AWARD NUMBER: W81XWH-19-1-0612

TITLE: Precision Oncology-Based Therapeutic Targeting in Mesothelioma

PRINCIPAL INVESTIGATOR: Mark Klein

CONTRACTING ORGANIZATION: Center for Veterans Research and Education

REPORT DATE: Sept 2020

TYPE OF REPORT: Annual

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

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1. REPORT	**2. REPORT TYPE**	**3. DATES COVERED**
Sept 2020	Annual	8/15/2019 – 8/14/2020

4. TITLE AND SUBTITLE

Precision Oncology-Based Therapeutic Targeting in Mesothelioma

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5b. GRANT NUMBER
W81XWH-19-1-0612

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Mark Klein

E-Mail: mark.klein2@va.gov

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Minneapolis VA Healthcare System
1 Veterans Dr., 151
Minneapolis, MN 55417

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

Purpose: Given that mesothelioma nearly universally exhibits cell cycle abnormalities and the cell cycle interacts with multiple pathways important to the growth of mesothelioma, disruption of the cell cycle presents as a likely effective approach (or will contribute to a multiple pathway-targeted combination approach) to treating mesothelioma clinically. Our hypothesis is that combined inhibition of 1) multiple cell cycle proteins, and 2) one of 3 separate and alternative molecular pathways will serve as an effective therapy against multiple molecular subtypes of mesothelioma.
Scope: We are utilizing in vitro and in vivo studies to evaluate how to best target molecular subtypes of mesothelioma.
Major Findings: We have determined in multiple cell lines that cell cycle inhibitors (dinaciclib, abemaciclib, palbociclib) and inhibitors of antioxidant defense (gentian violet and auranofin) have significant activity against mesothelioma in vitro.

15. SUBJECT TERMS

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	19	**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.*

Mesothelioma is a devastating cancer with a poor prognosis. Defects in cell cycle machinery are the most common molecular feature of mesothelioma tumors. Low expression of the CDK4/CDK6 inhibitor and tumor suppressor p16INK4a has been demonstrated in multiple basic and clinical studies of mesothelioma, affecting up to 90% of all tumors. The cell cycle machinery also interacts with other important targetable pathways within the cell, most notably the 1) PI3K/MTOR pathway, 2) mitochondrial antioxidant defense system, and 3) immune checkpoint system. In this research, we are utilizing in vitro and in vivo studies, as initially informed by genomic and molecular phenotypic information supplied by The NIH Cancer Genome Atlas program, to evaluate how to best target molecular subtypes of mesothelioma.

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

mesothelioma, cyclin-dependent kinase (CDK), cell cycle, mitochondrial antioxidant defense, immune checkpoint, phosphoinositide 3-kinase (PI3K), mammalian target of rapamycin (MTOR)

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.

Specific Aim 1. To determine the mechanisms by which cell cycle-specific proteins and interacting major molecular pathways contribute to mesothelioma cell survival and the most optimal cell cycle protein combination to target. (50%)

Major Task 1: Evaluate the mechanisms of CDK4/6 inhibition and prevention or rescue of resistance to CDK4/6 inhibition via CDK2 inhibition by examining the immune system and tumor microenvironment response. Months 1-12. (75%)

Major Task 2: Evaluate whether CDK4/6 inhibition enhances tumor antigen and immune cytokine expression. Months 12-18. (50%)

Specific Aim 2. To evaluate the mechanism by which select major molecular pathways overcome cell cycle inhibition and identify the most effective combination of agents to treat mesothelioma in these molecular subtypes. (0%)

Major Task 3: Determine effects of CDK2 and CDK4/6 inhibitors on T cells in vitro and in vivo. Months 12-18. (0%)

Major Task 4: Determine the efficacy of combined CDK4/6 and immune checkpoint inhibition in a syngeneic mesothelioma xenograft. Months 9-18. (0%)

Major Task 5: Determine the efficacy of combined CDK2 and immune checkpoint inhibition in a syngeneic mesothelioma xenograft. Months 12-18. (0%)

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.

Major activities - Major Tasks 1 and 2

We have dedicated the time predominantly to in vitro experiments in specific aim 1. This has included numerous proliferation assays to evaluate in a robust fashion (with experiments conducted in multiple replicates) dinaciclib, auranofin, gentian violet, palbociclib, and abemaciclib. This has included multiple cell lines, including 4 mesothelioma cell lines plus non-malignant cell line Met5A. In addition, we've conducted numerous immunoblot experiments to evaluate protein expression.

