AWARD NUMBER: W81XWH-21-1-0269

TITLE: Utilizing the Immune Response to Tumor Neoantigens for Kidney Cancer Early Detection

PRINCIPAL INVESTIGATOR: Fan, Alice C.

CONTRACTING ORGANIZATION: The Leland Stanford Junior University, Redwood City, CA

REPORT DATE: August 2022

TYPE OF REPORT: Final

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

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Alice C. Fan, MD (PI)

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n/a

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Stanford University
Office of Sponsored Research
485 Broadway, University Hal
Redwood City, CA 94063

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

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Approved for public release. Distribution is unlimited.

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n/a

14. ABSTRACT

Advanced-stage renal cell carcinoma (RCC) results in markedly reduced survival compared to curable early-stage RCC, which highlights the need for better cure rates through early detection. Screening assays are needed that allow for detecting all RCC at stage I.

Here, we tested the hypothesis that immune response to clear cell RCC (ccRCC) neoantigens provides a signal of stage I ccRCC in blood. Using the Serum Epitope Repertoire Analysis (SERA) platform, which utilizes a library of peptides that are displayed on bar-coded bacteria to identify antibodies that are present in serum, we profiled the antibody repertoire in 177 ccRCC patients across stages and grades and compare these to 23 patients with benign kidney lesions and to 1519 non-cancer controls. We found that ccRCC patients have a richer antibody repertoire. However, each epitope is shared only in up to ~10% of ccRCC patients. Additionally, many antibodies that are enriched in ccRCC patients correspond to epitopes that do not map to the linear human proteome. Further work is needed to reveal the nature of these epitopes and to develop methods for 'binning' enriched epitopes in RCC, e.g., on the protein level, to reveal common antigenic proteins and pathways in ccRCC.

15. SUBJECT TERMS None listed.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	Unclassified	26	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

Renal cell carcinoma (RCC) suffers from a lack of early detection assays. Here, we test the hypothesis that the immune response to RCC neoantigens provides a signal of stage I RCC in blood. We profile serum or plasma of 200 patients with kidney tumors and known pathology to identify an auto-antibody signature to distinguish RCC patients from patients with benign or no kidney tumors and high-grade from low-grade RCC.

2. KEYWORDS:

Kidney cancer, renal cell carcinoma, immune response, cancer early detection, auto-antibodies, biomarker

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Define and Validate Autoantibody Signature of ccRCC
Major Task 1: Profile autoantibody repertoire in 200 plasma samples (ccRCC and benign lesions) using SERA – COMPLETED
Major Task 2: Define signature for ccRCC vs. healthy controls, benign renal lesions, and other cancers and conditions –COMPLETED, but no identified shared epitopes for validation in task 3.
Major Task 3: Experimental Validation of Top Hits – NOT COMPLETED

Specific Aim 2: Define and Validate Autoantibody Signature of High-Grade ccRCC
Major Task 4: Profile autoantibody repertoire in 180 ccRCC plasma samples using SERA – COMPLETED
Major Task 5: Define signature for high-grade vs. low-grade ccRCC – COMPLETED, but no identifiable shared epitopes for validation in task 6.
Major Task 6: Experimental Validation of Top Hits – NOT COMPLETED

What was accomplished under these goals?

