AWARD NUMBER: W81XWH-20-1-0747

TITLE: Imaging and Exosomal Genomics as an Early Identifier of Lung Cancer

PRINCIPAL INVESTIGATOR: Sandy NAPEL, PhD

CONTRACTING ORGANIZATION: Board of Trustees of the Leland Stanford Junior University

STANFORD UNIVERSITY

STANFORD CA 94305-2004

REPORT DATE: October 2021

TYPE OF REPORT: Annual Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
October 2021	Annual Report	1SEPT2020 - 31AUG2021

4. TITLE AND SUBTITLE

Imaging and Exosomal Genomics as an Early Identifier of Lung Cancer

5a. CONTRACT NUMBER

W81XWH-20-1-0747

5b. GRANT NUMBER

LC190293P1

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Board of Trustees of the Leland Stanford Junior University
STANFORD UNIVERSITY
450 JANE STANFORD WAY
STANFORD CA 94305-2004

8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Development Command
FORT DETRICK MD 21702-5014

10. SPONSOR/MONITOR'S ACRONYM(S)

USAMRAA

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Lung cancer is the predominant form of cancer in the United States due to its high incidence, often escaping diagnoses at early stages. Around 234,000 new cases of lung cancer and over 154,000 Americans are estimated to die from this disease in 2018. Lung cancer screening by low dose computed tomography (LDCT) results in the detection of a significant number of small lung nodules. The majority of these nodules do not represent cancer; however, they cannot be discriminated based on the CT imaging alone. As a consequence, many patients will undergo unnecessary invasive procedures that could be avoided if we would have better tests to distinguish between malignant and benign nodules. Nanometer scale (30-150 nm) extracellular vesicles (EVs) that carry tumor specific proteins and nucleic acids in lung cancer patients' blood have recently received substantial attention, as they may contain biomarkers that indicate disease state and progression. Our goal is to develop a model correlating imaging data with exosomal genomic biomarker profiles to discriminate benign from malignant nodules.

15. SUBJECT TERMS

Annual report.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC.
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Lung cancer is the predominant form of cancer in the United States due to its high incidence, often escaping diagnoses at early stages. Lung cancer screening by low dose computed tomography (LDCT) results in the detection of a significant number of small lung nodules. Most of these nodules do not represent cancer; however, they cannot be discriminated based on the CT imaging alone. Therefore, many patients will undergo unnecessary invasive procedures that could be avoided if we would have better tests to distinguish between malignant and benign nodules. Our goal is to develop a more specific biomarker, imaging test, or combination of the two (integrated diagnostic test) to allow us to intervene early in patients with high-risk nodules and follow the patients with low-risk lung nodules using non-invasive surveillance methods.

Here, we will utilize a newly developed [18F]FSPG PET tracer for lung nodule imaging and integrate it with the exosomal genomic data to non-invasively identify biomarkers for high risk and low risk lung nodules at the disease onset and progression. This work has the potential to transform the field of clinical biomarker discovery and improve the diagnosis, prognosis, and therapy response monitoring strategies for lung cancer. We will compare our strategy with currently existing models for lung nodule stratification.

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

Lung cancer, low-dose computed tomography (LDCT), PET, imaging, exosomes, genomics

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.

Aim 1: *To evaluate the performance of [18F]FSPG PET/CT imaging in discriminating between benign and malignant lung nodules.*

Subtask 1: IRB review and approval

Subtask 2: HRPO review and approval

Subtask 3: Patient recruitment

- *Patients with indeterminate lung nodules (7-30 mm) will be recruited and undergo novel [18F]FSPG PET/CT imaging as well as standard of care [18F]FDG PET/CT imaging.*
- *Blood samples will be collected from these patients (for Aims 2 and 3) (n=70). Patients diagnosed with malignant lung nodules will be compared against patients with benign lung nodules.*
- *The total number of participants planned to be enrolled is 120. 70 of these individuals will be recruited/funded by the current grant. The remaining 50 participants enrolled are currently being funded through another federal grant, Stand Up 2 Cancer (SU2C), from which we will obtain blood samples and CT images.*