Specific Objectives

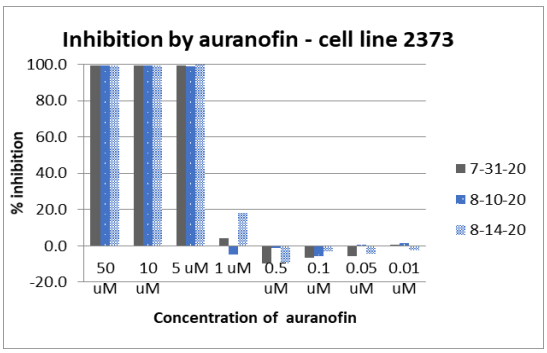
Specific Aim 1. To determine the mechanisms by which cell cycle-specific proteins and interacting major molecular pathways contribute to mesothelioma cell survival and the most optimal cell cycle protein combination to target.

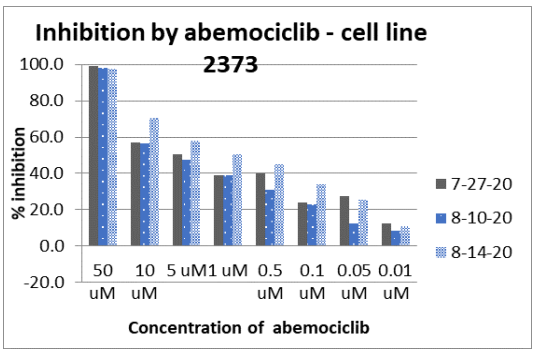
Specific Aim 2. To evaluate the mechanism by which select major molecular pathways overcome cell cycle inhibition and identify the most effective combination of agents to treat mesothelioma in these molecular subtypes.

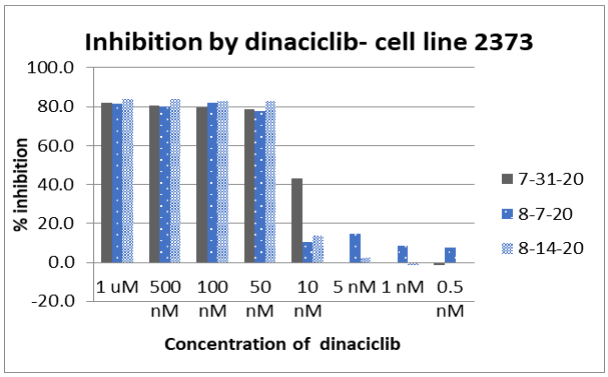
Methodology Proliferation assays in 96 well plates will be performed using a CCK-8 viability assay. At 24-72 hrs after treatment with palbociclib, abemaciclib, dinaciclib, auranofin, or gentian violet, cells (H2052, H2373, H2452, and Met5A) were incubated with CCK-8 for 2 h at 37 °C and the absorbance relative to media alone were determined. All experiments were done in triplicate and analyzed for the IC50. Multiple western blots have been performed on CDKs, cyclins, Trx2, and related proteins. In addition, abemaciclib (other drugs currently under evaluation) at the IC_{50} concentration were be added to cells, and 24-72 h post–treatment the % of the cells in G_0/G_1, S, and G_2 will be determined by propidium iodide (PI) staining and FACS analysis to determine the effects on the cell cycle.

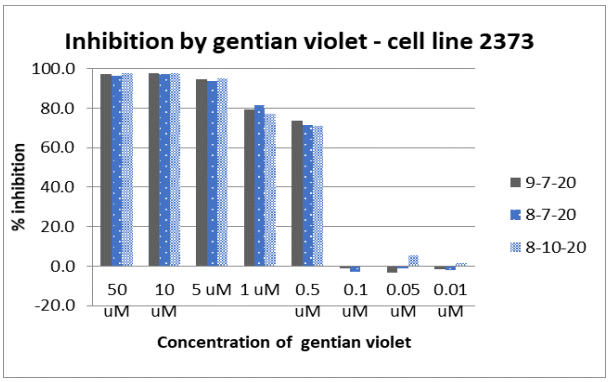
Significant results/key outcomes

First, we confirmed potency of dinaciclib, auranofin, gentian violet, palbociclib, and abemaciclib against cell lines H2052, H2373, H2452. Example IC50s for these include against H2373 cells lines as follows: abemaciclib 4.67 μM, palbociclib 17.63 μM, dinaciclib 18.15 nM, and gentian violet 305.2 nM. Results from other cell lines are similar. Example proliferation curves are provided here for H2373 cell lines and similar for H2052 and H2452.