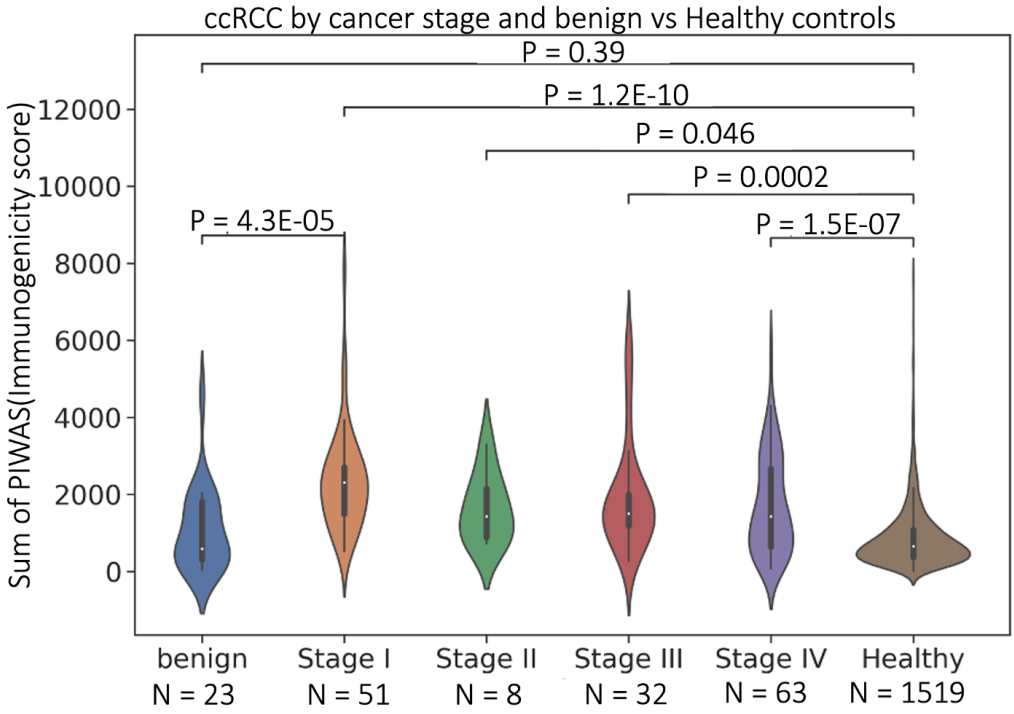
Specific Aim 1: Define and Validate Autoantibody Signature of ccRCC

Major Task 1: Profile autoantibody repertoire in 200 plasma samples (ccRCC and benign lesions) using SERA

We profiled the autoantibody repertoire in the cohort of 200 patients with kidney tumors (177 ccRCC, 23 benign kidney lesions) using SERA, mapped the enriched peptides bound to these autoantibodies to the human proteome, and scored the enrichment of the mapped epitopes over healthy controls, yielding an enrichment score for each position in the human proteome (PIWAS score). Based on previous work, we consider a PIWAS score of greater than 6 significant.

Major Task 2: Define signature for ccRCC vs. healthy controls, benign renal lesions, and other cancers and condition and Major Task 3: Experimental Validation of Top Hits

To compare autoantibody repertoires between patients, we use the sum of all significant PIWAS scores as a measure for the degree of outliers, thereby quantifying the extent of autoantibody abundance and diversity. Comparing the 154 out of the 177 patients with ccRCC that had staging information and were treatment-naïve to the 23 patients with benign lesions and 1519 healthy controls (selected for age 41 or older), we found that autoantibody abundance/diversity is greater across all stages of ccRCC, including stage I ($p = 4.3*10^{-5}$ for stage I ccRCC vs. benign kidney lesions; $p = 1.2*10^{-10}$ for stage I ccRCC vs. healthy controls using Welch's t-test).



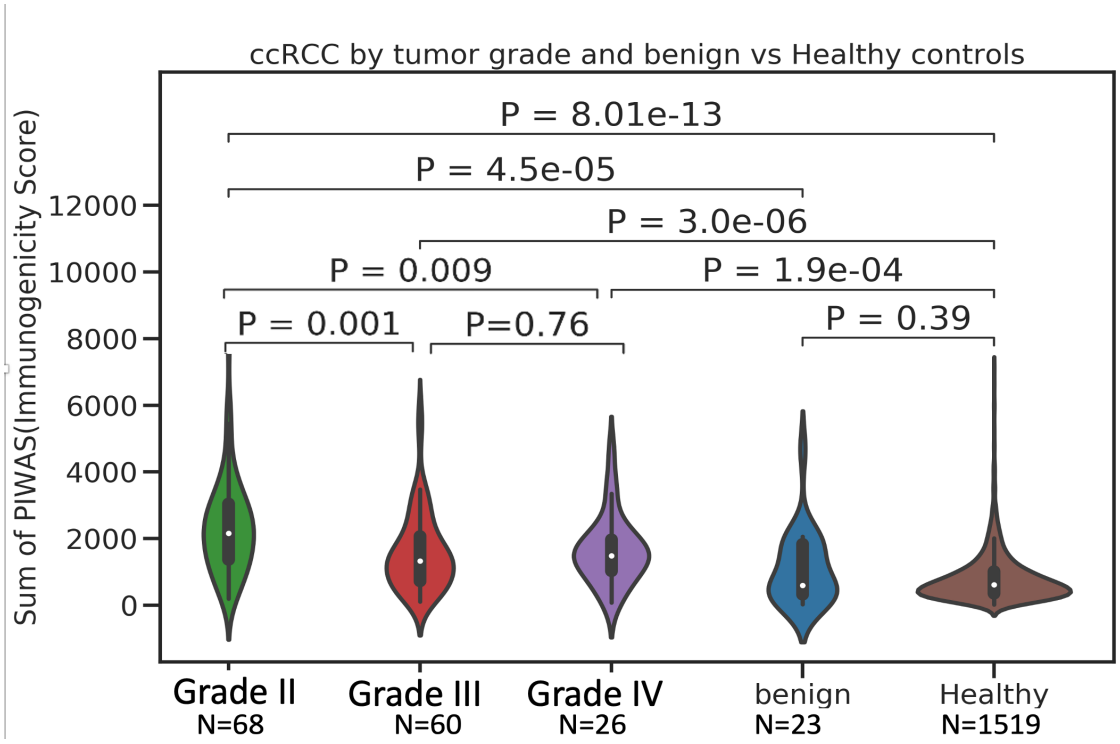
While the enrichment of autoantibodies even in in early-stage ccRCC is encouraging, we also found that the antigens corresponding to these autoantibodies are not widely shared among ccRCC patients: each antigen is enriched in max. 10% of ccRCC patients, indicating that each tumor might solicit its own unique immune response rather than generating repetitive autoantibody patterns characteristic to this type of cancer. The large number of enriched autoantigens in this limited-sized cohort prevented us from building a classifier for ccRCC vs. non-cancer without overfitting. No top candidates emerged for experimental validation with ELISA for Task 3 (discussed in more detail in section 5).

