcomes.
Specific Aims: Aim 1. Determine the accuracy of EB-OCT to detect high-risk microscopic features and predict disease progression in smokers with ILA undergoing nodule resection.
Aim 2. Determine the accuracy of EB-OCT to predict disease progression in subjects with ILA and family history of PPF.
Overlap: None

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*