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TITLE: Integrated Analysis of Somatic Genomic Mutations and Antigen Presentation as Predictive Biomarkers for Combination Immunotherapy in Kidney Cancer

PRINCIPAL INVESTIGATOR: Chung-Han Lee

CONTRACTING ORGANIZATION: Sloan Kettering Institute for Cancer Research, New York, NY

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
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5e. TASK NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER

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

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The proposal seeks to integrate various genomic biomarkers to better predict response to immune checkpoint inhibitor therapy in patients with renal cell carcinoma. Our proposal seeks to establish HLA diversity as a key predictive marker for response to immunotherapy, and also combine this predictive marker with other genomic factors to better refine its predictive capability.

In the annual report period, we have completed major task 1 as referenced in specific aim 1 and are actively continuing to work on completing other major tasks in specific aim 1 and 2. We also published our preliminary findings on HLA diversity in molecular cancer research, demonstrating the critical role of HLA diversity.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

With the rapid development and regulatory approval of multiple novel immunotherapy regimens, the treatment landscape for RCC has rapidly evolved from initial treatment with single-agent tyrosine kinase inhibitors (TKI) to combination therapies with immuno-oncology agents (IO), namely immune checkpoint inhibitors (ICI) such as anti-CTLA-4 and PD-1/PD-L1 inhibitors. The fundamental role of the immune system is to distinguish between self and non-self, whereas cancer can be seen as an insidious form of non-self with origins within self. The tumor antigen burden depends on multiple factors including tumor mutation burden (TMB), expression of mutations, and peptide presentation by major histocompatibility complex (MHC) molecules. Our proposal seeks to better characterize and integrate the various components that comprise of the tumor antigen burden to establish a new predictive biomarker for RCC.

2. KEYWORDS:

Kidney cancer (RCC), tyrosine kinase inhibitors (TKIs), immune-oncology (IO), immune checkpoint inhibitors (ICI), tumor mutation burden (TMB), biomarker

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1:

- Major Task 1: Prospective whole exome sequencing of patients who have been treated at MSK on immunotherapy either as monotherapy or in combination
- Major Task 2: Using publicly available sequencing and expression data from TCGA and University of Tokyo, correlate somatic mutations with expression of mutation-containing genes
- Major Task 3: Determine whether the expressed mutome correlates to response to immunotherapy

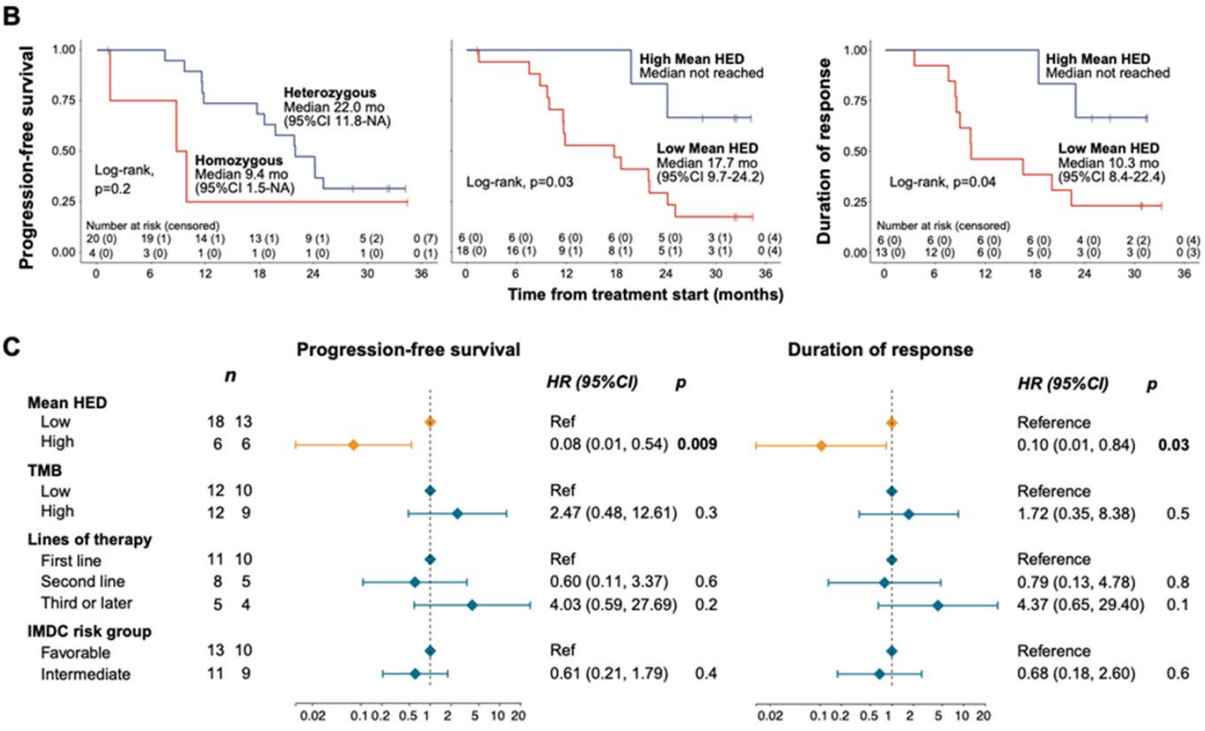
Specific Aim 2:

- Major Task 1: Determine the distribution of HLA diversity in independent RCC cohorts
- Major Task 2: Determine the association between HLA diversity and response to immunotherapy
- Major Task 3: Determine whether DDR mutations represent a distinct subgroup of RCC that is sensitive to ICI
- Major Task 4: Perform a combined analysis of 1)TMB and somatic mutations with 2) HLA diversity

What was accomplished under these goals?

During the reporting period, specific aim 1 major task 1 was completed, which included obtaining regulatory approval from USAMRMC and IRB approval from MSKCC and Cleveland Clinic for the proposed research, training of research staff for tissue processing and sequencing, identification of samples for prospective whole exome sequencing. Currently, sequencing is ongoing, and we are awaiting the results from analysis. We have currently completed 100 of the proposed 200 samples to be sequenced.

We have also published preliminary findings of a limited subset of patients on the role of HLA diversity as a biomarker for combination therapy of lenvatinib/pembrolizumab in Molecular Cancer Research. We demonstrated that even in regimens that have high levels of efficacy, patient outcomes can be stratified be on levels of HLA diversity. In patients with high levels of HLA diversity, patients had prolonged responses; whereas low diversity is associated with shorter responses. These findings were also independently validated in a separate dataset.



For specific aim 2, major task 2, which was also scheduled during the reporting period, we decided to delay the start time of initiation of analysis due to pandemic related staffing issues, and a realization that the clinical annotation of patient outcomes necessary for completion of subsequent major tasks was not included as a major task and we prioritized those efforts to

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

Nothing to report.

How were the results disseminated to communities of interest?

The initial findings were published in Molecular Cancer Research, and presented at the 2021 Kidney Cancer Research Symposium in Philadelphia, PA on October 2021, which includes a diverse set of participants including clinical, translational, basic science investigators, industry partners, and patient advocates.

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

We plan to proceed with the stated major tasks as specified in the statement of work.

4. IMPACT:

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

Our preliminary work has demonstrated in a limited dataset that HLA diversity is a key component for understanding the response to immunotherapy, where high diversity is associated with improved response to treatment. This insight has translated into further proposed research into HLA diversity and is the basis of further research proposals of novel research. The presentation of the data also generated significant enthusiasm in the RCC community and discussion on how this can be extended and applied to patient care.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

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

There was a brief staffing and resource challenge during COVID, but that has now been resolved.

Changes that had a significant impact on expenditures

Nothing to report

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

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

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.

Presentation at 2021 Kidney Cancer Research Symposium, Philadelphia, PA, October 2021

- **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?

What individuals have worked on the project?

