AWARD NUMBER: W81XWH-14-1-0342

TITLE: Development of Cytomegalovirus-Based Vaccines Against Melanoma

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
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Development of Cytomegalovirus-Based Vaccines Against Melanoma

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The presence of tumor infiltrating CD8+ T cells is associated with tumor regression. Cytomegalovirus (CMV) infection elicits a robust and long-lasting CD8+ T cell response, which makes CMV a potentially promising vaccine vector against cancer. In the last funding period, we used recombinant murine CMV (MCMV) strains as prophylactic and therapeutic vaccines in an aggressive Bl6 lung metastatic melanoma model. We engineered MCMV to express a modified Bl6 melanoma antigen gpl00 (MCMV-gpl00KGP). Immunization with MCMV-gpl00KGP was highly effective in overcoming immune tolerance to self-antigen and induced a strong, long-lasting gpl00-specific CD8+ T cell response even in the presence of pre-existing CMV immunity. Furthermore, both prophylactic and therapeutic vaccination of mice with MCMV-gpl00KGP effectively protected mice from highly aggressive lung Bl6-F10 melanoma. Collectively, our studies demonstrated that CMV is a promising vaccine vector to prevent and treat tumors.
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**INTRODUCTION:** Melanoma is a malignant tumor of melanocytes, accounting for majority of the deaths due to skin cancer. The primary treatment of patients with cutaneous metastasized melanoma is surgical excision or chemotherapy. Cytotoxic CD8 T cells are crucial in the defense against cancer, thus vaccination aimed at generating a large number of functional effector and memory CD8 T cells specific to tumor antigens has become the principle goal of immunotherapy. Cytomegalovirus (CMV) belongs to herpesviridae family and establishes a lifelong, asymptomatic infection in immunocompetent hosts. CMV infection induces a strong inflammatory innate immune response, which is followed by a robust CD8 T cell expansion. Interestingly, in mice and in humans, long after the establishment of latency several CMV specific CD8 T cell populations continue to proliferate for the life of the host, a process called T cell inflation. A large percentage of these 'inflationary' CD8 T cells are functional as exhibited by their ability to secrete multiple cytokines. The inflationary CD8 T cell populations are widely distributed in lymphoid and non-lymphoid organs such as lung, liver and the brain. A remarkable characteristic of CMV infections is that a robust superinfection is observed despite the presence of CMV-specific immunity. Furthermore, CMV vectors can be effectively used to prime a diverse repertoire of antigen specific CD8 T cell populations. The overall hypothesis to be tested in this proposal is that the aforementioned unique properties of CMV infection make CMV an excellent vaccine candidate against melanoma.

**KEYWORDS:** Melanoma, Tumor, Vaccine, Cytomegalovirus, Tumor Immunology

**ACCOMPLISHMENTS:**

What were the major goals of the project?

**Major Goal 1.** To generate and determine the efficacy of CMV-based tumor vaccines that express single or multiple tumor antigens for immunization against melanoma and determine the efficacy of CMV-based tumor vaccines that express single or multiple tumor antigens (timeline 1-12 months)

65% of the goals above have been accomplished. A vaccine with a single epitope was generated and its efficacy was tested. However, a vaccine that expresses multiple epitopes is currently being generated and its efficacy will be tested.

**Major Goal 2:** To determine the mechanisms of protective immunity provided by CMV-based tumor vaccines (10-24 months)

60% of the task is completed. We have tested the mechanisms that are responsible for this protection. However, if the mechanisms are similar in the multiple epitope vaccine is not known yet. In addition, we have yet to use the spontaneous model (BRAF-10) of melanoma for our vaccine studies.

<table>
<thead>
<tr>
<th>Specific Aim 1(specified in proposal)</th>
<th>Timeline</th>
<th>Site 1</th>
</tr>
</thead>
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<tr>
<td>To generate and determine the efficacy of CMV-based tumor vaccines that express single or multiple tumor antigens for immunization against melanoma</td>
<td>1-12 Months</td>
<td>Dr. Khanna (650 mice used in first year)</td>
</tr>
</tbody>
</table>
**Major Task 1: Determine the efficacy of CMV-based tumor vaccines that express single or multiple tumor antigens.**

