

AWARD NUMBER: W81XWH-22-1-0672

TITLE: Deciphering Altered Metabolism and Immune Evasion in
FAT1-Mutated Head and Neck Cancer

PRINCIPAL INVESTIGATOR: Luc Morris

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

REPORT DATE: October 2023

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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REPORT DOCUMENTATION PAGEForm Approved
OMB No. 0704-0188

1. REPORT DATE October 2023		2. REPORT TYPE Annual		3. DATES COVERED 30Sep2022-29Sep2023	
4. TITLE AND SUBTITLE Deciphering Altered Metabolism and Immune Evasion in FAT1-Mutated Head and Neck Cancer				5a. CONTRACT NUMBER W81XWH-22-1-0672	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Luc Morris E-Mail: morrisl@mskcc.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Sloan Kettering Institute for Cancer Research 1275 YORK AVE NEW YORK NY 10065-6007				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT During year 1 of this award, we have accomplished the major tasks for this period as outlined in the approved Statement of Work; specifically, finalizing all required regulatory approvals, achieving ACURO approval, generating additional tumors and cell line models, optimizing protocols for reproducible cell line preparations and metabolic assays, and beginning the work on comprehensive metabolomic profiling and immunophenotyping of the tumors generated by these novel mouse models of head and neck cancer.					
15. SUBJECT TERMS head and neck cancer, squamous cell carcinoma, tumor suppressor gene, tumor metabolism					
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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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	7
5. Changes/Problems	7
6. Products	8
7. Participants & Other Collaborating Organizations	8
8. Special Reporting Requirements	9
9. Appendix	10

1. **INTRODUCTION:**

With this PRCRP Idea Award, we proposed to carry out the mechanistic investigation of a poorly understood genomic finding: the frequent (~30%) inactivation of the gene *FAT1* in head and neck squamous cell carcinoma (HNSCC) as well as other cancer types. Since the initial description by our lab of *FAT1* as a tumor suppressor gene in several cancer types, the mechanism by which loss of this gene promotes cancer development has remained largely elusive. With our recent development of a novel genetically engineered mouse model that includes knockout of this gene, we are now leveraging this unique tool to dissect the biology of *FAT1* inactivation in HNSCC. To achieve our overall goal of improving precision therapies for HNSCC, we must develop a means to target the sizeable subgroup of these tumors harboring mutation or homozygous deletion of this gene. Unexpectedly, our initial analyses of this new mouse model of HNSCC have revealed a link between *FAT1* and metabolic and immunologic alterations, which we this project investigates through 2 specific aims over a 3-year timeline:

Aim 1. Define the metabolic processes altered in *FAT1*-mutated HNSCC tumors

Aim 2. Dissect the immunosuppressive mechanisms of *FAT1* mutation in the tumor microenvironment

2. **KEYWORDS:** head and neck cancer, squamous cell carcinoma, tumor suppressor gene, tumor metabolism

3. **ACCOMPLISHMENTS:**

o **What were the major goals of the project?**

- Below are listed the major goals (specific aims), and associated major tasks of this project, as outlined in the approved SOW.

Specific Aim 1: Define the metabolic processes altered in *FAT1*- mutated HNSCC tumors

Initial milestone: Achieve approved amendments to regulatory protocols. Milestone date was by 3 months (Dec 30, 2022). This was completed with ACURO approval of our IACUC protocol on October 21, 2022.

Major Task 1: Assemble library of KPP/KFPP mouse tumors and cell lines and optimize conditions for Seahorse experiments.

Associated milestone: Optimize tumor and cell line conditions for Seahorse assays. Milestone date was by month 12 (September 30, 2023). This was completed by June 1, 2023.

Major Task 2: Profile mitochondrial activity and extracellular flux of KPP and KFPP cells.

Associated milestone: Characterize mitochondrial function and cellular flux. Milestone date was by month 22 (July 30, 2024). This task is 75% complete and will be complete by the milestone date.

Major Task 3: Examine *FAT1* protein interaction with mitochondrial membrane proteins

Associated milestone: This task is planned for years 2-3 in the

SOW.

Specific Aim 2: Dissect the immunosuppressive mechanisms of *FAT1* mutation in the tumor microenvironment

Major Tasks 4 and 5: Perform immunophenotyping of the immune microenvironment of KPP and KFPP tumors at baseline and after checkpoint inhibitor immunotherapy

Associated milestone: Describe immune microenvironmental changes associated with *FAT1* knockout, at baseline and after anti-PD-1 therapy. The milestone date for this task is month 32 (May 30, 2025). This task is 20% complete.

Major Task 6: Determine whether *FAT1* knockout is associated with immunosuppressive changes to the microenvironment

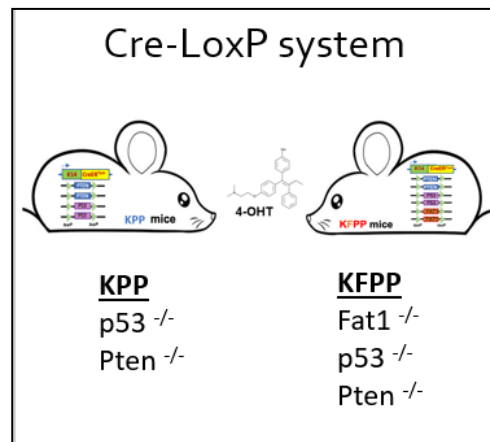
Associated milestone: Define the immune microenvironmental consequences of the metabolic phenotype associated with *FAT1* knockout. The milestone date for this task is month 36 (September 30, 2025). This task is 10% complete.

○ **What was accomplished under these goals?**

- In this first annual reporting period, we have made significant progress toward all major tasks specified for this project.

Initial important tasks were to complete all IACUC, IRB, institutional biosafety protocols necessary for this project, and to complete requirements for ACURO approval. These were all completed in the first month of this award.