Specific Aim 2: Define and Validate Autoantibody Signature of High-Grade ccRCC

Major Task 4: Profile autoantibody repertoire in 180 ccRCC plasma samples using SERA (see Major Task 1 above)

Major Task 5: Define signature for high-grade vs. low-grade ccRCC and Major Task 6: Experimental Validation of Top Hits

Using the same approach as in Specific Aim 1, we compared the autoantibody repertoire of the cohort of ccRCC patients divided up by tumor grade (grade II, III, or IV, no patients with grade I tumors were part of this cohort) to the 23 patients with benign lesions and the 1519 healthy controls. Consistent with the results from Specific Aim 1, we found that autoantibody abundance/diversity is greater across all grades of ccRCC than in patients with benign kidney tumors or healthy controls. Comparing low-grade (grade 2) to high-grade ccRCC (grade 3 or 4), we found that interestingly, grade 2 ccRCC appears to have an even greater autoantibody abundance/diversity than high-grade ccRCC ($p = 0.001$ for grade 2 vs. grade 3 ccRCC; $p = 0.009$ for grade 2 vs. grade 4 ccRCC; $p = 0.76$ for grade 3 vs. grade 4 ccRCC using Welch's t-test).



Similar to the results in Specific Aim 1, we found that the antigens corresponding to these autoantibodies are not widely shared among ccRCC patients: each antigen is enriched in max. 10% of ccRCC patients. The large number of enriched autoantigens in this limited-sized cohort prevented us from building a classifier for high-grade vs. low-grade ccRCC without overfitting. As above, no identifiable top candidates to bring forward for experimental validation with ELISA task 6 (discussed in more detail in section 5).

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Results were presented in form of poster at 2 scientific conferences:

1. The Early Detection of Cancer Conference, October 2021 (international conference, virtual)
2. ASCO Genitourinary Cancers Symposium, February 2022 (international conference, San Francisco, CA)

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to Report

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This is the first study that comprehensively profiles the autoantibody repertoire in ccRCC and found that the antibody repertoire is rich in this type of cancer, however very diverse across patients. Therefore, this study furthers our understanding of the complex interplay between kidney cancer and the immune system. It marks the first step to explore the potential of novel markers in the immune response to the presence of kidney cancer for new screening assays to detect kidney cancer early and for new diagnostic tools to distinguish between patients who need surgery and patients who are better off on surveillance.

What was the impact on other disciplines?

The method of comprehensively profiling the autoantibody repertoire can easily be utilized for other cancer types that are equally in need for better screening assays and better diagnostics.

What was the impact on technology transfer?

A candidate marker in the autoantibody repertoire of kidney cancer – after validation in an independent larger patient cohort – could be developed further into a commercial screening or diagnostic blood test.

What was the impact on society beyond science and technology?