<table>
<thead>
<tr>
<th>Subtask 1: Determine the functional capacity of CD8 T cells that are generated after vaccination by determining the ability of tumor specific CD8 T cells ability to secrete cytokines and kill target cells.</th>
<th>Months</th>
<th>Dr. Khanna (total 500 mice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice used: WT C57Bl/6 and the studies will be confirmed by using the Braf/Pten and Pten$^{lox/lox}$</td>
<td>1-8</td>
<td></td>
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<tr>
<th>Subtask 2: Generate a CMV based vaccine that expresses multiple tumor antigens: using MCMV BAC methods we will insert another B16 tumor antigen (i.e. TRP-2 ). Virus will be generated by transfecting the recombinant BAC into mouse embryonic fibroblast cells. and then test if the new CMV based vaccine containing 2 antigens is better that a CMV vaccine that expresses 1 antigen. Efficacy will be examined in mice by vaccination at 7, 14, and 21 days after tumor induction through monitoring tumor incidence, size, survival kinetics, and metastasis.</th>
<th>Months</th>
<th>Dr. Khanna (total 50 mice)</th>
</tr>
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<tbody>
<tr>
<td>Mice used: WT C57Bl/6 and the studies will be confirmed by using the Braf/Pten and Pten$^{lox/lox}$</td>
<td>4-10</td>
<td></td>
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</table>

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<tr>
<th>Subtask 3: determine if immunization offer long-term protection against melanoma. Mice that are protected after vaccine inoculation will be challenged again by secondary B16 tumors and their ability to clear tumors will be assessed by monitoring tumor incidence, size, survival kinetics, and metastasis.</th>
<th>Months</th>
<th>Dr. Khanna (total 50 mice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice used: WT C57Bl/6 and the studies will be confirmed by using the Braf/Pten and Pten$^{lox/lox}$</td>
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<tr>
<th>Subtask 4: Determine if the presence of latent/persistent virus and T cell inflation required to achieve long term tumor protection by generating VSV based vectors that contain the same tumor antigen gp-100. The experiments in subtask 1 will be repeated with the VSV based vaccine to compare tumor protection provided by MCMV based vaccines vs. VSV based tumor vaccines - ability to clear tumors will be assessed by monitoring tumor incidence, size, survival kinetics, and metastasis.</th>
<th>Months</th>
<th>Dr. Khanna (total 100 mice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice used: WT C57Bl/6 will be used for these studies and if needed the results will be confirmed by using the Braf/Pten and Pten$^{lox/lox}$</td>
<td>1-12</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Milestone(s) Achieved: Develop and test CMV based vaccine and determine the efficacy of these vaccines to</th>
<th>Months</th>
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<td>12</td>
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Specific Aim 2

<table>
<thead>
<tr>
<th>Specific Aim 2: To determine the mechanisms of protective immunity provided by CMV-based tumor vaccines</th>
<th>10-24</th>
</tr>
</thead>
</table>

Major Task 1: To determine how the CMV based vaccines provide the protection against tumors.

<table>
<thead>
<tr>
<th>Subtask 1: Determine if B cells are required: B cells will be depleted by antibody treatment prior to immunization and then tumor growth will be measured by monitoring tumor incidence, size, survival kinetics.</th>
<th>Months</th>
<th>Dr. Khanna (total 100 mice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice used: For these studies we will primarily use WT C57Bl/6 since the Braf/Pten and Pten&lt;sup&gt;lox/lox&lt;/sup&gt; system is complicated and very expensive. Since these studies will confirm the mechanisms that are at play we will try and limit the use of Braf/Pten and Pten&lt;sup&gt;lox/lox&lt;/sup&gt; mice.</td>
<td>10-12</td>
<td>---</td>
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<tr>
<th>Subtask 2: Determine if the protection is mediated by CD8 T cells, and is CD4 T cell help required: CD8 and CD4 T cells will be depleted by antibody administration in mice and mice will be challenged with tumors, and tumor growth will be measured by monitoring tumor incidence, size, survival kinetics.</th>
<th>Dr. Khanna (total 250 mice)</th>
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<tbody>
<tr>
<td>Mice used: For these studies we will primarily use WT C57Bl/6 since the Braf/Pten and Pten&lt;sup&gt;lox/lox&lt;/sup&gt; system is complicated and very expensive. Since these studies will confirm the mechanisms that are at play we will try and limit the use of Braf/Pten and Pten&lt;sup&gt;lox/lox&lt;/sup&gt; mice.</td>
<td>12-18</td>
</tr>
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### Subtask 3: Can the vaccine efficacy be improved by using combination therapy?