Subtask 4: Determination of imaging parameters

- *Patients that undergo an [18F]FSPG PET/CT will have various parameters and measures analyzed: uncorrected maximum lesion intensity (SUVmax), corrected for blood pool uptake (SUVRmax), and uptake (absent, minimal, moderate, and high).Subtask 5: Utilizing PET tracer [18F]FSPG*

Subtask 5: Determination of imaging parameters

- *FSPG and FDGPET/CT imaging procedures scheduled at least >24 hours apart but not more than two weeks apart to allow for imaging agent washout (n=70 patients)*
- *All imaging agent and associated materials will be recorded, handled, stored and disposed of in accordance with all applicable regulatory guidelines and used in accordance with this protocol. If any discrepancies arise, an explanation will be provided by the principal investigator, nuclear physician, or designee.*

Milestone(s): Imaging parameter determination and use of a novel PET tracer in 70 subjects.

Aim 2: *Isolate and profile exosomal genomic data of the sample cohort to identify biomarker signatures.*

Subtask 1: To isolate EVs from plasma samples using the ExoTIC.

- *Plasma samples obtained from recruited patients will be processed for EV isolation (n = 70 plasma samples from Aim 1).*
- *Plasma samples obtained from recruited patients will be processed for EV isolation.*

Subtask 2: To quantify EVs isolated by ExoTIC.

- *EVs isolated from patient samples will be quantified via NTA and characterized via TEM, ELISA and WB.*

Subtask 3: Designing the engineering limits for ExoTIC.

- *Maximizing EV yield by upscaling the filter surface area of ExoTIC*

Subtask 4: Performing exosomal DNA and RNA analyses.

- *RNA extraction from EVs isolated from all plasma samples of the individuals recruited (n=70) (collected in Aim 1) to evaluate signature of mRNAs and miRNAs to distinguish individuals with lung cancer from cancer-free patients.*
- *DNA extraction from EVs isolated from all plasma samples to evaluate signatures of copy number aberrations to distinguish individuals with lung cancer from cancer-free patients.*
- *Analysis will be done on all 120 samples (70 patients recruited by this award and 50 patients recruited by the SU2C award).*

Milestone(s): Profiling exosomal RNA and DNA signatures of individuals with and without cancer to establish "health and cancer" signatures.

Aim 3: *To correlate and combine the data obtained from exosomal DNA and RNA profiles with PET/CT imaging results.*

Subtask 1: Integration of prediction models

- *Candidate signatures from EV-derived DNA-seq, RNA-seq and CT signatures will be identified.*
- *Identified signatures will be integrated for building a model.*
- *Data will be obtained for all 120 samples (70 patients recruited by this award and 50 patients recruited by the SU2C award).*

Milestone(s): Integrating imaging data and exosomal genomic profiles.

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.

*Earlier we studied twelve plasma samples obtained from individuals with a smoking history and lung cancer (n=12). These patients were recruited through Stand Up 2 Cancer (SU2C) program. Plasma samples from these individuals have been processed for exosome isolation in comparison to healthy control samples (n=10). Healthy samples were purchased from Stanford Blood Center. After exosome isolation, RNA was extracted from the exosome preparations. The exosomal RNA concentrations and total RNA (**Figure 1**) extracted from the samples allowed us to analyze disease signatures via RNA sequencing. RNA sequencing libraries were generated and sequenced on an Illumina NextSeq. Preliminary analysis revealed that thousands of transcripts were detected in each sample (**Figure 2**).*

During this quarter, we have obtained three additional samples (bringing the total sample number to 15) through the SU2C program, to study exosomal RNA cargo.