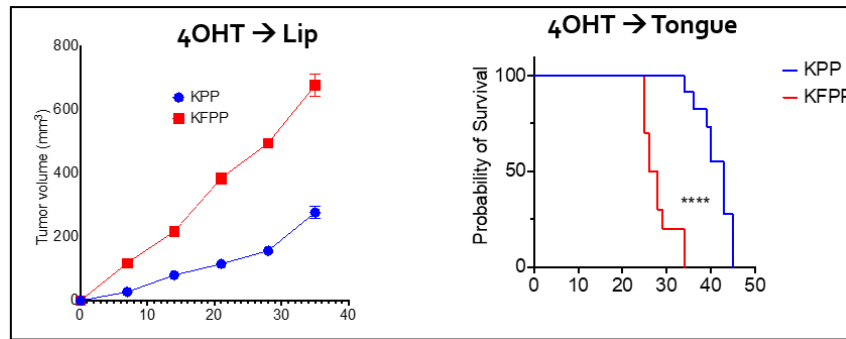
In the first year, we have made several additional important refinements to our spontaneous autochthonous mouse model of HNSCC. We are now able to reliably and efficiently generate tumors in the oral cavities of mice using a topically-induced Cre-LoxP system under the control of a Keratin-14 promoter. There are 2 models in use:



KPP (Keratin 14 promoter driving expression of Cre recombinase after tamoxifen activation, to delete Pten and p53)

KFPP (Keratin 14 promoter driving expression of Cre recombinase after tamoxifen activation, to delete Fat1, Pten and p53)

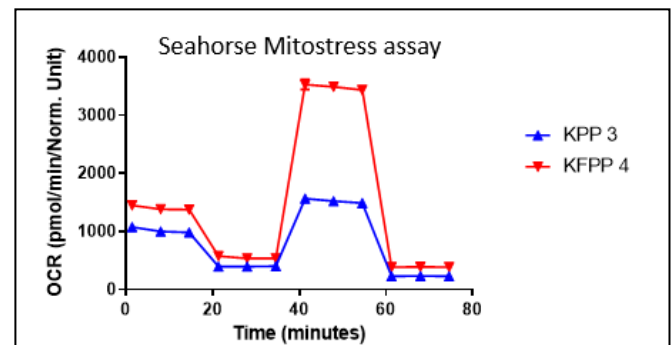
After application of 4-OHT to the oral cavities of these mice, we are able to reliably and efficiently generate oral tongue and lip tumors, with data below demonstrating tumor growth and animal survival in days after 4-OHT application:



As proposed we have been able to generate and freeze down tumors from early, middle and late timepoints for further experiments. We also had proposed to generate cell lines from both the KFPP and KPP models in the first year. We have now successfully performed this and have cell lines that can be passaged, and successfully engrafted and propagated in both NSG (immunodeficient) and BL6 (immunocompetent) mice in the orthotopic location (here, oral cavity) and used for further experimentation. We have achieved the major task goal for year 1 of having reliable models, and new cell lines suitable for experimentation both in vitro and in vivo.

Here is representative data from 3 replicate experiments using the Seahorse MitoStress extracellular flux assay, obtained from KPP and KFPP cell lines, demonstrating increased

mitochondrial respiration as measured by oxygen consumption rate in the KFPP compared to KPP cells. The goal for year 1 of this award as stated in the SOW was to develop the needed cell lines and optimize cell line protocols to obtain reliable and reproducible data



from the Seahorse assay, and we have completed this task. We are now preparing to move forward with more focused mitochondrial complex assays that will allow for more precise delineation of the effects of FAT1 on mitochondrial function and cellular flux.

Overall, in year 1 of this award, we have completed all tasks as outlined on the SOW. We have expanded and optimized our model system of HNSCC, which is the most efficient and genetically faithful mouse model of HNSCC in the field, to our knowledge. We have now optimized protocols for experimental assays of tumors and cell lines derived from this model to answer the questions posed in Specific Aim #1: to define the metabolic processes altered in FAT1-mutated HNSCC tumors.

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

- Nothing to report.
- How were the results disseminated to communities of interest?

- Nothing to report. As work continues and results are more mature, we will be able to disseminate our findings to scientific and other communities.
 - **What do you plan to do during the next reporting period to accomplish the goals?**
 - We are continuing on with the major tasks 3-6 under Specific Aims #1 and #2, as detailed above in Section 3. Building on progress in year 1, we have the necessary models and reagents to carry out these tasks. The focus in year 2 will be more detailed experiments investigating mitochondrial function (major task 2) and initial work on immunophenotyping of the tumors that we can now generate efficiently and reproducibly (major task 5).
4. **IMPACT:** *Describe 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?**
 - Nothing to report in year 1.
 - **What was the impact on other disciplines?**
 - Nothing to report in year 1.
 - **What was the impact on technology transfer?**
 - Nothing to report in year 1.
 - **What was the impact on society beyond science and technology?**
 - Nothing to report in year 1.
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**
 - Nothing to report.
 - **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**
 - Nothing to report.
 - **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.**
 - Nothing to report.
 - **Website(s) or other Internet site(s)**
 - Nothing to report.
-
- **Technologies or techniques**

The research activities in year 1 have further optimized our novel mouse model of HNSCC, which we anticipate will be widely used in the field, once fully characterized.
- **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:	Luc Morris
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	ORCID 0000-0002-4417-2280
Nearest person month worked:	1.2
Contribution to Project:	Luc Morris as PI has overseen the project, supervised all experiments and data analyses
Funding Support:	nil

Name:	Xinzhu Deng
Project Role:	Senior research scientist
Researcher Identifier (e.g. ORCID ID):	0000-0003-1914-7240
Nearest person month worked:	0.6
Contribution to Project:	Xinzhu Deng performs the outlined experiments and analyses in collaboration with PI Morris and other co-investigators and consultants not listed in this section who have <1 CYM effort.
Funding Support:	nil

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
 - Yes. Updated Active Other Support for the PI and all other key personnel are included in the Appendix.
- **What other organizations were involved as partners?**
 - Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

- Nothing to report.

9. **APPENDIX:** Updated PCPS (other support) for the PI and key personnel are appended below.

MORRIS, LUC

PREVIOUS (completed since award was received)

Title: Identifying and targeting neoantigens in aggressive salivary carcinomas

Grant number: 3R01DE027738-04S1

Time commitment: 0.12 calendar

Role: PD/PI

Supporting agency: National Institute of Dental and Craniofacial Research

Contracting/Grants Officer: Susan Medve

Performance period: 4/1/2021 - 6/30/2022

Level of funding:

Brief description of the project's goals: This is an application in support of Mr. James Cevallos for an NIDCR research supplement to promote diversity in health-related research.

Specific aims: We propose to use FusionCatcher4 to identify putative fusions from a cohort of ACC tumors that have undergone RNA sequencing, NetMHCpan 4.1 to identify neoantigens from fusions based on their likelihood to bind to MHC-Class I for the HLA-A2.1 allele, and ELISpot to screen for 12 of the most predicted immunogenic peptides. Our results will allow us to better understand the performance of MHC-Class I binding algorithms in the prediction of fusion-derived neoantigens in salivary gland ACC.