Name:	*Chung-Han Lee*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	0000-0001-5511-0635
Nearest person month worked:	*4*
Contribution to Project:	Oversees the project as a whole
Funding Support:	DOD/CDMRP

Name:	*Robert Motzer*
Project Role:	*Career Guide*
Researcher Identifier (e.g. ORCID ID):	0000-0001-6925-2327
Nearest person month worked:	*1*
Contribution to Project:	Career guide and mentor for the PI
Funding Support:	DOD/CDMRP, NIH/NCI

Name:	Samuel Murray
Project Role:	Clinical Research Associate
Researcher Identifier (e.g. ORCID ID):	0000-0003-0074-6462
Nearest person month worked:	6
Contribution to Project:	Coordinates samples and manages clinical outcomes database
Funding Support:	DOD/CDMRP

Name:	*David Kuo*
Project Role:	Post-Doctoral Associate
Researcher Identifier (e.g. ORCID ID):	0000-0003-1797-2896
Nearest person month worked:	2
Contribution to Project:	Analysis of genomic data
Funding Support:	DOD/CDMRP

Name:	*Timothy Chan*
Project Role:	*Subaward PI*
Researcher Identifier (e.g. ORCID ID):	0000-0002-9265-0283
Nearest person month worked:	0.21 CM
Contribution to Project:	Dr. Chan oversees the sequencing and analysis of RCC tumor samples.
Funding Support:	NIH/NCI, DOD/CDMRP, Michael J. Fox Foundation

Name:	*Vlad Makarov*
Project Role:	*Bioinformatician*
Researcher Identifier (e.g. ORCID ID):	0000-0001-8026-824X
Nearest person month worked:	0.96 CM
Contribution to Project:	Dr. Makarov conducts the bioinformatics analysis.
Funding Support:	NIH/NCI, DOD/CDMRP, Michael J. Fox Foundation

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

Active changes since award started on 9/30/2020:

Chung-Han Lee
(NEW)
W81XWH2110942 (PI: Kotecha) 9/30/2021 - 9/29/2025 0.60 calendar
Congressionally Directed Medical Research Programs
Evaluating HLA Class II Evolutionary Divergence as an Immunotherapy Specific Kidney Cancer Biomarker
Role: Co Investigator

Active changes since award started on 9/30/2020 (cont'd):

Robert Motzer
(NEW)
W81XWH2110942 (PI: Kotecha) 9/30/2021 - 9/29/2025 1.20 calendar
Congressionally Directed Medical Research Programs
Evaluating HLA Class II Evolutionary Divergence as an Immunotherapy Specific Kidney Cancer Biomarker
Role: Mentor

(NEW)
W81XWH2110731 (PI: Motzer) 9/30/2021 - 9/29/2023 1.80 calendar
Congressionally Directed Medical Research Programs
Implementation of Kidney Cancer Specific Training for Clinical Research Nurses
Role: PD/PI

Timothy Chan
(NEW)
ASAP-000312 10/1/2020 – 9/30/2023 1.20 calendar
From Cancer Associations to Altered Immunity in the Pathogenesis of Parkinson's Disease
Role: Co-Investigator

(NEW)
U01CA260513 9/30/2020-8/31/2022 1.20 calendar
Pre-Exposure Immunologic Health and Linkages to SARS-COV2 Serologic Responses, Endothelial Cell Resilience, and Cardiovascular Complications: Defining the Mechanistic Basis of High Risk Endotypes
Role: Co-Investigator

Vlad Makarov
(NEW)
ASAP-000312 10/1/2020 – 9/30/2023 1.20 calendar
From Cancer Associations to Altered Immunity in the Pathogenesis of Parkinson's Disease
Role: Co-Investigator

What other organizations were involved as partners?

Due to Dr. Timothy Chan's new affiliation with Cleveland Clinic Foundation (CCF), located in Cleveland, Ohio a subaward agreement has been established between MSK and CCF.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: This is an non-collaborative award – only one single PI.

QUAD CHARTS: Not applicable.

9. APPENDICES:

N/A