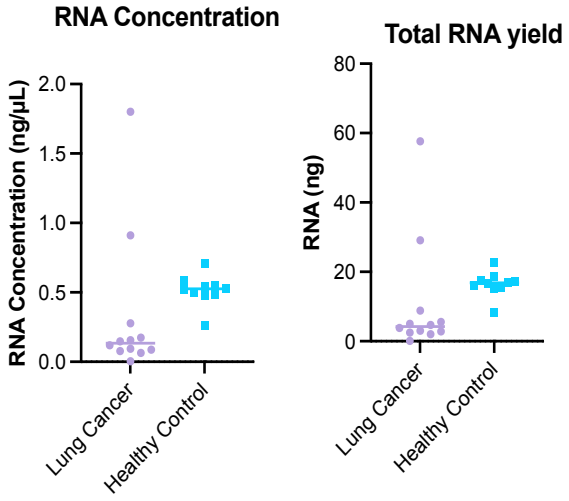

Figure 1. *RNA extracted from Lung cancer and healthy control plasma samples. Exosomal RNAs extracted and quantified from lung cancer (n=12) and healthy control (n=10) plasma samples.*

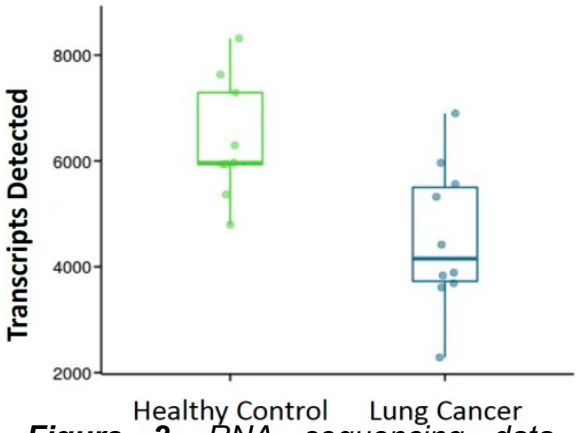

Figure 2. *RNA sequencing data showing the number of transcripts detected from Lung cancer and healthy control plasma samples. RNA sequencing libraries were made from exosomal RNAs extracted from lung cancer (n=12) and healthy control (n=10) plasma samples.*

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.

Nothing to Report.

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.

During the next reporting period, we are planning to process the three additional samples (and any additional samples available to us through the SU2C study) and perform exosomal RNA sequencing. By doing this, we will reach a sample size of 15 for lung cancer patient samples in addition to samples from 10 healthy controls. Furthermore, we will collect de-identified imaging data in addition to the RNA sequencing data, and develop a protocol for extracting radiomic features from relevant portions of the images. The unique RNA signatures identified from the study will be correlated with the imaging results in the next period.

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:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

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.

The project officially started on 09/01/2020. However, due to the lengthy HRPO approval process, the experimental activities started later in April 2021.

Due to the COVID-19 restrictions on clinical activities, the recruitment of human subjects for clinical research was delayed. With the recent availability of COVID-19 vaccines and the proportion of the number of patients who are getting vaccinated, we expect to start receiving additional samples very soon.

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.

Because of these delays, expenditures for processing are less than anticipated. Also, we delayed engaging staff to perform the work related to these samples. We anticipate getting back track in both these areas over the next 6 months.

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

Nothing to Report.

Significant changes in use or care of vertebrate animals

Not applicable.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

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).*

*The Demirci Lab has **published a review paper that acknowledges this DoD award** as follows:*

> *Emerging biofabrication approaches for gastrointestinal organoids towards patient specific cancer models. Fernando Soto, Carlos F. Guimaraes, Rui L. Reis, Walfre Franco, Imran Rizvi, Utkan Demirci. Cancer Letters 504 (2021) 116–124.*

This review paper was written when Carlos F. Guimarães' visit at Stanford University as a visiting graduate student visiting from Dr. Rui Reis' Lab (03/01/2020 to 02/28/2021) and he was supported by a fellowship (Fundação para a Ciência e Tecnologia, Grant no. PD/BD/135253/2017, and Fundação Luso-Americana para o Desenvolvimento, FLAD) from Portugal. All the work was done at Stanford University. The scholarship funds are given directly to the individual and funds did not come to Demirci Lab.