Overlap: None

Title: Altered metabolism in head and neck cancer

Grant number: Geoffrey Beene Cancer Research Center - Morris

Time commitment: 1.20 calendar

Role: PD/PI

Supporting agency: Geoffrey Beene Cancer Research Center

Contracting/Grants Officer: Julia E. Rudolph

Performance period: 9/1/2021 - 8/31/2023

Level of funding:

Brief description of the project's goals: In HNSCC translational research, the primary obstacle to progress is a lack of efficient, genetically faithful preclinical models. Our proposal seeks to address these 2 obstacles. We have developed a novel genetically engineered mouse model of HNSCC that reflects the genetics of human disease and recapitulates the progression of normal oral epithelium to dysplasia and invasive carcinoma. This is a one year pilot grant to characterize our novel genetically engineered mouse model of head and neck cancer, using inducible Cre-mediated knockout of Trp53, Fat1 and Pten, to determine the feasibility of this model future research linking these genes to targetable biologic pathways that are likely to have therapeutic relevance to approximately 30% of patients with head and neck cancer

Specific aims: N/A

Overlap: None

Current

Newly Added Current Support:

Title: Understanding mechanisms of immune escape in early stage tumors

Grant number: DBG 23 1036155 01 CDP

Time commitment:

1. 2025 0.60 calendar

PI: Morris, L

Supporting agency: American Cancer Society

Contracting/Grants Officer: Lynne Elmore, PhD

Performance period: 11/1/2023 10/31/2025

Level of funding:

Brief description of the project's goals: Our long term goal is to generate data to guide the development of prognostic biomarkers for early stage tumors. This would help patients with these tumors avoid unnecessary toxic treatments, reserving anti cancer therapies for patients with tumors likely to progress. As a first step toward this goal, we now propose to identify the biological mechanisms associated with indolent tumor behavior, and the transformation to clinically significant cancers. We hypothesize that indolent tumors are in a state of immune equilibrium, and that clinical progression reflects immune escape.

Specific aims: Aim 1. Validate mechanisms of immune escape in overdiagnosed tumors. Aim 2. Differentiate antigenic immunoediting in overdiagnosed vs. non-overdiagnosed cancer types. Aim 3. Compare immunogenomic features in progressing and non-progressing tumor samples from patients undergoing active surveillance.

Overlap: None

Title: Defining the Genetic Determinants of Head and Neck Cancer Progression and Immune Evasion through Computational and Functional Investigation

Grant number: CA220766_E01 HT9425 23 1 0556

Time commitment:

1. 2024 1.20 calendar

2. 2025 1.20 calendar

3. 2026 1.20 calendar

4. 2027 1.20 calendar

PI: Morris, L

Supporting agency: Congressionally Directed Medical Research Programs

Contracting/Grants Officer: Teresa Parker-Reeser

Performance period: 9/1/2023 8/31/2027

Level of funding:

Brief description of the project's goals: We hypothesize that the list of prevalent genetic alterations in HNSCC contains several prognostically useful biomarkers, and several novel genes that drive tumorigenesis and are therefore candidate therapeutic targets. Our translational objectives are to catalyze progress in HNSCC clinical care in 3 areas: 1) identifying prognostic and predictive biomarkers, and developing a prognostic tool for clinicians; 2) linking genetic alterations to biological mechanisms, to identify the genomic targets of highest priority for clinical trials; and 3) understanding mechanisms of immune escape, to identify the most promising approaches for clinical trials of immunotherapy.

Specific aims: Aim 1. Identify prognostic genetic biomarkers in HNSCC using deep learning. Aim 2. Functionally validate genetic drivers of HNSCC patient outcome and treatment resistance in murine isogenic systems. Aim 3. Characterize genomic determinants of the HNSCC immune microenvironment and response to immunotherapy.

Overlap: None

Title: Immunogenicity and Targeting of Shared Neoantigens in Adenoid Cystic Cancer

Grant number: RA220201

Time commitment:

1. 2024 0.60 calendar

- 2. 2025 0.60 calendar
- 3. 2026 0.60 calendar

PI: Morris, L

Supporting agency: Congressionally Directed Medical Research Programs

Contracting/Grants Officer: Chris Baker

Performance period: 9/1/2023 8/31/2026

Level of funding:

Brief description of the project's goals: Our objective is to develop new immunotherapeutic strategies targeting tumor specific neoantigens in ACC. Based on our previous findings, we hypothesize that most ACCs harbor immunogenic neoantigens, including shared or "public" neoantigens resulting from the prevalent MYB NFIB gene fusion, that can be targeted for T cell directed therapies.

Specific aims: Aim 1. Define the mechanisms of immune escape in ACC tumors with MYB-NFIB fusions treated with Immunotherapy. Aim 2. Identify shared immunogenic MYB-NFIB neoepitopes in ACC. Aim 3. Develop and test a library of therapeutic TCRs that recognize shared MYB-NFIB fusion-derived neoantigens

Overlap: None

Title: Deciphering altered metabolism and immune evasion in FAT1-mutated head and neck cancer

Grant number: W81XWH 22 1 0672 (CA210784)

Time commitment:

- 2. 2024 1.20 calendar
- 3. 2025 1.20 calendar

PI: Morris

Supporting agency: Congressionally Directed Medical Research Programs

Contracting/Grants Officer: Jamie A. Shortall

Performance period: 9/30/2022 9/29/2025

Level of funding:

Brief description of the project's goals: During the genomic investigation of our novel genetically engineered mouse model of HNSCC, we identified a link between FAT1 loss, altered tumor metabolism and an altered immune microenvironment. We have now assembled a collaborative team with the expertise to define the role of FAT1 in HNSCC metabolism, and the connections between FAT1-mediated deranged cellular metabolism and tumor immune evasion.

Specific aims: Aim 1. Define the metabolic processes altered in FAT1-mutated HNSCC tumors
Aim 2. Dissect the immunosuppressive mechanisms of FAT1 mutation in the tumor microenvironment

Overlap: None

Previously Reported Current Support:

Title: Mechanoregulation of cytotoxic lymphocyte function

Grant number: 2R01AI087644-11A1

Time commitment:

- 3. 2024 0.36 calendar
- 4. 2025 0.36 calendar
- 5. 2026 0.36 calendar

PI: Huse, M.

Supporting agency: National Institutes of Health

Contracting/Grants Officer: Svetlana E Alperovich

Performance period: 7/1/2021 - 6/30/2026

Level of funding:

Brief description of the project's goals: Cytotoxic lymphocytes, which are critical for immune responses against viruses and cancer, kill infected or transformed target cells via specialized cell-cell contacts known as

cytolytic immune synapses. This proposal seeks to understand how the dynamic physical activity of the cytolytic synapse and the mechanical properties of the lymphocyte and target cell contribute to the killing response. Understanding the biophysical basis of cytotoxic lymphocyte function could aid immunotherapeutic efforts to fight cancer and other diseases.

Specific aims: 1) Determine how mechanosurveillance shapes anti-tumor immunity. 2) Establish the mechanochemical choreography of cytotoxic function.

Overlap: None

Title: Identifying and targeting neoantigens in aggressive salivary carcinomas

Grant number: 5 R01 DE027738-04

Time commitment:

5. 2024 0.60 calendar

PI: Morris, L

Supporting agency: National Institute of Dental and Craniofacial Research

Contracting/Grants Officer: Susan Medve

Performance period: 4/1/2018 - 3/31/2024 NCE

Level of funding:

Brief description of the project's goals: The ultimate goal is effective neoantigen-directed immunotherapy that will improve survival for patients with recurrent or metastatic salivary gland cancer.

