AWARD NUMBER: W81XWH-21-1-0592

TITLE: Targeting Retinoic Acid Signaling for Immunotherapy in Hepatocellular Carcinoma

PRINCIPAL INVESTIGATOR: Malay Haldar, MD, PhD

CONTRACTING ORGANIZATION: University of Pennsylvania, Philadelphia, PA

REPORT DATE: August 2023

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
August 2023	Annual	15Jul2022 - 14Jul2023

4. TITLE AND SUBTITLE

Targeting Retinoic Acid Signaling for Immunotherapy in Hepatocellular Carcinoma

5a. CONTRACT NUMBER
W81XWH-21-1-0592

5b. GRANT NUMBER
W81XWH-21-1-0592

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

University of Pennsylvania
3451 Walnut Street
Franklin Building, 5th Floor
Philadelphia, PA, 19104

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

The objective of this proposal is to examine our hypothesis that *inhibition of RA signaling can elicit therapeutic immune responses in hepatocellular carcinoma*. We will test this hypothesis in murine models of HCC by (1) reducing RA production with novel RALDH1 inhibitors we developed, (2) inhibiting RA signaling with commercially available small molecule inhibitor of RAR/RXR, and (3) boosting T cell responses by anti-PD1. To our knowledge, this would be the first attempt to inhibit RALDH1 for immunotherapy of any cancer. We have made significant progress towards these goals in this reporting period (2021 – 2022). We demonstrate that our novel RALDH1 inhibitors can abrogate RA production in HCC cells. RA derived from HCC suppressed DC and promoted macrophage differentiation from monocytes; an effect that was reversed upon treatment of HCC cells with our RALDH1-inhibitors. *In vivo*, our RALDH1 inhibitors reduced immunosuppressive macrophages and suppressed tumor growth in HCC. Finally, we genetic deletion of RALDH1 in HCC and RALDH1 inhibitors showed similar tumor suppressive effects in HCC. Taken together, our findings thus far strongly supports RA inhibition as a therapeutic strategy in HCC.

15. SUBJECT TERMS
Retinoic Acid, Retinaldehyde Dehydrogenase, Hepatocellular Carcinoma, Immunotherapy

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
U	U	U	UU	14	**19b. TELEPHONE NUMBER** *(include area code)*

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

In the United States, nearly 33,000 people are diagnosed with liver cancer and 27,000 die from this disease each year. Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the third leading cause of cancer-related death worldwide. Once the disease has spread (metastasized), treatment options are limited and the prognosis is very poor. Overall, the 5-year survival drops from about 32% in 'early stage' to less than 2% in metastatic HCC. Given this dismal prognosis, immune checkpoint blockade (ICB) therapy was recently approved for advanced metastatic HCC. However, ICB is not as effective in HCC as in some other types of tumor and the majority of patients do not respond. While the majority of current modalities in cancer immunotherapy act on T-cells, our laboratory is interested in targeting another key cell-type of the immune system – antigen-presenting cells. We have discovered that many solid tumors produce retinoic acid, which acts on antigen-presenting cells to create an immune-suppressive tumor microenvironment. Importantly, we showed that blocking retinoic acid in such tumors lead to anti-tumor immune responses. Hence, retinoic acid represents a new target for cancer immunotherapy. *The primary objective of this project is to determine whether targeting retinoic acid signaling is effective for HCC immunotherapy*. Towards this goal, we will first examine whether RALDH1 inhibition with our novel compounds can reduce retinoic acid levels in HCC to promote anti-tumor immune responses and then test whether this approach alone or in combination with ICB can restrain HCC growth. We will test our hypothesis using human and mouse HCC cell lines as well as mouse models.

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

Retinoic acid, Retinaldehyde dehydrogenase 1, Dendritic Cells, Macrophages

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

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

What were the major goals of the project?