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:	*Sandy Napel, PhD*
Project Role:	*PD/PI*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0003-2784-1590*
Nearest person month worked:	*2.48 % (Sept 2020 – Aug 2021)*
Contribution to Project:	*Dr. Napel oversaw collection of data and building of infrastructure to collect and analyze imaging data*
Funding Support:	*-*

Name:	*Harmeet Bedi, MD*
Project Role:	*Clinical Scientist*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/ 0000-0002-7241-4881*
Nearest person month worked:	*1.96 % (Sept 2021 – Aug 2021)*
Contribution to Project:	*Dr. Bedi managed patient recruitment and sample collection.*
Funding Support:	*-*

Name:	*Pritam Mukherjee, PhD*
Project Role:	*Post-doctoral Research Associate*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0001-7999-3479*
Nearest person month worked:	*14.67 % (Sept 2021 – Aug 2021)*
Contribution to Project:	*Dr. Mukherjee organized the structure and systems needed to collect the imaging data on our subjects.*
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?
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.

Please see Dr. Napel's "Other Support" document in "Appendices" below.

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://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) 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.*

DOD FORMAT OTHER SUPPORT DOCUMENT: NAPEL, SANDY

ACTIVE

R01 CA222512 (Li, Ruijiang) 02/01/18 – 01/31/23 0.60 calendar
NIH $309,040
Multiregional Imaging Phenotypes and Molecular Correlates of Aggressive Versus Indolent Breast Cancer
Major Goals: To develop associations linking imaging phenotypes to molecular subtypes with different prognoses.
Specific Aims: We propose to develop and improve methods to explicitly quantify multiregional MRI phenotypes including those of intratumoral subregion and parenchyma, and systematically assess their reproducibility, to develop a prognostic imaging signature using a large retrospective cohort of >1000 patients curated by the Stanford Oncoshare Project, and validate it in the prospective multi-center I-SPY 1 cohort, and to construct a radiogenomic signature to perform additional testing of its prognostic value in 13 public gene expression cohorts of >5000 breast cancer patients. To further improve prognostication, we will build a multifactorial model that integrates imaging with clinical and genomic markers**.**
Program/Grants Officer:
Yisong Wang, Ph.D. yisong.wang@nih.gov
National Cancer Institute
BG 9609 RM 4W422
9609 Medical Center Drive
Rockville, MD 20850

R01 CA233578 (Li, Ruijiang) 02/01/19 – 01/31/24 0.60 calendar
NIH $350,555
Imaging and Circulating Tumor DNA Markers to Assess Early Treatment Response in Lung Cancer
Major Goals: To characterize the imaging phenotype for lung cancer patients and, with the association of circulating tumor cells, to build a predictive model for treatment response.
Specific Aims: To improve methods to identify tumor subregions and characterize spatial heterogeneity, to systematically evaluate the repeatability and reproducibility of the image features, to develop and validate imaging biomarkers to predict patterns of failure in NSCLC, and to integrate imaging with circulating tumor DNA markers to improve predictive accuracy.
Program/Grants Officer:
Christopher (Chris) Hartshorn, Ph.D. christopher.hartshorn@nih.gov
National Cancer Institute
BG 9609 RM 4W220
9609 Medical Center Drive
Rockville, MD 20850