This study, though at the early stage of biomarker discovery, could lay the foundation for the first screening assay for kidney cancer. Such a test would enable us to detect kidney cancer early in every case, thereby avoiding the morbidity and mortality of late-stage cancer and the financial burden of treating it with costly drugs.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report, since no significant changes in the project or its principal approach

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

A major challenge in this project was the large number of identified autoantigens identified in our cohort of 200 patients with kidney tumors. The large number of autoantigens relative to the number of patients prevented a straightforward approach to building a classifier for distinguishing ccRCC from benign kidney tumors and healthy controls and high-grade from low-grade ccRCC and their experimental validation using ELISA. Many of these autoantigens were not shared among larger subsets of patients. Additionally, a significant portion of identified antigenic epitopes did not map to the linear human proteome, indicating that these represent either conformational epitopes that only exist in the 3D structure of the respective antigen or are cancer-specific antigens that arose from mutations and don't have any equivalent in the normal human proteome or have non-human origins (e.g., microorganisms).

Nevertheless, this dataset provides a rich source to mine with novel approaches. For example, together with Dr. Anshul Kunjade, whose laboratory has expertise in computational biology, data can be re-analyzed using different 'binning' strategies to reduce the number of features by clustering peptides into corresponding proteins and then assess enrichment at the protein level in ccRCC. Separately, a future subanalysis can be done specifically on those peptides that do not map to the human proteome, as these are particularly interesting as biomarker candidates due to their potential specificity to cancer.

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.

Nothing to Report

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

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

Not applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

Results were presented in form of poster at 2 scientific conferences:

1. Hoerner CR, Jharto M, Waitz R, Kamath K, Zhang M, Dahl A, Shon J, Fan AC. Utilizing the Autoantibody Immune Response to Tumor Antigens for Kidney Cancer Early Detection. The Early Detection of Cancer Conference, October 2021 (international conference, virtual)
2. Hoerner CR, Jharto M, Waitz R, Kamath K, Zhang M, Dahl A, Shon J, Fan AC. Utilizing the Autoantibody Immune Response to Tumor Antigens for Kidney Cancer Early Detection. Abstract 369. ASCO Genitourinary Cancers Symposium, February 2022 (international conference, San Francisco, CA)

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: *Alice Fan*
Project Role: *PI*
Researcher Identifier (e.g., ORCID ID): *0000-0002-4813-5444*
Nearest person month worked: *1*
Contribution to Project: *Dr. Fan led the project.*

Name: *Christian Hoerner*
Project Role: *Research Scientist*
Researcher Identifier (e.g., ORCID ID): *0000-0002-8685-1126*
Nearest person month worked: *5*

Contribution to Project:	*Dr. Hoerner compiled the patient samples for analysis and the corresponding clinical data, interfaced with and oversaw activities of all other parties involved in the project, and led the efforts to address the challenges and problems.*
Name:	*Eran Kotler*
Project Role:	*Postdoctoral Researcher*
Researcher Identifier (e.g., ORCID ID):	*0000-0002-1463-7462*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Kotler led the computational analysis.*

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

Dr. Alice Fan:

Previously Active Grants That Now Have Closed

NIH U54 (PI: Gambhir; Core Director: Fan) 09/01/15-07/31/21 1.2 calendar
NIH
"Center for Nanotechnology Excellence for Translational Diagnostics (CCNE-TD)"

Overall Aim 1. Monitoring cancer therapy response (lung cancer).
Overall Aim 2. Merging of nano-based in vitro and in vivo nano-based imaging for earlier detection of aggressive cancer (prostate cancer).
NCI Office of Cancer Nanotechnology Research (OCNR)
National Cancer Institute Center for Strategic Scientific Initiatives Building 31
Room 10A52 31 Center Drive, MSC 2580
Bethesda, MD 20892-2580
Telephone:
Attn: Christopher Hartshorn

Clinical Trial (PI: Fan) 05/01/17-04/30/21 0.35 calendar
Calithera Inc. "A
Phase 1/2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Glutaminase Inhibitor CB-839 in Combination with Nivolumab in Patients with Clear Cell Renal Cell Carcinoma and Other Solid Tumors"

Aim 1: Primary endpoint is to evaluate response rate of RCC to nivolumab in combination with CB-839.
Aim 2: Secondary endpoints are to evaluate PFS and OS.