Specific aims: Aim 1. Define the mechanisms of immunogenicity and immune evasion in salivary cancers. Aim 2. Identify the genetic and immunologic determinants of response to immune checkpoint inhibition in salivary cancers. Aim 3. Create and test an engineered T cell targeting adenoid cystic carcinoma-specific neoantigens.

Overlap: None

Previous/Current Support

PREVIOUS (completed since award was funded):

Title: Deciphering altered metabolism and immune evasion in head and neck cancer

Grant number: Geoffrey Beene Cancer Research Center - Morris

Time commitment: 1.20 calendar

PI: Morris, L

Supporting agency: Geoffrey Beene Cancer Research Center

Contracting/Grants Officer: Julia E. Rudolph

Performance period: 9/1/2021 - 8/31/2022

Level of funding:

Brief description of the project's goals: In HNSCC translational research, the primary obstacle to progress is a lack of efficient, genetically faithful preclinical models. Our proposal seeks to address these 2 obstacles. We have developed a novel genetically engineered mouse model of HNSCC that reflects the genetics of human disease and recapitulates the progression of normal oral epithelium to dysplasia and invasive carcinoma. This is a one year pilot grant to characterize our novel genetically engineered mouse model of head and neck cancer, using inducible Cre-mediated knockout of Trp53, Fat1 and Pten, to determine the feasibility of this model future research linking these genes to targetable biologic pathways that are likely to have therapeutic relevance to approximately 30% of patients with head and neck cancer

Specific aims: N/A

Overlap: None

Title: Discovering metabolic vulnerabilities in aggressive lung cancer subtypes with NRF2 dysregulation

Grant number: AWD-GC-259579

Time commitment: 0.60 calendar

PI: Ziv

Supporting agency: Druckenmiller Center for Lung Cancer Research

Contracting/Grants Officer: Christian Brodala

Performance period: 4/15/2020 - 4/14/2022

Level of funding:

Brief description of the project's goals: The central hypothesis of the proposed research is that NRF2 dysregulation exposes cells to metabolic dependencies that can be targeted therapeutically. The objective of this proposal is to determine metabolic dependencies over a panel of NRF2 over-expressing patient-derived NSCLC organoids.

Specific aims: Aim 1: To compare metabolic vulnerabilities in tumor organoids with and without NRF2 overexpression. Aim 2: To compare metabolic profiles of high and low NRF2 expressing tumor organoids after ischemia. Aim 3: To determine drivers of cell fate under ischemic stress using single cell transcriptomics.

Overlap: None

Title: Detection of Impending Infections in Immunocompromised

Grant number: I13-0013

Time commitment: 1.80 calendar

Role: PI

Supporting agency: Starr Cancer Consortium

Contracting/Grants Officer: Annmarie L. Pacchia

Performance period: 1/1/2020 - 12/31/2022

Level of funding:

Brief description of the project's goals: The intestinal microbiome enhances immune defenses against cancer and infectious diseases, but cancer treatments that damage the microbiota result in loss of health-associated commensal bacteria and the metabolites they produce.

Specific aims: N/A

Overlap: None

CURRENT :

Newly Added Current Support:

Title: The role of bile acid metabolomics in graft versus host disease

Grant number: 2 R01 CA228308-06 (Contact PI: Van Den Brink, M)

Time commitment: 1.20 calendar

Role: MPI

Supporting agency: National Cancer Institute

Contracting/Grants Officer: Olivia Paolucci

Performance period: 4/1/2023 - 3/31/2028

Level of funding:

Brief description of the project's goals: The major goal of this proposal is to ameliorate graft versus host disease (GVHD) and improve outcomes in allogeneic hematopoietic cell transplantation (allo-HCT) recipients by targeting bile acids, which are potential regulators of the microbiome and donor T cells, using strategies informed by preclinical and clinical studies.

Specific aims: Aim 1: To study the role of bile acids in aGVHD after allo-HCT in preclinical models. Aim 2: To study the role of bile acids in GVHD in allo-HCT patients. Aim 3: To study strategies targeting bile acid metabolism to ameliorate aGVHD after allo-HCT.

Overlap: None

Title: Dopamine Metabolism and Nonpharmacologic Insomnia Interventions Among Cancer Survivors

Grant number: 5R21CA274059-02 (PI: Mao, J)

Time commitment: 0.60 calendar

Role: Co-Investigator

Supporting agency: National Cancer Institute

Contracting/Grants Officer: Jennifer Meininger

Performance period: 7/1/2022 - 6/30/2024

Level of funding:

Brief description of the project's goals: Our study will bring initial novel biological insights to the field of behavioral and integrative sleep management. Further elucidating the potential metabolic mechanisms of these interventions may inform future development of more targeted interventions to improve sleep and metabolic health for millions of cancer survivors.

Specific aims: AIM 1: Evaluate the effect of acupuncture versus CBT-I on the dopamine-related metabolic signatures with targeted metabolomics. AIM 2: Identify the potential effect of acupuncture and CBT-I on additional metabolic signatures with nontargeted metabolomics approaches.

Overlap: None

Title: Comparative studies on the regulation of metabolism during sperm capacitation

Grant number: 5R01HD088571-07 (PI: Buck, J)

Time commitment: 0.60 calendar

Role: Co-Investigator

Supporting agency: Eunice Kennedy Shriver National Institute of Child Health and Human Development (PTE: Weill Medical College of Cornell University)

Contracting/Grants Officer: Patricia Kearins

Performance period: 12/1/2022 - 11/30/2027

Level of funding:

Brief description of the project's goals: This grant focuses on the rapid metabolic transition that sperm cells undergo during capacitation, a process required for successful fertilization. The proposal seeks to apply LC-MS based metabolite profiling, stable isotope tracing and lipidomics to uncover substrate dependencies, the role of mitochondrial oxidative metabolism and the pentose phosphate pathway. The proposal also leverages existing genetic models of the major signaling pathways (soluble adenylylase).

Specific aims: N/A

Overlap: None

Title: Identification of Mycobacterium tuberculosis-derived metabolites acting as ligands for MR1-restricted T cells

Grant number: 1R21AI171578-01A1 (PI: Vorkas, C)

Time commitment: 0.60 calendar

Role: Co-investigator / site PI

Supporting agency: National Institute of Allergy and Infectious Diseases (PTE: Stony Brook University)

Contracting/Grants Officer: Selamu Shega

Performance period: 4/4/2023 – 3/31/2025

Level of funding:

Brief description of the project's goals/Specific aims: There is a growing appreciation of the role of innate-like T cells in control TB infection, eg. MAIT cells that recognized MR1-presented ligands. This proposal seeks to use mass spectrometry and pull-down strategies to identify novel MR1-presented metabolites produced during TB infection that control T cell responses.