R01 CA260271 (Gevaert, Olivier) 05/01/21 – 04/30/26 0.24 calendar
NIH $397,686
Multiscale modeling of Glioma for the Prediction of Treatment response, Treatment Monitoring and Treatment Allocation
Major Goals: To employ AI and radiogenomics techniques for management of patients with glioma.
Specific Aims: To create a multi-scale framework for treatment allocation, treatment follow-up and treatment monitoring to provide precision medicine for patients with brain tumors. We will develop informatics methods integrating clinical, molecular and imaging data for therapeutic purposes. We will focus on the development of multi-scale signatures that are predictive of treatment response, actionable and suggest the use of novel drugs.
Program/Grants Officer:
Christopher L. Hatch, Ph.D. christopher.hatch@nih.gov
National Cancer Institute
BG 9609 RM 7W554
9609 Medical Center Drive
Rockville, MD 20850

W81XWH2010747 (Napel, Sandy) 09/01/20 – 08/31/23 0.31 calendar
USAMRAA $135,564
Imaging and Exosomal Genomics as An Early Identifier of Lung Cancer
Major Goals: To evaluate the performance of [18F]FSPG PET/CT imaging in relation to exosomal genomics in discriminating between benign and malignant lung nodules.
Specific Aims: (1) To evaluate the performance of [18F]FSPG PET/CT imaging in discriminating between benign and malignant lung nodules. (2) To isolate and profile exosomal genomic data of the sample cohort to identify biomarker signatures. (3) To correlate and

combine the data obtained from exosomal DNA and RNA profiles with PET/CT imaging results.

Program/Grants Officer:
Michael D. Hall, Ph.D. Michael.d.hall14.ctr@mail.mil
Science Officer | Congressionally Directed Medical Research Programs
Lung Cancer Research Program, Kidney Cancer Research Program, Goldbelt Frontier
301.619.8922

AWD101462-D (NIH Prime: Univ of Chicago (Giger, M. PI))
NIH
Stanford subcontract PI: Langlotz, Curt 08/21/21 – 08/20/22 1.27 calendar
University of Chicago $531,707
Medical Imaging and Data Resource Center (MIDRC) for Rapid Response to COVID-19 Pandemic
Major Goals: To develop and implement new diagnostics, including machine learning algorithms, that will empower population-wide preventive and management strategies for COVID-19.
Specific Aims: (1) Create a data repository for the aggregation, processing, analysis and dissemination of COVID-19 images and associate data. (2) Engage the data science community through a series of data science challenges, and (3) Provide an algorithm benchmarking service using the aggregated data to provide comparative accuracy statistics for designated use cases.
Program/Grants Officer:
Guoying Liu, Ph.D. guoying.liu@nih.gov
National Institute of Biomedical Imaging and Bioengineering
GB 2DEM RM 233
6707 Democracy Blvd
Bethesda, MD 20817

SPO 207900 (Demirci, Utkan) 05/16/21 – 08/31/22 .72 calendar
Philips Healthcare $965,166
Advancing Precision Health: Enabling Personalized Diagnostics and Treatment Delivery
Major Goals: To develop new care paradigms generally at the intersection of advanced clinical monitoring/imaging, novel diagnostic mechanisms, and predictive/prescriptive analytics.
Specific Aims: This research collaboration is focused on Precision Health with the aim of enabling definitive personalized diagnostics and treatment delivery. This program will support high-impact projects to define new care paradigms at the intersection of advanced clinical imaging, novel diagnostic mechanisms, and predictive analytics, with a potential pathway to translation and providing the basis for continued larger studies. Specifically, this component of the collaboration is for oversight and management of (a) the process of selecting projects to be funded and (b) oversight of the selected projects.