Clintrax Global, Inc.
4600 Marriot Drive, Suite 200
Raleigh, NC 27612
Direct:
Kristen L Masters, Contracts Analyst

Clinical Trial (PI: Fan) 09/27/17-09/30/21 0.2 calendar
Calithera Inc.
"A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing CB-839 in Combination with Everolimus (CBE) vs. Placebo with Everolimus (PboE) in Patients with Advanced or Metastatic Renal Cell Carcinoma (RCC)"

Aim 1: The primary endpoint is to evaluate progression free survival of patients with RCC treated with CB839+ everolimus vs. everolimus alone.
Aim 2: The secondary endpoint is OS.

Clintrax Global
5000 Centregreen Way, Suite 150
Cary, NC 27513
o
Andrew J. Rogers, J.D. Contracts Analyst

Clinical Trial (PI: Fan) 10/16/18-10/31/21 0.2 calendar
Calithera Inc.
"A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing CB-839 in Combination with Cabozantinib vs. Placebo with Cabozantinib in Patients with Advanced or Metastatic Renal Cell Carcinoma (RCC)"

Aim 1: The primary endpoint is to evaluate progression free survival of patients with RCC treated with CB839+cabozantinib vs. cabozantinib alone.
Aim 2: The secondary endpoint is OS.

Clintrax Global
5000 Centregreen Way, Suite 150
Cary, NC 27513
o/
Learla Stefanics, Contracts Analyst

Previously Pending Grants That Are Now Active or New Active Support

International Alliance for Cancer Early Detection ACED Pilot Award (PIs: Woodward/Fan/Maher)

03/24/21-09/30/22
0.6 calendar

"Early Detection of Hereditary Renal Cell Cancer"

Aim: To determine whether the platelet transcriptome carries a signature of early-stage hereditary RCC.
Note: This funding is internal to Stanford (each institution's portion of this award comes from internal funds).

International Aliance for Cancer Early Detection (ACED)
Cancer Research UK
2 Redman Place
London, E20 1JQ
United Kingdom
Nicole Lyons, Programme Manager
Telephone:

ACED Skills Exchange and Development Travel Award (recipient: Hoerner in Fan Laboratory)

"Skills Exchange for Platelet Isolation and Analysis" 09/01/21-09/30/22
(UK) + (Stanford)

Aim: This grant provides funds for Dr. Christian Hoerner to travel from Stanford to Manchester University (hosted by Dr. Woodward) and University of Cambridge (hosted by Dr. Maher), for a 1 month period, prior to initiation of our "ELECTRIC" grant. The purpose of Dr. Hoerner's trip is to provide hands-on training to the UK teams, so they can learn Fan Laboratory's meticulously optimized human platelet isolation protocol for RNA sequencing. The grant also provides funds for reagents and analysis of the quality of the platelet samples. I am Dr. Hoerner's supervisor for this project.

Note: This funding is internal to Stanford (each institution's portion of this award comes from internal funds).

International Aliance for Cancer Early Detection (ACED)
Cancer Research UK
2 Redman Place
London, E20 1JQ
United Kingdom
Nicole Lyons, Programme Manager
Telephone:

NIH 1R03CA252776 (PIs: Fan/Dahl) 08/14/20-07/31/23 0.24 calendar

"Early therapeutic monitoring of response to therapy with serial ultrasound in metastatic RCC"

Aim 1: Determine if changes in ultrasound parameters can be detected early during treatment in metastatic RCC patients treated with angiogenesis inhibitor plus immune checkpoint inhibitor
Aim 2: Determine if changes in quantitative imaging individually or together correlate with objective response to angiogenesis inhibitor plus immune checkpoint inhibitor

Administration: Program Official(PO)
Name: Liu, Christina
Phone:
Email: christina.liu@nih.gov

NIH 1R21CA259756 (PIs: Fan/Kamaya/Dahl) 03/09/22-02/29/24 0.72 calendar

"Serial Ultrasound to Detect Early Response to Immunotherapy in Metastatic RCC"

Aim 1: Determine if changes in ultrasound parameters can be detected early during treatment in metastatic RCC patients treated with combined immune checkpoint inhibitors
Aim 2: Determine if changes in quantitative imaging individually or together correlate with objective response to combined immune checkpoint inhibitors

National Cancer Institute (NCI)
Administration**:** Program Official(PO)
Name**:** Hatch, Christopher L.
Phone**:** 240-276-6454

Filtricine, Inc. (PI: Stafford; co-PI: Fan)

10/06/20 – 12/31/22
effort as needed

"A Phase I Study of the Tolerability/Palatability of Tality^{TM} Synthetic Meal Replacement in Patients with Prostate Cancer"

Aim: Determine if patients with prostate cancer can complete 4 weeks of this dietary replacement product.