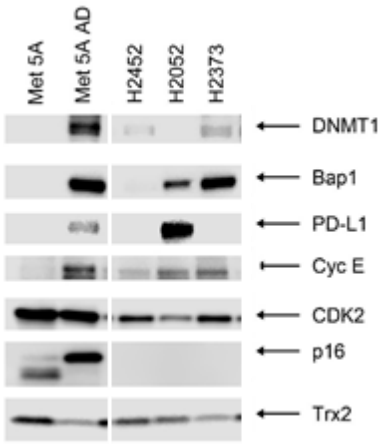






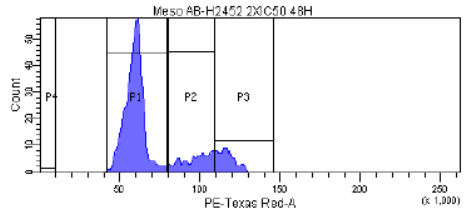


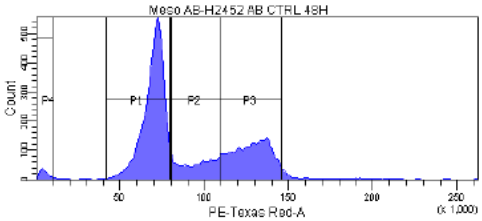
Here is an example of immunoblotting of mesothelioma cells in various cell lines (several additional proteins are being analyzed, but the blots are not ready for presentation yet). (As part of our tissue culture work, we modified culture conditions for Met5A cells as compared with that of the literature. We noted that growth rates were much improved and had a protein expression closer to that of mesothelioma cell lines.) Interestingly, and as hypothesized, DNMT1 expression was elevated in cell lines without PD-L1 expression and may correlate with CDK2 expression. Differences in PD-L1 expression between cell lines We verified that p16 expression was not present in any of the malignant cell lines. Trx2 (relevant for antioxidant defense) was present in all cell lines, providing support for a potential mechanism of action for gentian violet and auranofin.



Lastly, we are in the midst of flow cytometry analyses in cells treated with drugs listed above. An example in 2373 cell lines for the effects of abemaciclib is presented here, suggesting that abemaciclib does increase cell cycle arrest (control on the left, cells treated with twice the IC50 on the right, in 2452 cell lines).

H2452	CONTROL	IC50 48H	2 X IC50 48H
G1	52.9%	60.3%	69.3%
S	12.3%	11.9%	15.4%
M	29.4%	24.1%	13.4%





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

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report.

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

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

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

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

We have committed to submit a manuscript in preparation now to the journal Antioxidants by December 31 after recent discussions. In addition, we will submit a manuscript detailing results from Specific Aim 2 activities in spring 2021. We currently have our full complement of personnel and will conduct our first animal experiment in fall 2020. The second will be conducted in spring 2021. At this time, we feel that with COVID-related restrictions lifted, we can continue on the current trajectory to achieve the major tasks listed. If not, we would then ask for a no-cost extension after re-assessing our work product in spring 2021.

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).

Of note, we have further confirmed in addition cell lines the potency of palbociclib, abemaciclib, auranofin, and gentian violet. In addition, the finding that dinaciclib has an IC50 of around 20 nM was a bit unexpected. This is more potent and active than we anticipated, suggesting that this finding may be more clinically applicable than we had anticipated.

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

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

Nothing to Report.

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

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

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

Nothing to Report.

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

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

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

Nothing to Report.

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

We had a second grant in mesothelioma funded by the Veterans Affairs Office of Research and Development after starting the current DOD award. The aims of the VA grant were provided to the CDMRP Science Officer assigned to our award. We adjusted the Statement of Work slightly to assure there was no scientific or budgetary overlap. The new Statement of Work was approved, and we are working to achieve the goals set forth in that document.

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.

In March 2020, COVID-19 caused change in some policies at our VA facility. Our research lab space is located within the Minneapolis VA Medical Center, with animal facilities in a building nearby joined by a tunnel. Due to numerous demands for this emergency, I was required to conduct telework part of the time. For about 1-2 months, our laboratory personnel were teleworking part of the time due to concerns and unknowns about the virus. Early in the pandemic, one of our research personnel was out for at least 2 weeks for a COVID-19-like illness. At that time, there was a severe shortage in tests, so it was assumed it was COVID-19 based on clinical symptoms. In addition, for about 2 months our Animal Facility paused all new animal experiments due to COVID-19. Lastly, there was a multiple month delay in having our IAUCU animal protocol approved due to the complexity of our animal protocols. Currently, all the above delays are now over. However, some delays from lab supplies are still occurring. Namely, the company IDT, a normally robust supplier of RT-PCR probes and related materials has had delays due to COVID-19. This has delayed our RT-PCR experiments.