Specific Aim 1: Impact of RALDH1 inhibition on HCC		
Major Task 1: To identify the impact of RALDH1 inhibition on RA production by HCC cells		
Subtask 1: Measure retinoic acid levels in human HCC cells with and without RALDH1 inhibitors using LC/MS. Cell lines used: SNU398 [Source: Simon Lab] Progress: Completed and described in 2022 progress report.	1-3	Haldar Lab
Subtask 2: Measure retinoic acid levels in mouse HCC cells with and without RALDH1 inhibitors using LC/MS. Cell lines used: Hepa 1-6 [Source: ATCC] Progress: Major portion completed and described in previous progress report. We are developing a new LC/MS method that is more sensitive than our previously published method and, more importantly, can distinguish between 11-cis and all-trans isomers of retinoic acid. The method development is completed and we are	1-3	Haldar Lab

now testing extraction from different biological matrices before final application to cells and mice treated with RALDH1-INH.		
Major Task 2: To examine the impact of inhibiting HCC RA production on monocyte differentiation		
Subtask 1: Analyze human monocyte differentiation with reduced RA production by HCC. Cell lines used: SNU398 [Source: Simon Lab] and Primary human monocytes [Human immunology core, UPenn] Progress: Completed and described in 2022 progress report.	3-6	Haldar Lab
Subtask 2: Analyze mouse monocyte differentiation with reduced RA production by HCC. Cell lines used: Hepa 1-6 [Source: ATCC] and Primary mouse monocytes [Haldar Lab] Progress: Completed and described in 2022 progress report.	3-6	Haldar Lab
Major Task 3: To examine the impact of inhibiting HCC RA production on the tumor microenvironment		
Subtask 1: Analyze impact of RALDH1 inhibition on human HCC microenvironment. [3 treatment conditions X 3 endpoints X 8 mice per group X 5 overall experimental repeats = 360 mice total] Cell lines and Model: SNU398 [Source: Simon Lab] and Immunodeficient NU/J mice [Jackson Laboratory] Progress: Completed and described in 2022 progress report.	8-12	Haldar Lab
Subtask 2: Analyze impact of RALDH1 inhibition on murine HCC microenvironment. [3 treatment conditions X 3 endpoints X 8 mice per group X 5 overall experimental repeats = 360 mice total] Cell lines and Model: Hepa 1-6 [Source: ATCC] and Immunocompetent C57BL/6J mice [Jackson Laboratory] Progress: Completed and described below in 'accomplishments' As outlined in our previous progress report, C86 and C91 inhibit human but not murine RALDH1. We therefore identified a murine RALDH1 inhibitors – C99 – for these studies. However, we subsequently found that C99 has poor half-life in vivo and a high IC50 that makes it far less effective compared to C86 and C91 for in vivo studies. To overcome these limitations, we used murine Hep55 cells and examined the impact of genetic deletion of RALDH1.	8-12	Haldar Lab
Major Task 4: To examine the general impact of RALDH1 inhibition on immune cells *in vivo*		
Subtask 1: Examine the impact of compound 86 on immune cells. [2 treatment conditions X 8 mice per group = 16 mice total] Cell lines and Model: Immunocompetent C57BL/6J mice [Jackson Laboratory] Progress: Completed. As described above, the inhibitors (including C99 described in 2022 progress report) do not work well on murine RALDH1. Thus, we examined the immune impact of RALDH1-deletion in murine Hep55 HCC tumors.	12-14	Haldar Lab
Subtask 2: Examine the impact of compound 91 on immune cells. [2 treatment conditions X 8 mice per group = 16 mice total] Cell lines and Model: Immunocompetent C57BL/6J mice [Jackson Laboratory] Progress: Completed. As described above, in lieu of inhibitors, we studied the impact of RALDH1 deletion in murine HCC tumors.	12-14	Haldar Lab
Milestone(s) Achieved: Upon completion of aim 1 we will uncovering the impact of RALDH1 inhibition by C-86 and C-91 on (1) RA production by human and mouse HCC, (2) intratumoral monocyte differentiation into macrophages vs. DCs, (3) anti-	16	