Overlap: None

Title: Investigating the role of non-canonical tricarboxylic acid metabolism in kidney cancer.

Grant number: HT9425-23-1-0986 / Log # KC220206

Time commitment: 1.20 calendar

Role: PI

Supporting agency: Congressionally Directed Medical Research Programs

Contracting/Grants Officer: Kathleen Nagy

Performance period: 9/1/2023 - 8/31/2024

Level of funding:

Brief description of the project's goals: In this grant application, we assemble a team of leading scientists with complementary expertise, and propose an integrated approach to address whether SETD2 mutations alter the 3D chromosome architecture to activate oncogenic transcription programs that promote kidney cancer metastasis.

Specific aims: Aim 1. Apply cutting-edge positional stable isotope tracing strategies to examine TCA cycle compartmentalization and substrate dependencies in the presence or absence of SETD2. Aim 2. Use extracellular flux analysis and spent media profiling to assess substrate utilization and address whether nutrient limitation strategies can counteract the increase in mitochondrial activity observed in SETD2-deleted cells.

Overlap: None

Previously Reported Current Support:

Title: Tri-I Training Program in Metabolomics

Grant number: 5R25AI140472-05 (Contact PI: Rhee, K)

Time commitment: 1.80 calendar

Role: MPI

Supporting agency: National Institute of Allergy and Infectious Diseases (PTE: Weill Medical College of Cornell University)

Contracting/Grants Officer

Performance period: 08/01/2019–07/31/2024

Level of funding:

Brief description of the project's goals: This R25 proposal seeks to establish a structured didactic and laboratory training program in metabolomics and thereby enhance training of NIAID funded trainees in this emerging omics level science.

Specific aims: N/A

Overlap: None

Title: Transcriptional Control of NK Cell Metabolism

Grant number: 5R01AI155558-03 (PI: Sun, J)

Time commitment: 0.60 calendar

Role: Core Director

Supporting agency: National Institute of Allergy and Infectious Diseases

Contracting/Grants Officer: Svetlana Alperovich

Performance period: 02/10/2021–01/31/2026

Level of funding:

Brief description of the project's goals: This proposal seeks to understand the transcriptional mechanisms underlying natural killer (NK) cell metabolism in host immunity against CMV infection. Defining the molecular mechanisms by which NK cells respond to pathogens will potentially lead to therapeutic benefits.

Specific aims: Aim 1. Determine how individual STAT transcription factors downstream of proinflammatory cytokines control NK cell metabolism during viral infection. Aim 2. Investigate the requirement for aerobic glycolysis and fatty acid oxidation in NK cells responding to MCMV infection. Aim 3. Establish whether STAT4-induced transcription factor Bhlhe40 regulates mitochondrial fitness in antiviral NK cells.

Overlap: None

Title: SRA-A Longitudinal Pilot Study of Graft-vs.-Host Disease (GvHD)

Grant number: SK2020-0488

Time commitment: 0.60 calendar

Role: PI

Supporting agency: Merck & Co

Contracting/Grants Officer: redacted as

Performance period: 10/9/2020 - 11/9/2025

Level of funding:

Brief description of the project's goals: A longitudinal pilot study of Graft-vs-host-disease (GvHD) to determine if there is evidence for the microbiome and associated metabolites to influence the clinical outcomes of allogeneic-hematopoietic stem cell transplant (allo-HSCT) recipients. Identify specific subsets of $\gamma\delta$ T cells or other MR1-restricted T-cells, that expand in response to host/microbiome associated compounds.

Specific aims: redacted as

Overlap: None

Title: Copper Mediated Metabolic Reprogramming and ECM Alterations in TNBC Metastasis

Grant number: 5R01CA257254-03 (PI: Mittal, V)

Time commitment: 0.25 calendar

Role: Co-Investigator/site PI

Supporting agency: National Cancer Institute (PTE: Weill Medical College of Cornell University) Contracting/ Grants Officer: Sabrina Beaver

Performance period: 5/1/2021-4/30/2026

Level of funding:

Brief description of the project's goals: We will delineate novel copper signaling metabolic pathways for the development of novel therapeutic strategies against TNBC.

Specific aims: Aim 1 will establish the direct link between copper-mediated metabolic reprogramming and metastasis in TNBC and dissect key cellular and molecular mechanisms, and Aim 2 will investigate how copper deficiency reprograms the extracellular matrix in the distal metastatic organs to generate an inhospitable microenvironment to impair metastasis and develop clinically valuable biomarkers of response to TM.

Overlap: None

KUO, FENGSHEN

Previous/Current Support

PREVIOUS (completed since award was funded) :

Title: Precision Macrophage Targeting to Overcome Treatment Resistance in Renal Cell Carcinoma

Grant number: 2020 Cycle for Survival's Equinox Innovation

Time commitment: 1.20 calendar

PI: Hakimi, A

Role: Computational Biologist

Supporting agency: Cycle for Survival

Contracting/Grants Officer: Kathleen Bourke

Performance period: 1/1/2021–12/31/2022

Level of funding:

Brief description of the project's goals/Specific aims: Aim 1: Fully characterize the macrophage compartment in untreated and treated human ccRCC. Aim 2: Develop and refine novel immunogenomic models of response to systemic therapy in ccRCC.

Overlap: None

CURRENT:

Newly Added Current Support

Title: Understanding mechanisms of immune escape in early stage tumors

Grant number: DBG 23 1036155 01 CDP

Time commitment:

1. 2025 0.60 calendar

PI: Morris, L

Supporting agency: American Cancer Society

Contracting/Grants Officer: Lynne Elmore, PhD

Performance period: 11/1/2023 10/31/2025

Level of funding:

Brief description of the project's goals: Our long term goal is to generate data to guide the development of prognostic biomarkers for early stage tumors. This would help patients with these tumors avoid unnecessary toxic treatments, reserving anti cancer therapies for patients with tumors likely to progress. As a first step toward this goal, we now propose to identify the biological mechanisms associated with indolent tumor behavior, and the transformation to clinically significant cancers. We hypothesize that indolent tumors are in a state of immune equilibrium, and that clinical progression reflects immune escape.

Specific aims: Aim 1. Validate mechanisms of immune escape in overdiagnosed tumors. Aim 2. Differentiate antigenic immunoediting in overdiagnosed vs. non-overdiagnosed cancer types. Aim 3. Compare immunogenomic features in progressing and non-progressing tumor samples from patients undergoing active surveillance.