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.

We had some delays in hiring due to a combination of staff availability and HR process. Hiring dates are as follows:
George Scaria 9/23/2019
Betsy Kren 12/30/2019
Marian Kratzke 3/11/2020
Steph Porter 1/26/2020

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

IACUC approval date: 1/13/2020
As part of our revised SOW, we added human T cell experiments. We obtained a review from the IRB director at the Minneapolis VA Healthcare System. The direct stated that since we were purchasing the human T cells from a commercial vendor and the cells are not identifiable (we do not know who donated them), a formal review was not recommended. The IRB director provided a letter stating this. We filled out the request form, and it is under review by CDMRP. Cells will be purchased from AllCells, Inc.

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.

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

Nothing to report.

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

Nothing to Report.

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

Nothing to Report.

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

Nothing to Report.

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

Nothing to Report.

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

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	Mark Klein
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Dr. Klein is the PI on the project.
Funding Support:	The PI salary is provided by the Minneapolis VA Healthcare System.

Name:	Betsy Kren
Project Role:	co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Dr. Kren is a co-investigator. She works closely on animal experiments and immunblotting with Steph Porter. She also conducts the RT-PCR experiments.
Funding Support:	All effort on this project is supported by this DOD award.
Name:	George Scaria
Project Role:	Biologic Research Scientist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	9
Contribution to Project:	Dr. Scaria aids in animal experiments and conducts multiple in vitro experiments, including proliferation assays, flow cytometry, and apoptosis assays. He will be conducting the T-cell work.
Funding Support:	All effort on this project is supported by this DOD award.
Name:	George Scaria
Project Role:	Biologic Research Scientist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	9
Contribution to Project:	Dr. Scaria aids in animal experiments and conducts multiple in vitro experiments, including proliferation assays, flow cytometry, and apoptosis assays. He will be conducting the T-cell work.
Funding Support:	All effort on this project is supported by this DOD award.
Name:	Marian Kratzke
Project Role:	Biologic Research Scientist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Dr. Kratzke predominantly conducts in vitro experiments, including a bulk of the proliferation assays. She also prepares cells for animal experiments.
Funding Support:	All effort on this project is supported by this DOD award.
Name:	Stephan Porter
Project Role:	Biologic Research Scientist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Dr. Kratzke predominantly conducts in vitro experiments, including a bulk of the proliferation assays.

Name:	Khalil Ahmed
Project Role:	co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	Dr. Ahmed is a co-I on the project and provides regular input into experimental design and interpretation.
Funding Support:	The co-I salary is provided by the Minneapolis VA Healthcare System.
Name:	Robert Kratzke
Project Role:	co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	Dr. Kratzke is a co-I on the project and provides regular input into experimental design and interpretation. His lab also provides cell lines and experimental expertise as available.
Funding Support:	The co-I salary is provided by the University of Minnesota.

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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.

The following grant has ended for Dr. Klein.

The Randy Shaver Cancer Research and Community Fund
Grant
Title: Enhancing Immunotherapy Against Mesothelioma
PI: Mark Klein, M.D.
Percent Effort: 1.2 calendar months
Amount: $25,000
Dates: 02/01/2018-01/30/2020

The following 2 grants are new for Dr. Klein as PI. There is no scientific or budgetary overlap for each (the first had in the past – but the re-worked SOW on the current DOD award was approved to ensure that is not the case currently).

Veterans Affairs
BLR&D Merit Award
Title: Combinatorial Targeting of the Cell Cycle and Key Interacting Pathways in Mesothelioma
PI: Mark Klein, M.D.
Percent Effort: 3 calendar months
Amount: $200,000 year 1
Dates: 2/12/2020 – 2/11/2024

Cellworks, Inc.
Study Support
Title: Prediction of Optimal Personalized Treatment for Veterans with Non-Small Cell Lung Cancer (NSCLC)
Co-PI: Mark Klein, M.D.
Percent Effort: 0.6 calendar months
Amount: $205,353 for Minneapolis site
Dates: 09/01/2019-08/31/2022

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

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

Provide the following information for each partnership:
Organization Name:

Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

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

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

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