tumor immune responses in HCC, and (4) general immune cell distribution at steady state.		
Specific Aim 2: Targeting RALDH1 for immunotherapy of HCC		
Major Task 5: To test whether RA blockade can elicit therapeutic anti-tumor immune responses in HCC		
Subtask 1: To test single and combinatorial RA signaling blockade for HCC immunotherapy. [10 treatment conditions X 8 mice per group X 5 overall experimental repeats = 400 mice total] Cell lines and Model: Hepa 1-6 [Source: ATCC] and Immunocompetent C57BL/6J mice [Jackson Laboratory] Progress: Completed. As described above, the inhibitors are not very effective on murine RALDH1. Thus, monotherapy was tested on human HCC (described in 2022 progress report) and 'combination' therapy with immunce checkpoint blockade was tested in the setting of RALDH1-KO Hep55 tumors.	16-20	Haldar Lab
Subtask 2: To test single and combinatorial RA signaling blockade for HCC immunotherapy in a distinct HCC model. [10 treatment conditions X 8 mice per group X 5 overall experimental repeats = 400 mice total] Cell lines and Model: HCC-TM [Source: Simon Lab] and Immunocompetent C57BL/6J mice [Jackson Laboratory] Progress: As described above, we have done this in the Hep55 model. We are still looking for another syngeneic transplantation based model to test drug combination. Hepa 1-6 was not suitable as it induced strong T cell responses without any therapy (described in 2022 progress report). If we are not able to find another transplantation-based model, it is not a major limitation as we intend to test these in autochthonous models described below.	20-24	Haldar Lab
Subtask 3: To test single and combinatorial RA signaling blockade for HCC immunotherapy in an autochthonous murine model. [10 treatment conditions X 8 mice per group X 2 overall experimental repeats = 160 mice total] Cell lines and Model: Immunocompetent Sv129j mice [Jackson Laboratory] Progress: We have started planning these experiments. In the original review of our grant, the reviewers raised some concerns about the chemical carcinogen-based systems we had proposed. Thus, we are currently exploring additional models based on hydrodynamic tail vein injection with oncogenic plasmids – a method used by our collaborators on campus to induce aggressive HCC. We anticipate beginning testing both model types – DEN and Plasmid-based – approaches shortly.	24-32	Haldar Lab
Milestone(s) Achieved: Upon completion of Aim 2 we will have new insights into whether RA signaling blockade can be used for immunotherapy of HCC. We also anticipate publication of 1-2 peer reviewed papers and presentation of our work in 2-3 national or international meetings.	36	

What was accomplished under these goals?

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

Specific Aim 1, Major Task 1, Subtask 2

We developed a new LC/MS method that is more sensitive than our published method to measure RA in tissue (Figure 1). Moving forward, we will use this method to measure alterations in RA production in response to our inhibitors.