Overlap: None

Title: Defining the Genetic Determinants of Head and Neck Cancer Progression and Immune Evasion through Computational and Functional Investigation

Grant number: CA220766_E01 HT9425 23 1 0556

Time commitment:

1. 2024 1.20 calendar

2. 2025 1.20 calendar

3. 2026 1.20 calendar

4. 2027 1.20 calendar

PI: Morris, L

Supporting agency: Congressionally Directed Medical Research Programs

Contracting/Grants Officer: Teresa Parker-Reeser

Performance period: 9/1/2023 8/31/2027

Level of funding:

Brief description of the project's goals: We hypothesize that the list of prevalent genetic alterations in HNSCC contains several prognostically useful biomarkers, and several novel genes that drive tumorigenesis and are therefore candidate therapeutic targets. Our translational objectives are to catalyze progress in HNSCC clinical care in 3 areas: 1) identifying prognostic and predictive biomarkers, and developing a prognostic tool for clinicians; 2) linking genetic alterations to biological mechanisms, to identify the genomic targets of highest priority for clinical trials; and 3) understanding mechanisms of immune escape, to identify the most promising approaches for clinical trials of immunotherapy.

Specific aims: Aim 1. Identify prognostic genetic biomarkers in HNSCC using deep learning. Aim 2.

Functionally validate genetic drivers of HNSCC patient outcome and treatment resistance in murine isogenic systems. Aim 3. Characterize genomic determinants of the HNSCC immune microenvironment and response to immunotherapy.

Overlap: None

Title: Immunogenicity and Targeting of Shared Neoantigens in Adenoid Cystic Cancer

Grant number: RA220201

Time commitment:

1.	2024	0.60 calendar
2.	2025	0.60 calendar
3.	2026	0.60 calendar

PI: Morris, L

Supporting agency: Congressionally Directed Medical Research Programs

Contracting/Grants Officer: Chris Baker

Performance period: 9/1/2023 8/31/2026

Level of funding:

Brief description of the project's goals: Our objective is to develop new immunotherapeutic strategies targeting tumor specific neoantigens in ACC. Based on our previous findings, we hypothesize that most ACCs harbor immunogenic neoantigens, including shared or "public" neoantigens resulting from the prevalent MYB-NFIB gene fusion, that can be targeted for T cell directed therapies.

Specific aims: Aim 1. Define the mechanisms of immune escape in ACC tumors with MYB-NFIB fusions treated with Immunotherapy. Aim 2. Identify shared immunogenic MYB-NFIB neoepitopes in ACC. Aim 3. Develop and test a library of therapeutic TCRs that recognize shared MYB-NFIB fusion-derived neoantigens

Overlap: None

Title: Deciphering altered metabolism and immune evasion in FAT1-mutated head and neck cancer

Grant number: CA210784/ W81XWH 22 1 0672

Time commitment:

2.	2024	0.36 calendar
3.	2025	0.36 calendar

PI: Morris, L

Supporting agency: Congressionally Directed Medical Research Programs

Contracting/Grants Officer: Jamie A. Shortall

Performance period: 4/30/2022 - 4/29/2025

Level of funding:

Brief description of the project's goals: During the genomic investigation of our novel genetically engineered mouse model of HNSCC, we identified a link between FAT1 loss, altered tumor metabolism and an altered immune microenvironment. We have now assembled a collaborative team with the expertise to define the role of FAT1 in HNSCC metabolism, and the connections between FAT1-mediated deranged cellular metabolism and tumor immune evasion.

Specific aims: Aim 1. Define the metabolic processes altered in FAT1-mutated HNSCC tumors

Aim 2. Dissect the immunosuppressive mechanisms of FAT1 mutation in the tumor microenvironment

Overlap: None

Title: The Impact of DNA Damage Repair Abnormalities in Prostate Cancer (Genomics Core)

Grant number: P01CA228696

Time commitment:

4. 2024 1.20 calendar

5. 2025 1.20 calendar

PI: Offit, K / Solit, D

Supporting agency: National Cancer Institute

Contracting/Grants Officer: Michael Kluk

Performance period: 9/1/2019 - 8/31/2025

Level of funding:

Brief description of the project's goals: Aberrations in genes that help repair damaged DNA are seen in 20-25% of men with metastatic castrationresistant prostate cancer, the lethal form of prostate cancer. We have assembled a multidisciplinary team to increase our understanding of the role the spectrum of DNA repair aberrations play in early prostate cancer.

Specific aims: The Specific Aims of the Genomics Core are as follows: Specific Aim 1. To assist in the identification of genes associated with increased heritable cancer risk by conducting whole exome or targeted sequencing of known DDR pathway genes from clinically annotated cohorts of men diagnosed with high-risk, localized PC treated with standard of care (Harvard cohorts) and patients enrolled on the MetaCURE clinical trial. Specific Aim 2. To explore mechanisms of sensitivity and resistance to hormonal therapies and PARP inhibitors by analyzing tumors and cell-free DNA before and after treatment on the MetaCURE clinical trial. Specific Aim 3. To facilitate data sharing and scientific collaboration within the P01, with the broader research community, and with NCI.

Overlap: None

Title: Association between body composition and treatment-related outcomes among metastatic kidney cancer patients treated with immunotherapy

Grant number: 3 R01 CA233885-05 S14

Time commitment:

5. 2024 0.24 calendar

PI: Barnes, A

Supporting agency: National Cancer Institute

Contracting/Grants Officer: Sean Hine

Performance period: 8/1/2019 - 7/31/2024

Level of funding:

Brief description of the project's goals: Immunotherapy is a promising new treatment for kidney cancer but unfortunately does not work for all patients and dangerous side effects are common. Identifying factors that predict who will respond to immunotherapy or suffer from adverse events is essential to giving the best care possible.

Specific aims: N/A

Overlap: None

Previously Reported Current Support

Title: Body Composition and the Obesity Paradox in Clear Cell Renal Cell Carcinoma

Grant number: 5 R01 CA233885-02

Time commitment: 0.60 calendar

Role: Co-Investigator

PI: Barnes, A

Supporting agency: NCI

Contracting/Grants Officer: Joanne W. Elena

Performance period: 8/1/2019–7/31/2024

Level of funding:

Brief description of the project's goals: Our study will improve the measurement of BMI by calculating exactly how much muscle and fat a kidney cancer patient has and determining for the first time how those tissues relate to tumor aggressiveness and to survival.

Specific aims: Aim 1. Determine associations among BMI, body composition variables and molecular tumor subtype. Aim 2. Identify body composition variables that are independently associated with ccRCC prognosis after accounting for tumor subtype. Aim 3. Identify transcriptomic signatures of body composition and of prognosis.