Clinical Trial (PI: Hsieh; site-PI: Fan)
"A single arm, multicenter, phase 2 trial to evaluate the efficacy of lenvatinib (LEN) in combination with pembrolizumab (KEYtruda) in subjects with locally advanced or metastatic Non-clear cell renal cell carcinoma (The LENKYN Trial)"

The goal of this investigator-initiated study is to determine progression free survival and response rates of patients with non-clear cell RCC to combination lenvatinib plus pembrolizumab.

Project Number:	MISP#59111
Project Start and End Date:	02/05/21 - 02/28/23
Total Award Amount:	0.12 calendar

NIH R01CA257843 (PI: Wang; co-I: Fan)
"Rapid and affordable magneto-nanosensors for ctDNA-guided lung cancer management"

The goal of this proposal is to use a nanoscale magnetic detector to capture circulating tumor DNA from blood of lung cancer patients and measure changes with treatment.

Project Number:	R01CA257843
Project Start and End Date:	08/02/21 - 07/31/25
Total Award Amount:	0.36 calendar

NIH R21CA256271 (PI: Brooks; co-I: Fan)
"Identification of serum protein biomarkers by profiling N-glycoproteomes of patient-derived xenografts of clear cell renal cell carcinoma"

Major Goal: Our goal is to identify human-specific N-glycosylated proteins in a mouse background with high sensitivity using our clear cell renal cell carcinoma (ccRCC) PDX models and validate potential biomarkers associated with tumor volume in ccRCC patient sera. Dr. Fan's effort begins in Year 2 of the grant.

Project Start and End Date:	04/21/21 - 03/31/23
Total Award Amount:	0.36 calendar

University of Texas MD Anderson LCED Program (PI: Fan)
"Biospecimen banking and Biomarker Validation for Lung Cancer Early Detection in Cohort Receiving low dose helical computed tomography screening"

The goal of this study is to develop novel molecular biomarkers for lung cancer early detection, in a cohort of patients who receive annual low dose CT screening for lung cancer.

Project Start and End Date:	02/28/16 - 02/27/26
Total Award Amount:	0.12 calendar

Stanford Cancer Institute Clinical Innovation Fund (PI: Fan)
"A Pilot Study to Provide Intensive Psychological and Cardiopulmonary Services for Black Patients with Advanced Prostate Cancer".

This is an internal grant that funds an investigator-initiated study.

Major Goals: Provide counseling and cardiac training for Black men with prostate cancer who are receiving androgen deprivation therapy.

Project Start and End Date:	02/01/21 - 01/31/24
Total Award Amount:	effort as needed

ACED Research Project Award (PIs: Tischkowitz/Kurian/Evans; co-I: Fan)
"Stratifying Risk for Early Detection in Hereditary Breast and Ovarian Cancer"

Aim: Women undergoing predictive testing for BRCA1, BRCA2, PALB2, ATM or CHEK2 in US and UK genetics centres will be randomized to receive either the conventional risk estimate or the personalized risk estimate based on genetic/lifestyle/hormonal modifiers. We will assess feasibility in a clinical setting.

Note: This funding is internal to Stanford (each institution's portion of this award comes from internal funds).

Project/Proposal Start and End Date:	04/01/21 - 03/31/24
Total Award Amount:	effort as needed

Dr. Christina Curtis:

Previously Active Grants That Now Have Closed

None

Previously Pending Grants That Are Now Active or New Active Support

NIH, U54 CA261719 (role: PI) 09/14/21 - 08/31/26
2.40 calendar

Evolutionary dynamics and microenvironmental determinants of metastatic breast cancer

Project Goals: The major goal is to understand how and when breast tumors metastasize and strategies to interfere with this process.

Specific Aims:
Aim 1: Establish a collaborative, multidisciplinary systems biology platform to characterize the evolutionary dynamics and microenvironmental determinants of metastatic breast cancer within the Stanford Breast Metastasis Center.
Aim 2: Characterize the evolutionary dynamics and microenvironmental determinants of metastatic breast cancer through three complementary research projects supported by biospecimen/pathology and organoid cores.