Program/Grants Officer:
Marek Bartula marek.bartula@philips.com

Philips North America LLC
Clinical Research Board
222 Jacobs Street
Cambridge, MA 02141

PENDING

R01 DE030894 (Li, Ruijiang) 04/01/22 – 03/31/27 0.60 calendar
NIH $442,007
Precision imaging for risk stratification and personalized therapy of oropharyngeal cancer
Major Goals: To develop imaging-based prognostic models to improve risk stratification and guide personalized therapy of OPC.
Specific Aims: (1) Develop knowledge-based radiomic signatures to predict patterns of relapse. (2) Develop data-driven, multi-task deep learning imaging signatures to predict patterns of relapse. (3) Validate imaging signatures and integrate with clinical data to improve prognosis prediction. (4) Identify biological basis of the imaging signatures by correlating with molecular data.
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PO1 CA261652 (Xing, Lei) 04/01/22 – 03/31/27 1.80 calendar
NIH $1,250,000
Artificial Intelligence-Augmented Adaptive Radiation Therapy; Project "Deep Learning Enablers for Head and Neck Adaptive Radiotherapy"
Major Goals: To develop (1) near real-time segmentation of critical organs and targets for quick daily dose evaluation/re-planning and (2) non-rigid registration CT to cone beam CT to modify treatments to account for daily anatomy presentation and accumulated dose.
Specific Aims: (1) Develop automatic multi-organ segmentation of head and neck cancer (HNC) CT images using learned latent shape representations and deep convolutional neural network (DCNN) architectures. (2) Develop automatic, unbiased multi-organ deep learning segmentation of on-treatment cone-beam CTs (CBCTs) using shape-aware DCNN trained with exact ground truth segmentations. (3) Develop a weakly supervised segmentation-aware deep learning model for anatomically accurate (biofidelic) deformable registration of planning HNC CTs to on-treatment CBCTs.
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SPO 233641 (Wilson, Thomas) 07/01/22 – 06/30/24 0.60 calendar
DoD $293,458
Machine-learning Approach to Differentiation of Benign and Malignant Peripheral Nerve Sheath Tumors: A Multicenter Study
Major Goals: To develop and validate an image-based computerized system for distinguishing benign and malignant peripheral nerve sheath tumors.
Specific Aims: (1) Develop and evaluate advanced machine learning classifiers for differentiating BPNSTs and MPNSTs using our previously developed multi-institutional clinicoradiological dataset. (2) Develop and evaluate advanced machine learning classifiers for differentiating BPNSTs and MPNSTs trained on T1W-gad and T2W images. (3) Develop and validate an automated segmentation algorithm capable of identifying and annotating PNST borders for classifier analysis
Program/Grants Officer: unassigned

COMPLETED

R56 EB020527 (Gevaert, Olivier) 02/15/15 – 08/31/21 0.60 calendar
NIH $290,695
Radiogenomics Framework for Non-Invasive Personalized Medicine
Major Goals: To develop a computational framework to identify quantitative imaging biomarkers that mirror molecular properties of tumors.
Specific Aims: We will develop a radiogenomics framework to identify non-invasive biomarkers mirroring relevant molecular tumor properties that impact treatment and clinical outcome of human brain tumors. We will offer innovative new algorithms to represent medical images. We will have image signatures that are prognostic and image signatures reflecting actionable molecular properties of a tumor such as drug target activity or drug signatures.
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U01 CA190214 (Rubin, Daniel) 06/01/15 – 05/31/21 0.96 calendar
NIH $372,067
Qualification and Deployment of Imaging Biomarkers of Cancer Treatment Response
Major Goals: To produce a software resource and tools for researchers to qualify new biomarkers of cancer response to treatment, and to facilitate getting these biomarkers into clinical trials.
Specific Aims: We will develop a platform and tools through which to deploy new imaging biomarkers into clinical trials, extending our previously developed Web-based image viewing