Overlap: None

Title: Investigation of the Role of Epithelial-Mesenchymal Plasticity in Renal Cell Carcinoma

Grant number: 1R01CA258226-01

Time commitment: 0.76 calendar

Role: Bioinformatics Engineer

PI: Genovese, G (MSK PI: Hakimi, A)

Supporting agency: NIH (PTE: MD Anderson Cancer Center)

Contracting/Grants Officer: Joanna M. Watson

Performance period: 4/1/2021–3/31/2026

Level of funding:

Brief description of the project's goals: The proposed research is relevant for patients with aggressive renal cell carcinoma because it will explore the molecular and genetic routes to disease progression, metastatic dissemination and response to therapy. The project is relevant to the mission of the NIH because it will shed light on a new opportunity to intervene therapeutically in this disease that currently has dismal outcomes and very limited therapy options, and it will expand our knowledge of the biology and context-specific vulnerabilities of renal cell carcinoma.

Specific aims: In the first aim we will provide a detailed spatial and temporal annotation of epithelial and mesenchymal population dynamics during malignant progression and in response to pharmacological interventions. The second aim will define the genomic and transcriptomic landscape of the malignant subpopulation and the interplay between these cellular compartments and the components of the TME. In the third aim we will identify context-specific vulnerabilities, defining the genetic dependencies of epithelial and mesenchymal cells.

Overlap: None

Title: Mechanoregulation of Cytotoxic Lymphocyte Function

Grant number: 2 R01 AI087644-11A1

Time commitment:

3. 2024 1.20 calendar

4. 2025 1.20 calendar

5. 2026 1.20 calendar

Role: Bioinformatic Engineer

PI: Huse, M

Supporting agency: NIAID

Contracting/Grants Officer: Conrad M. Mallia

Performance period: 7/1/2021–6/30/2026

Level of funding:

Brief description of the project's goals: Cytotoxic lymphocytes, which are critical for immune responses against viruses and cancer, kill infected or transformed target cells via specialized cell-cell contacts known as cytolytic immune synapses. This proposal seeks to understand how the dynamic physical activity of the cytolytic synapse and the mechanical properties of the lymphocyte and target cell contribute to the killing response.

Specific aims: 1) Determine how mechanosurveillance shapes anti-tumor immunity. 2) Establish the mechanochemical choreography of cytotoxic function.

Overlap: None

Title: Investigating the Immunologic Basis of the Obesity Paradox in Renal Cell Carcinoma

Grant number: Hakimi AICR Award

Time commitment: 0.60 calendar

Role: **Computational Biologist**

PI: Hakimi, A

Supporting agency: American Institute for Cancer Research

Contracting/Grants Officer: Nigel Brockton, PhD

Performance period: 1/1/2022 - 12/31/2023

Level of funding:

Brief description of the project's goals: The overall goal is to understand the role of obesity-induced changes in patients' immune systems in the obesity paradox in clear cell renal cell carcinoma (ccRCC), specifically, obese patients' better outcomes after immune checkpoint blockade (ICB) therapy.

Specific aims: **Aim 1: Compare obese and nonobese patients with advanced ccRCC in terms of the tumor immune microenvironment and the spatial arrangement of immune cells. Aim 2: Model the effect of obesity on tumor development and progression in novel immunocompetent ccRCC murine models.**

Overlap: None

Previous/Current Support
Ed Reznik

Previous: (Completed since grant was awarded)

Grant Number: AWD-GC-259440 (PI: Reznik, E):
Sponsor Name: Brown Performance Group

Project Dates: 9/1/2020-8/31/2022
Total Award Amount:

Title: Multimodal Metabolic Analysis of Tumors and Therapeutic Response

Project Goals: The overarching goal of this proposal is to use the MMM to develop a multimodal metabolic analysis of tumors, and to leverage it to democratize metabolomic data for translational cancer research by the broader scientific community.

Specific Aims: Specific Aim 1: Define multimodal metabolic portraits of tumors and their microenvironment. Specific Aim 2: RNA-based signatures of metabolite abundance for *in silico* metabolomics. Specific Aim 3: A Public Portal to the Multimodal Metabolism Map

Effort:

Year 1	2.40 cal months
Year 2	2.40 cal months

Role: Principal Investigator

Name of Contracting/Grants Officer:

Grant Number: AWD-GC-259389 (PI: Miloushev):
Sponsor Name: Imaging and Radiation Sciences Program

Project Dates: 3/1/2020-2/28/2022
Total Award Amount:

Title: Hyperpolarized Pyruvate Metabolic Imaging of Previously Irradiated Recurrent Metastases in vivo

Project Goals: unknown

Specific Aims: 1. For brain metastases previously treated with radiation therapy, we hope to learn whether the lesion metabolism, as gauged by HP pyruvate MRSI, correlates with active tumor and specific tumor markers. 2. HP pyruvate metastatic brain tumor 3D metabolic imaging. 3. Use the data collected in this study to plan a trial gauging treatment response at multiple timepoints (before and after radiation therapy), which will be submitted as an NIH R01 proposal; further, we aim to incorporate this approach into clinical practice to help optimize patient care and radiation therapy.

Effort:

Year 1	0.60 cal months
Year 2	0.60 cal months

Role: Co-Investigator

Name of Contracting/Grants Officer: Nicole Garner

Grant Number: AWD-GC-262300 (PI: Reznik, E):
Sponsor Name: Cycle for Survival

Project Dates: 9/1/2019-11/30/2022 NCE
Total Award Amount:

Title: Prospective Metabolomic Profiling for Biomarkers of Response to Metabolic Therapies in Acute Myeloid Leukemia

Project Goals: We hypothesize that intrinsic metabolic heterogeneity and metabolic flexibility/adaptation underlie *de novo* and acquired resistance to BCL2 and IDH inhibitors in AML. To test this hypothesis, we will leverage the prospective MSK-IMPACT initiative and several recently completed and ongoing clinical trials led by MSKCC investigators to perform longitudinal metabolomic profiling of patients treated with BCL2 or IDH inhibitors.

Specific Aims: Aim 1. Identify metabolic biomarkers that predict for response or intrinsic resistance to metabolic therapies in AML patients. Aim 2. Define metabolic mechanisms of acquired resistance to metabolic therapies in AML patients.

Effort:

Year 1	0.66 cal months
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Year 2	0.66 cal months
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Role: Principal Investigator

Name of Contracting/Grants Officer: Kathleen Bourke

Current:

Newly reported current support:

Grant Number: KC220010 (PI: Reznik, E):

Project Dates: 9/30/2023 - 9/29/2026

Sponsor Name: Congressionally Directed Medical Research Programs

Total Award Amount:

Title: Coevolution of Metabolism and Immune Microenvironment as a Driver of Therapeutic Response and Metastasis in ccRCC

Project Goals: The central hypothesis of this proposal is that the metabolism and immune microenvironment of ccRCC coevolve to produce unique, spatially-delimited immunometabolic niches with defined metastatic potential and sensitivity to immunotherapy.

Specific Aims: Specific Aim 1: Define immunometabolic subtypes and identify metabolite biomarkers of response to therapy in ccRCC. Specific Aim 2: Define the immunometabolic identity of metastatic subclones in ccRCC. Specific Aim 3: Define the effect of immunotherapy on ccRCC immunometabolic heterogeneity.