Address: National Cancer Institute, Office of Grants Administration, 9609 Medical Center Drive, West Tower, 2nd floor. Rockville MD 20850
Contracts/Grants Officer: Amy R Bartosch, amy.bartosch@nih.gov

Susan G. Komen, SAC210103 12/02/2021 – 12/01/2023
0.12 calendar

Molecular determinants of breast cancer progression and resistance

Project Goals: The overarching objectives of this proposal are directed at understanding: (1) how the oncogenic drivers of the high-risk ER+ ICs modulate the TME and how the TME changes through metastasis and in response to therapy (2) differential response of the high-risk ER+ ICs to targeted and endocrine therapies in patient samples and representative *in vitro* models.

Specific Aims:
Aim 1: Characterizes the TME in longitudinal BC cohorts and evaluate the association between IC, response to therapy and relapse.
Aim 2: Evaluates response to clinical therapies across the ICs drawing on our powerful computational frameworks and extensive patient cohorts. Aim 3: Establishes a biobank of high- risk ER+ patient-derived breast cancer organoids that capture the heterogeneity of disease to enable investigation of mechanisms of resistance to targeted and endocrine therapies and evaluation of novel therapeutic approaches.

Address: Susan G. Komen, 13770 Noel Road, Suite 801889, Dallas, Texas 75380
Contracts/Grants Officer: Kelsey Hampton, khampton@komen.org

Chan Zuckerberg Biohub Investigator Award 03/01/22 – 02/28/27
effort as needed

Project Goals: The Chan Zuckerberg Biohub was established with the goals of understanding the mechanisms underlying disease and developing new technologies that will enable fresh avenues of scientific discovery and lead to actionable diagnostics and effective therapies. Biohub's Investigator Program provides unrestricted funds to faculty members to pursue their most exciting, risky, and innovative ideas. The award will be used at the discretion of Dr. Curtis. It is anticipated that these funds will support research on mechanisms and biomarkers of tumor progression.

Specific Aims: N/A

Supporting Agency: Chan Zuckerberg Biohub
Address: Chan Zuckerberg Biohub, 499 Illinois St., 4th Floor, San Francisco, CA 94158
Contracts/Grants Officer: Bill Burkholder, bill.burkholder@czbiohub.org

Dr. John Leppert:

Previously Active Grants That Now Have Closed

NIH 1R01CA211141 (PI: Chung; co-I: Leppert)

08/01/2017 - 07/31/2022
0.72 calendar

Active surveillance and patient reported outcomes in a diverse population of prostate cancer patients

The goal of this project is to oversee a survey of clinicians in the greater San Francisco Bay Area on their attitudes, perceptions, and practices regarding discussions with patients about and implementation of active surveillance in the treatment of low-risk prostate cancer.

Program Officer:
Prabhu Das, Irene
National Cancer Institute
Division of Cancer Control & Population Sciences
6130 Executive Blvd., EPN 5124
Bethesda, MD
USA 20892
Email**:** prabhudasi@mail.nih.gov

Previously Pending Grants That Are Now Active or New Active Support

American Cancer Society (role: co-I)

01/01/2021 - 12/31/2024
0.60 calendar

'FTO in Kidney Cancer: Molecular Mechanisms and Targeted Therapy'

Project Goals: Our goal is to identify and develop novel therapeutic agents for the treatment of kidney cancer.

Specific Aims: The goals of this grant are to determine the mechanisms by which FTO promotes the growth and survival of renal cell carcinoma cells (Aim 1); determine the biological function of FTO in the pathogenesis of renal cell carcinoma using an autochthonous mouse model (Aim 2); and compare the efficacy and safety of FTO inhibitors alone and in combination with antiangiogenic agents on renal cell carcinoma tumor growth (Aim 3).

Address:
250 Williams Street, NW, 6th Floor
Atlanta, CA 30303
Contracting/Grants Officer: Lynne Elmore

VA HSR&D IHX (role: multi-PI) 10/01/2020 - 09/30/2024
3.0 calendar

'Defining Optimal Care for Urinary Stone Disease in the Veterans Health Administration'

Project Goals: To identify secondary prevention strategies for urinary stone disease that are effective for Veterans receiving care in the VHA.

Specific Aims: Aim 1: Determine which prevention measures are associated with lower USD recurrence in Veterans receiving care in the VHA. Aim 2: Evaluate how VHA providers are currently implementing prevention measures for USD. Aim 3: Identify current barriers to implementing effective prevention measures for USD in the VHA.