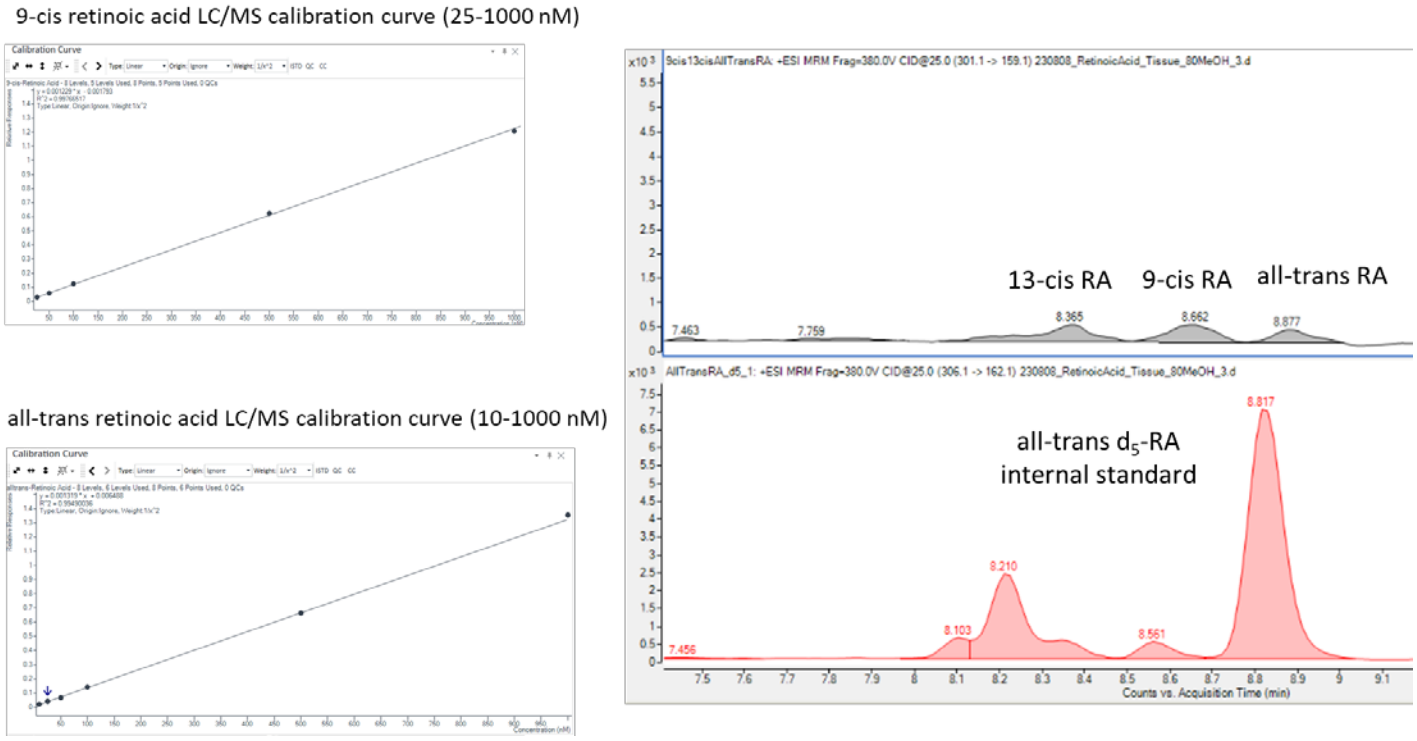
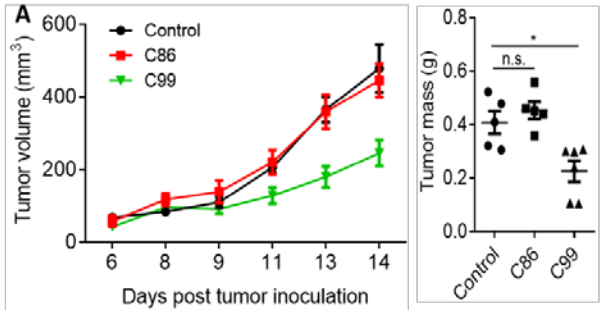


Figure 1. Liver homogenates were prepared by homogenizing 10 mg of liver in 500 uL of 80% methanol. For extraction and quantitation of RA isomers, a 100 uL aliquot of liver homogenate was spiked with 10 uL of internal standard (5000 nM d5-all-trans RA), 10 uL of 10 M HCl, and 10 uL of ascorbic acid (1 M) followed by the addition of 800 uL of acetonitrile. The samples were vortexed and centrifuged for 5 minutes at 4 degrees C. A 750 uL aliquot of the supernatant was dried down under nitrogen at 35 degrees Celsius in a 96-well plate and reconstituted with 100 uL of methanol for LC/MS. Calibration solutions for 9-cis (25-1000 nM) and all-trans RA (10-1000 nM) with d5-all-trans RA (500 nM) were similarly prepared by spiking 10 uL of concentrated solutions in 100 uL aliquots of water followed by the extraction procedure above.

An Agilent 1290 Infinity HPLC/6495B triple quadrupole mass spectrometer was used to separate RA isomers (13-cis, 9-cis, and all-trans) and quantitate 9-cis and all-trans RA. RA isomers were separated on a Waters Acquity BEH C18 1.7 um column (2.1x100 mm) using an 11 minute linear gradient of 0.1% formic acid in water (solvent A) and 30% IPA/70% acetonitrile with 0.1% formic acid (solvent B) at 0.4 mL/min coupled to the mass spectrometer. RA isomers were quantitated by multiple reaction monitoring mode and quantitated using standard linear calibration curves with Agilent MassHunter software.