Effort:

Year 1	1.80 cal months
Year 2	1.80 cal months
Year 3	1.80 cal months

Role: Principal Investigator

Name of Contracting/Grants Officer: Abigail Strock Overlap: None

Grant Number: 1R01CA283578 (PI: Rahimi Keshari, K) Project Dates: 7/1/2023 - 6/30/2028

Sponsor Name: National Institutes of Health

Total Award Amount:

Title: Interrogation of the oxidative-stress-induced leukemia program in vivo using metabolic imaging Project

Goals: Leukemia remains difficult to treat, indicating an urgent need to develop new therapeutic strategies; thus, the overarching goal of the proposed research is to explore leukemia metabolism and develop novel biomarkers and therapeutic strategies. Our preliminary data demonstrates that specific metabolic pathways driving serine biosynthesis are increased in leukemia; these reflect vulnerabilities that we can develop imaging biomarkers to target. Our proposed work will facilitate future patient-specific treatment planning and novel experimental strategies for cancer treatment.

Specific Aims: SA1. Uncover myeloid LSC ROS metabolic heterogeneity after PHGDH modulation. SA2. Characterize LSC metabolism using hyperpolarized magnetic resonance. SA3. Develop a hyperpolarized MRI strategy to interrogate leukemia metabolism in vivo.

Effort:

Year 1	0.60 cal months
Year 2	0.60 cal months
Year 3	0.60 cal months
Year 4	0.60 cal months
Year 5	0.60 cal months

Role: Biostatistician

Name of Contracting/Grants Officer: Olivia M. Paolucci

Overlap: None

Grant Number: 1R37CA276200-01 (PI: Reznik, E)

Project Dates: 1/1/2023 - 12/31/2027

Sponsor Name: National Institutes of Health

Total Award Amount:

Title: Defining the function of Complex I truncating mutations in cancer

Project Goals: We propose integrative computational/experimental studies to test the overarching hypothesis that CI-truncating mutations produce physiologically significant and therapeutically actionable metabolic changes in tumors.

Specific Aims: Aim 1: Define the genomic context and functional consequences of CI-truncating mutations. Aim 2: Define the quantitative effect of heteroplasmy on the metabolic and non-metabolic phenotypes of CI-truncating mutations. Aim 3: Identify therapeutic strategies for targeting cells with CI-truncating mutations.

Effort:

Year 1	4.20 cal months
Year 2	4.20 cal months
Year 3	4.20 cal months
Year 4	4.20 cal months
Year 5	4.20 cal months

Role: Principal Investigator

Name of Contracting/Grants Officer: Olivia M. Paolucci

Overlap: None

Grant Number: AWD00002166 (PI: Hakimi, A) Project Dates: 10/1/22 - 9/30/24

Sponsor Name: Alan and Sandra Gerry Metastasis Total Award Amount:

and Tumor Ecosystems Center

Title: Immunometabolic Coevolution as a Determinant of Response to Immunotherapy in ccRCC

Project Goals: The overarching hypothesis of this proposal is that the metabolism and immune microenvironment of ccRCC coevolve to produce unique microenvironments with defined sensitivities to immunotherapy. To address this hypothesis we will analyze bulk, multimodal metabolomic/microenvironmental profiling of ccRCC tumors

Specific Aims: (Aim 1) and the direct effect of immunotherapy on novel, immunocompetent, mouse models of ccRCC (Aim 2).

Effort:

Year 2	1.80 cal months
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Role: Co- Investigator

Name of Contracting/Grants Officer: Benjamin Hegel

Overlap: None

Previously reported current support:

Grant Number: 5 R37CA251543-04 (PI: Intlekofer, A): Project Dates: 9/1/2020 - 5/31/2025

Sponsor Name: National Cancer Institute Total Award Amount:

Title: Metabolic control of normal and malignant hematopoiesis

Project Goals: New drugs that target metabolic pathways have shown promise for the treatment of cancer, but the benefits of these drugs have been restricted to rare patients whose cancers have mutations in metabolic enzymes. We have identified a metabolic pathway whereby normal stem cells and almost all Cancer cells produce a metabolite called Lhydroxyglutarate (L-2HG) that regulates key aspects of cell identity and function. The proposed research will test the importance of L-2HG in normal blood stem cells.

Specific Aims: Aim 1. Define the molecular mechanisms by which L-2HG regulates blood cell differentiation in vitro. Aim 2. Determine how L-2HG functions to control normal and malignant hematopoiesis in vivo. Aim 3. Elucidate the oncogenic mechanisms and therapeutic potential of L-2HG in human leukemia.

Effort:

Year 4	0.60 cal months
Year 5	0.60 cal months

Role: Co- Investigator

Name of Contracting/Grants Officer: Sarah M Lee

Overlap: None

Grant Number: 5 R01 CA252037-04 (PI: Rahimi-Keshari, K): Project Dates: 6/1/2020 - 5/31/2025
Sponsor Name: National Cancer Institute Total Award Amount:

Title: Visualizing oxidative stress using hyperpolarized magnetic resonance

Project Goals: The overarching goal of the proposed research is to develop a new MRI technology for imaging oxidative stress: hyperpolarized dehydroascorbate (HP DHA) MRI. Oxidative stress is implicated in the pathogenesis of many diseases, including neurodegeneration and brain tumors, and there is an urgent need to develop more sensitive and specific imaging approaches to characterize it.

Specific Aims: SA1. Quantitatively interrogate oxidative stress in the normal brain and brain tumors in vivo using HP DHA. SA2. Utilize novel approaches to enhance the ability to image HP DHA. SA3. Demonstrate the feasibility of HP DHA in humans.

Effort:

Year 4	0.60 cal months
Year 5	0.60 cal months

Role: Biostatistician

Name of Contracting/Grants Officer: Mohammed Helmy Kurtom

Overlap: None

Grant Number: W81XWH-22-1-0672 (PI: Morris, L): Project Dates: 9/30/2022 - 9/29/2025
Sponsor Name: Congressionally Directed Medical Research Programs Total Award Amount:

Research Programs

Title: Deciphering altered metabolism and immune evasion in FAT1-mutated head and neck cancer

Project Goals: Our long-term goal is to develop novel, rational genomically targeted therapies for HNSCC. Here, we propose to make a first step toward this goal by identifying how the 2nd most common genetic alteration in HNSCC mediates treatment resistance and immune evasion.

Specific Aims: Aim 1. Define the metabolic processes altered in FAT1-mutated HNSCC tumors. Aim 2. Dissect the immunosuppressive mechanisms of FAT1 mutation in the tumor microenvironment

Effort:

Year 1	0.60 cal months
Year 2	0.60 cal months
Year 3	0.60 cal months

Role: Co- Investigator

Name of Contracting/Grants Officer:

Overlap: None