tool and developing four unique capabilities, we will develop methods to repurpose existing imaging data from clinical trials for studying new imaging biomarkers by developing automated image segmentation methods to enable efficient calculation of novel quantitative imaging biomarkers; and we will deploy and evaluate our platform and tools in two cancer centers and the ECOG-ACRIN national cooperative group, and demonstrate their ability to efficiently collect image biomarker data and to facilitate the qualification of new imaging biomarkers.
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U01 CA187947 (Napel, Sandy) 09/01/15 – 08/31/20 2.40 calendar
NIH $365,514
Computing, Optimizing, and Evaluating Quantitative Cancer Imaging Biomarkers
Major Goals: To develop a cloud-based resource for generating image features of tumors and evaluating their absolute and relative efficacy for predicting dependent variables, such as response, survival, cancer genomics.
Specific Aims: We will create an expandable library of quantitative imaging feature algorithms capable of comprehensive characterization of the imaging phenotype of cancer. We will build a cloud-based software architecture for creating, executing, and comparing quantitative image feature-generating pipelines, including algorithms in the library and/or those supplied by QIN or other researchers as plug-ins. QIFP will also have (a) a machine learning engine that lets users specify a dependent variable (e.g., progression-free survival) that the quantitative image features can used to predict, and (b) an evaluation engine that compares the utility of particular features for predicting the dependent variable. We will assess the QIFP in four ways.
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None (Napel/Shah) 08/16/19 – 08/15/20 0.37 calendar
2019 Stanford AIMI Center Seed Grant Program $75,000
Machine Learning for Distinguishing Non-small Cell Cancer From Small-cell Cancer From Benign Pulmonary Nodules on Chest CT in a Multi-Center VA Cohort
Major Goals: To build a database from which to develop artificial intelligence approaches to classifying the types of nodules, so as to hopefully identify the most aggressive cancers more quickly than we do currently.
Specific Aims: To develop a radiomic-based machine learning model to distinguish benign nodules from small cell lung cancer from non-small cell lung cancer for diagnostic intervention risk stratification, to develop a multi-institution cohort of over 500 patients from the Veterans

Affairs Health Care System, together with comprehensive clinical data unique to these patients, and to build a. robust machine learning model for stratifying patients into the most efficacious treatments with minimal delay for the most at-risk patients.

Program/Grants Officer:
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U24 CA180927 (NIH Prime: MGH (Rosen, B. PI))
NIH
Stanford subcontract PI: Napel, Sandy 09/01/14 – 08/31/19 1.8 calendar
MGH $87,522
Informatics Tools for Optimized Imaging Biomarkers for Cancer Research & Discovery
Major Goals: To develop a cloud-based infrastructure for on-going quantitative comparison and evaluation of segmentation and characterization tools.
Specific Aims: We will develop the C-BIBOP for the large-scale central analysis of multi-institutional quantitative image data by developing a cloud-based infrastructure to support customized computing environments, "experiments" that include images and associated meta-data, and a reporting module that performs comparisons, statistical analyses and visualizations of the results of segmentation and characterization. We will host at least two permanent online collections of images and maintain the best segmentations and characterizations available that can be utilized by participants at anytime.
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SPO 124869 (Demirci, Utkan) 09/01/16 – 05/31/19 .60 calendar
Philips Electronics North America Corp. $2,345,617
Advancing Precision Health: Enabling Personalized Diagnostics and Treatment Delivery
Major Goals: To develop new care paradigms generally at the intersection of advanced clinical monitoring/imaging, novel diagnostic mechanisms, and predictive/prescriptive analytics.
Specific Aims: This research collaboration is focused on Precision Health with the aim of enabling definitive personalized diagnostics and treatment delivery. This program will support high-impact projects to define new care paradigms at the intersection of advanced clinical imaging, novel diagnostic mechanisms, and predictive analytics, with a potential pathway to translation and providing the basis for continued larger studies. Specifically, this component of the collaboration is for oversight and management of (a) the process of selecting projects to be funded and (b) oversight of the selected projects.
Program/Grants Officer:
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U01 CA196405 (NIH Prime: Vanderbilt (Massion, P. PI))
NIH
Stanford subcontract PI: Napel, Sandy 09/01/16 – 04/30/19 .60 calendar
Vanderbilt University $63,694
Vanderbilt project title: Cellular, Molecular and Quantitative Imaging Analysis of Screening-Detected Lung Adenocarcinoma
Stanford subcontract title: Radiomics & Deep Learning Approaches to Screen Detected Lung Adenocarcinoma
Major Goals: To improve prediction models by integrating quantitative imaging, molecular and cellular determinants to be paradigm-shifting in the clinical management of patients with early adenocarcinoma.
Specific Aims: We will develop a retrospective and a prospective repository for both tissue (ADC fresh frozen tissues, blood) and images from which we will derive detailed quantitative structural imaging analysis, targeted genomic analysis and single cell analysis to interrogate the functional genomics of these tumors. The integration of this multidimensional data imaging/molecular/cellular/epidemiology will allow us to identify and validate cellular and molecular determinants of tumor behavior in the context of their inter- and intra-tumor heterogeneity. With these results, we will be able to build integrated models of ADC behavior, validate a new genomic molecular test on circulating DNA and propose prospective studies that would eventually offer a different intervention based on these predictions.
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R01 CA160251 (Napel/Plevritis) 09/15/11 – 07/31/17 1.20 calendar
NIH $362,935
Tools for Linking and Mining Image and Genomic Data in Non-Small Cell Lung Cancer
Major Goals: To develop tools for creating an integrated database of imaging, clinical, and genomic features in non-small cell lung cancer and to mine it for relationships to prognosis.
Specific Aims: We will develop, validate and make publicly available, controlled vocabularies and software tools to be used in building databases with vectors that quantitatively describe features of human tumors in CT and PET images, create and make publicly available a novel multidimensional database that integrates these features of CT and PET images with clinical and gene expression microarray data of excised tumors from 400 patients with NSCLC, and demonstrate the utility of the integrated imaging/genomic/clinical database, by (a) implementing bioinformatics approaches that create an association map from CT and PET image features and