Specific Aim 1, Major Task 3, Subtask 2

In our previous progress report, we identified C99 as an inhibitor that works on murine RALDH1 *in vitro*. We therefore tested this in vivo and found it to suppress murine HCC growth (Figure 2A). Nonetheless, tumor suppression with C99 was less than what we had observed for C86 on human HCC. This could be explained by the significantly inferior PK/PD characteristics of C99 (Figure 2B).



B

Raldh-INH	Route	Species	Sample	Cmax (ng/mL)	t1/2 (h)	AUC0-∞ (h•ng/mL)	Vss (L/kg)	CLp (mL/min/kg)	F (%)
C-91	IV	mouse	plasma	1997	1.3	1830	1.4	18	-
	PO	mouse	plasma	1530	2.2	6980	-	-	76
C-86	IV	mouse	plasma	2350	0.3	1141	0.7	30	-
	PO	mouse	plasma	1234	1.6	2518	-	-	44
C-99	IV	mouse	plasma	117	0.1	37	2.7	887	-
	PO	mouse	plasma	16	0.5	11	-	-	6.3

Figure 2. (A) C57BL6/J mice were implanted subcutaneously with Hepa1-6 cells and the tumor-bearing mice and treated with C86 or C99 (intraperitoneal, 20mg/kg) every day. Graph on the right shows tumor mass at end point. C99, but not C86 (human-specific), suppress murine HCC growth.(B) Plasma pharmacokinetic comparisons of C86, C91, and C99 in mice for parameters outlined in the table.

Given the inferior drug profile of C99, we refrained from using it in our *in vivo* studies to avoid underestimating the potential of RALDH1 inhibition on murine HCC immune microenvironment. Since C86 and C91 completely abrogate RALDH1 activity (shown in 2022 progress report), we reasoned that a CRISPR/Cas9-based deletion of RALDH1 gene from murine HCC would model RALDH1 inhibition. As anticipated, RALDH1 deletion leads to a profound tumor suppression (Figure 3A). Importantly, tumor suppression was associated with increased T cell infiltration and activation (Figure 3B).

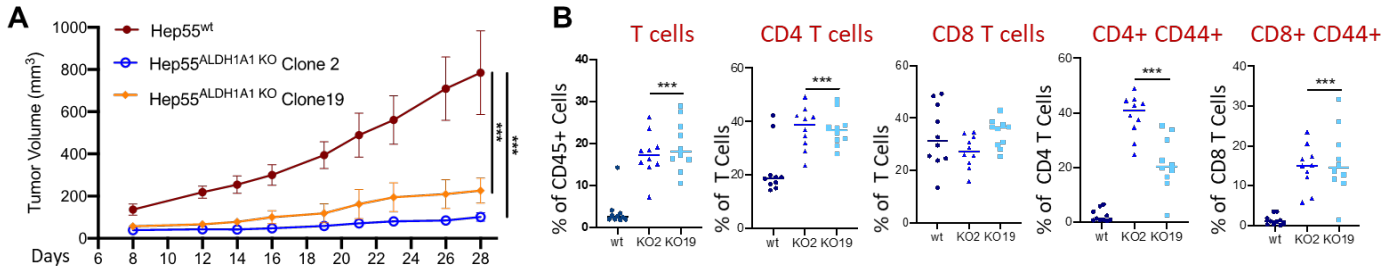


Figure 3. (A) RALDH1 was deleted with CRISPR/Cas9 in murine Hep55 HCC cell line. Two independent clones – 2 and 19 – were selected based on confirmation of gene deletion. Cell lines of indicated genotypes were implanted subcutaneously into immunocompetent syngeneic C57BL6/J mice and tumor size monitored over time. (B) Tumors from (A) were harvested at endpoint and T cell infiltration analyzed by flow cytometry for T cell characteristics.