Mice will be immunized with vaccines and at the same time receive checkpoint inhibitor therapy to block PD-1 and/or CTLA-4 by administering antibodies against PD-1 and CTLA-4. Tumor growth will be measured by monitoring tumor incidence, size, survival kinetics following combination therapy treatment..

Mice used: For these studies we will primarily use WT C57Bl/6 since the Braf/Pten and Pten\(^{lox/lox}\) system is complicated and very expensive. However, for these experiments we will confirm our findings by using the Braf/Pten and Pten\(^{lox/lox}\) mice.

### Milestone(s) Achieved

Identification of the immune cell type most responsible for providing tumor protection following vaccination. In addition, identifying which combination therapy works best for enhancing tumor vaccine efficacy.

| Dr. Khanna (total 300 mice) | 16-24 |

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### What was accomplished under the goals (only for the second year):

**Subtask 2: Generate a CMV based vaccine that expresses multiple tumor antigens:** Using MCMV BAC methods we will insert another B16 tumor antigen (i.e., TRP-2). Virus will be generated by transfecting the recombinant BAC into mouse embryonic fibroblast cells, and then test if the new CMV based vaccine containing 2 antigens is better than a CMV vaccine that expresses 1 antigen. Efficacy will be examined in mice by vaccination at 7, 14, and 21 days after tumor induction through monitoring tumor incidence, size, survival kinetics, and metastasis.

We have generated 2 BAC's. One contained an altered gp100 epitope and the unaltered sequence for the mouse TRP2 epitope (MCMVgp100KGP-Trp2). The second contained the altered gp100 epitope and an altered TRP2 epitope (MCMVgp100KGP-Trp2-2m). The two melanoma epitopes were separated by an Internal Ribosomal Entry Sequence to ensure independent translation from a single mRNA transcript. *(Figure A)*

![Figure A: schematic depicting the dual tumor antigen vector](image)
This process took 5-6 months. We validated the BAC sequence by restriction digest (Figure B) and DNA sequencing before transfecting the viral genome into Mouse Embryonic Fibroblasts (MEFs) to produce infectious virus. We were able to generate productive virus from both BACs.

![Restriction digest](image)

**Figure. B: Restriction digest to show that the vector was inserted in the right manner. The arrows point to the expected bands**

<table>
<thead>
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<th>M: Marker</th>
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<tbody>
<tr>
<td>A: MCMVgp100KGP</td>
</tr>
<tr>
<td>B: MCMVgp100KGP-Trp2</td>
</tr>
<tr>
<td>C: MCMVgp100KGP-Trp2-2M</td>
</tr>
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</table>

However, Western blot of infected MEFs suggested that MCMVgp100KGP-Trp2-2M was not expressing the Trp2 protein. MCMVgp100KGP-Trp2, in contrast, did appear to express the unaltered Trp2 protein. **Figure C.** Nonetheless, we continued to test these viruses for antitumor activity for 2 reasons: A) we have had difficulty detecting ova expression by MCMV-ova in this assay despite potent antitumor responses following vaccination. B) Previous literature suggests that MCMV vectors expressing unaltered Trp2 may also generate antitumor B cell responses (Xu et al. Biochem Biophys Res Commun. 2013 Jul 26;437(2):287-91). We tested these two combination viruses against the single epitope virus in the metastatic lung model. Mice receiving MCMVgp100KGP-Trp2-2M or MCMVgp100KGP-Trp2 showed similar tumor burden to MCMVgp100KGP. **Figure D.**
This was confirmed in an intradermal solid tumor model as outlined below. However, the data was similar to what is shown in Figure D (data not shown). Although, previous literature has suggested that MCMV vectors expressing unaltered Trp2 could delay tumor growth, our experiments suggest that addition of this antigen to MCMVgp100KGP does not enhance tumor protection. MCMVgp100KGP-Trp2-2M likely did not influence enhance tumor protection due to the low expression of the altered epitope. Whether this low expression was a direct result of the mutated Trp2 peptide is still unknown.

Subtask 3: determine if immunization offer long-term protection against melanoma. Mice that are protected after vaccine inoculation will be challenged again by secondary B16 tumors and their ability to clear tumors will be assessed by monitoring tumor incidence, size, survival kinetics, and metastasis.