clinical data to gene expression, and (b) discovering prognostic signatures that incorporate imaging, gene expression and other clinical data. While specifically developed and validated for CT and PET images of lung cancer, our tools will be extensible to other modalities and disease scenarios.

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5U01 CA142555 (Rubin, Daniel) 05/01/10 – 04/30/17 1.2 calendar
NIH $524,789
Computerized Quantitative Imaging Assessment of Tumor Burden
Major Goals: The goal of this project is to develop tools that use imaging data to be able to better predict response to treatments in clinical trials.
Specific Aims: To develop software infrastructure that meets these needs of cancer researchers through three aims: creating tools leveraging caBIG technologies to standardize quantitative imaging assessment of tumor burden, through a commercial partnership, we will incorporate features of our tools in a commercial image interpretation workstation to introduce our methods into clinical practice, developing methods to analyze quantitative image metadata and to help oncologists evaluate quantitative criteria on images collected as part of clinical trials; and evaluating the utility of our infrastructure by applying our tools in two clinical trials and demonstrating the ability of our software infrastructure to quantitatively and more reproducibly measure tumor burden, helping researchers to assess the response to treatment in individual patients and patient cohorts.

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R01 EB014955 (NIH PRIME: Kitware, Inc; (Schroeder, W. PI))
NIH
Stanford subcontract PI: Napel, Sandy 05/01/13 – 04/30/17 1.03 calendar
Kitware, Inc. $28,385
Accelerating Community-Driven Medical Innovation with VTK
Major Goals: To accelerate the development and adoption of the Kitware platforms to advance medical imaging applications of software on a major scale.
Specific Aims: We will update the VTK graphics infrastructure to support efficient representation and rendering of large data, visualizing data over the web and on mobile platforms, and interactively exploring data using 3D widgets, manage the growth of VTK and its large open-source community by enabling multiple channels whereby code can be easily

contributed, discovered, downloaded, and used as modular extensions to VTK, and conduct targeted outreach to maximize the impact of the proposed VTK enhancements on the medical community.

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OVERLAP

No budgetary or scientific overlap.