Specific Aim 2, Major Task 5, Subtask 1

As described above and in our 2022 progress report, our inhibitors do not suppress murine RALDH1 to the same extent as human RALDH1. To overcome this, we generated RALDH1 knockout murine HCC cells to model RALDH1 inhibition in mice. As shown above, absence of RALDH1 leads to profound tumor suppression and T cell infiltration. To further examine potential synergy between RALDH1 inhibition and immune checkpoint blockade, we treated RALDH1-KO Hep55 tumors with anti-PDL1, finding further tumor suppression with immune checkpoint blockade (Figure 4). Of note, the additional suppression with anti-PDL1 was not impressive, mostly because lack of RALDH1 alone leads to a dramatic suppression. We anticipate that this synergy will be more obvious and significant when/if tested in human tumors.

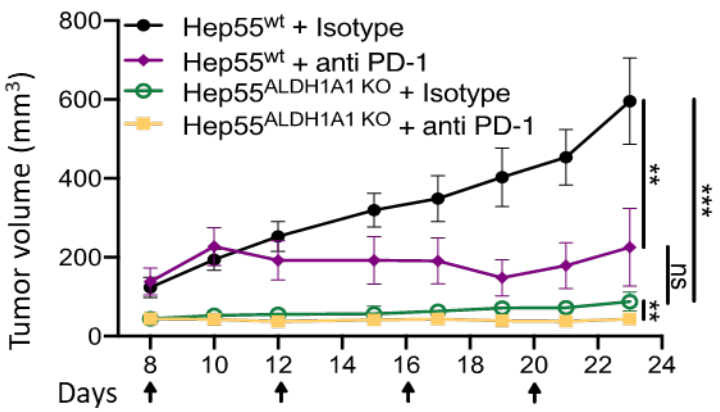


Figure 4. Graph shows growth of tumors of the indicated genotypes and treatment syngeneically transplanted into C57BL/6 mice. Of note, there is a small but significant synergy between loss of RALDH1 and anti-PD1 treatment (green vs. yellow line). Clone 2 was used for RALDH1-KO Hep55 cell line.

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

Nothing to report.

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

Nothing to report.

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

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

We have completed a significant portion of the originally proposed work. In the next and final reporting period, the major emphasis will be on testing the drugs in an appropriate autochthonous mouse model.

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

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

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

Results from this reporting period clearly highlights the promise of RALDH1-inhibitors as a new approach in the treatment of HCC. The strong supporting preclinical data has prompted us to begin thinking about a potential clinical trial in the near future.

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

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

Our results suggest that RALDH1 inhibition might be an effective therapeutic approach in other types of cancer that express high levels of this enzyme.

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

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

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

Nothing to report.

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

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

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

Nothing to report.

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

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

Nothing to report

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

Nothing to report

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

Nothing to report

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

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

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

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

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

Nothing to report. However, a manuscript described this work has been submitted and we anticipate publication in the next reporting period.

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

Nothing to report

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

Nothing to report

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

Nothing to report

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

Nothing to report

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

Nothing to report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

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

Name:	Shuwen Cao, PhD
Project Role:	Postdoctoral research associate
Researcher Identifier (e.g. ORCID ID):	79311857 (Penn ID)
Nearest person month worked:	12
Contribution to Project:	Dr. Cao planned, performed, and analyzed experiments described in this progress report.
Funding Support:	This grant (W81XWH-21-1-0592)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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

A New grant was funded by the NIH.

Title: Delineating how nucleic acid sensing in tumor cells regulate anti-tumor immune responses.
Major Goals: The goal of this grant, which is part of a larger PO1 program project, is to examine how DNA damage responses in tumor cells elicit anti-tumor immune responses.
Project Number: 1 P01 CA265794-01A1
Name of PD/PI: Roger Greenberg
Source of Support: National Cancer Institute (NCI), NIH
Project/Proposal Start and End Date: 04/01/2023 – 03/31/2028
Total Award Amount (including Indirect Costs): $915,000 (Dr. Haldar's allocation, direct)
Effort for Dr. Haldar (Person Months): 1.2 calendar months.

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

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

Provide the following information for each partnership:

Organization Name: National Center for Advancing Translational Sciences (NCATS)
Location of Organization: NIH, Bethesda, MD, USA
Partner's contribution to the project: Synthesize and provide RALDH1 inhibitors used in this project.

8. SPECIAL REPORTING REQUIREMENTS

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

Nothing to report.

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