Supporting Agency: 003091A
Address:
VA Merit Award Program
VA Biomedical Laboratory Research and Development Central Office
1100 1st Street NE, Suite 6
Washington, DC, 20002
Contracting/Grants Officer:
vhacoscirev@va.gov

VA Merit Award Program (role: co-I) 10/01/2020 - 09/30/2024
0.6 calendar

'Personalized assessment of bladder cancer treatment response using urinary molecular biomarkers'

Project Goals: The goal of this project to validate a panel of urinary mRNA biomarkers for bladder cancer screening, surveillance, and treatment response assessment.

Specific Aims: Aim 1: To validate the integrated u-mRNA panel for bladder cancer surveillance and risk stratification. Aim 2: To validate the integrated u-mRNA panel to improve bladder cancer screening and risk stratification in patients referred for hematuria. Aim 3: To validate the integrated u-mRNA panel for response assessment and monitoring in patients with high-risk non-muscle invasive bladder cancer undergoing BCG immunotherapy treatment.

Supporting Agency: VA BSR&D 1BX 004962
Address:
VA Merit Award Program
VA Biomedical Laboratory Research and Development Central Office
1100 1st Street NE, Suite 6
Washington, DC, 20002
Contracting/Grants Officer:
vhacoscirev@va.gov

What other organizations were involved as partners?

Organization Name: Serimmune, Inc.
Location of Organization: Goleta, CA
Partner's contribution to the project: Collaboration (data analysis)

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Appendix A: Conference Abstract from The Early Detection of Cancer Conference 2021 Appendix B: Conference Abstract from the ASCO Genitourinary Cancers Symposium 2022

Utilizing the Autoantibody Immune Response to Tumor Antigens for Kidney Cancer Early Detection

Christian R. Hoerner*, Michael Jhatro^, Rebecca Waitz^, Kathy Kamath^, Minlu Zhang^, Abilash Dahl^, John Shon^, Alice C. Fan*

*Stanford University School of Medicine
^ Serimmune, Inc

Background: Kidney cancer (renal cell carcinoma, RCC), the 8th most common U.S. cancer, is in need for better cure rates through early detection (5-year survival for stage I RCC: ~95%; for stage IV RCC ~19%). Autoantibodies are common in cancer and result from the altered expression, localization, or post-translational modification of endogenous proteins in tumor cells (autoantigens) and from the expression of mutated genes that give rise to new proteins (neoantigens). In contrast to cellular immune responses in cancer, autoantibodies are less well characterized, yet hold promise to enable cancer early detection by immune amplification of the 'cancer signal' while retaining specificity to cancer types including RCC. Autoantibodies may therefore be useful for kidney cancer early detection and diagnosis.
Objective: Our goal was to profile the autoantibody repertoire in blood from patients with clear cell RCC (ccRCC), the most common form of RCC, in order to: 1) determine if autoantibodies can be detected in patients with early stage and late stage ccRCC; 2) identify common epitopes amongst ccRCC patients that could suggest common RCC antigens; and 3) determine specificity and sensitivity of potential autoantibody biomarkers for ccRCC vs. other non-cancer conditions.
Methods: We use the SERA platform (https://serimmune.com/publications/) to compare putative autoantibody signal in blood from 177 patients with ccRCC, 23 with benign kidney lesions, and ~800 healthy controls. SERA utilizes a random bacterial display 12mer peptide library of 10^{10} diversity in conjunction with next generation sequencing to ascertain epitope enrichment across the entire human proteome.
Results: We find significant differences in epitope repertoires in ccRCC compared to the healthy human cohort. Patients with ccRCC exhibit a rich repertoire of rare, enriched epitopes which may comprise putative autoantibody signal. This epitope signal is present with high abundance in all ccRCC stages, including stage I ccRCC. In contrast, healthy controls/patients with benign kidney lesions demonstrate more restricted repertoires. However, we do not find evidence of common ccRCC antigens: epitopes are not conserved across ccRCC patients. Our initial results suggest that each patient may develop an individualized tumor-associated antibody response. Whether measuring epitope diversity in a patient's blood could be useful, without needing to identify specific epitopes, warrants further study.

Utilizing the Autoantibody Immune Response to Tumor Antigens for Kidney Cancer Early Detection

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