As discussed in our initial publication, MCMVgp100KGP protects mice from B16 tumor challenge 7 and 25 days following vaccination. Mice receiving vaccination developed fewer tumor nodules upon intravenous injection of B16 melanoma. Mice also survived longer following vaccination and tumor challenge. However, the mice lived longer but none of the mice survived. And thus, this task cannot be completed and is moot.

**Major Goal 2: To determine the mechanisms of protective immunity provided by CMV-based tumor vaccines (10-24 months)**
Subtask 3: Can the vaccine efficacy be improved by using combination therapy: Mice will be immunized with vaccines and at the same time receive checkpoint inhibitor therapy to block PD-1 and/or CTLA-4 by administering antibodies against PD-1 and CTLA-4. Tumor growth will be measured by monitoring tumor incidence, size, survival kinetics following combination therapy treatment.

For this task, we tested whether antibodies to PD-1 or CTLA-4 would enhance the efficacy of MCMVgp100KGP. This task was tested in the intradermal B16 solid tumor model. Mice were inoculated with B16F10 and 3 days later were vaccinated with MCMVgp100KGP. For one experiment, mice were treated with anti-PD-1 on Days 3, 6, and 9. In another experiment, mice were treated with anti-CTLA-4 on Days 6, 9, and 12. Neither combination regimen significantly delayed tumor growth. *Figure E.*

Answers to specific questions raised during the review process:

Q1. Can you please justify why you feel reporting on the CD8+ T cell response from MCMV-OVA immunized mice is relevant to a project that is funded for the generation and characterization of virus expressing gp100(KPG) and/or TRP2 epitopes? Especially when CD8+ T cell response for your duel epitope expressing virus was not presented. Work utilizing MCMV-OVA was not in the approved SOW and I would like to remind you that prior approval is required if DoD funding is to be used for work outside of the outlined SOW tasks. PLEASE only report on those tasks for which DoD funding was used, or make clear that other funding sources were employed for the accomplishment of these tasks.

A1. We did not report on studies using MCMV-OVA. The only MCMV-OVA data was used in the original grant as preliminary data. In the current progress report we merely mentioned that in the past "we have had difficulty detecting ova expression by MCMV-ova in this assay despite
potent antitumor responses following vaccination", and thus, we still used the dual expressing virus that we had created (that expresses gp100 as well as, TRP2) in anti-tumor assays in spite of the fact that by western blotting we had difficulty detecting TRP2 expression. Since the genetic analysis of the virus clearly showed that TRP2 gene was in the right frame in the recombinant virus.

Q2. One of the major goals of the funded work was to compare the effect of a single epitope containing virus versus a dual epitope virus. However, from the experiments performed and data reported, it doesn't seem possible to make this comparison. Do you plan to include a more compelling comparison of the anti-tumor activity of the three viruses in your final report?

A2. As shown in Figs. A to D, we did construct this virus (which was a challenge and took a lot of effort and time), but the efficacy of the virus for tumor protection was not any better than KGP virus alone. As a result we did not perform too many more experiments with this virus. However, we do plan to test it with other single virus vectors. We are doing that now.

Q3. Furthermore, will you be using your duel epitope virus for Major Goal 1 Subtask3? I understand the rationale for not following through with this subtask for the single epitope virus as the mice did not live long enough to complete the task; however, I see no report on what happened with your duel epitope expressing virus.

A3. In the subtask 3 we had proposed the following:

"determine if immunization offer long-term protection against melanoma. Mice that are protected after vaccine inoculation will be challenged again by secondary B16 tumors and their ability to clear tumors will be assessed by monitoring tumor incidence, size, survival kinetics, and metastasis".

Indeed, even after we use the single epitope virus the mice failed to clear the tumors completely and thus, none of the mice live long enough to carry out these studies.

Q4. Can you please provide me with your plan for how you will utilize the Braf/Pten and Pten floxed mice in the coming months to finish the requirements within your SOW? There has been a large percent of the award budget set aside for the use of these mice and we will need to see results from these experiments.

A4. Indeed these mice were very expensive and were purchased from JAX labs. We have performed initial experiments with these mice. Although, experiments with these mice have been challenging and we are currently determining how to deal with the challenges. The challenge with these mice in our facility has been the fact that they appear to be 'leaky'. As in, some mice show tumor growth even when they are not treated with Tamoxifan. This issue has caused a substantial delay and we have had to use a fair amount of mice in order to perform the experiments that we proposed. Currently, we are using these mice and have begun to perform protection studies in this mice. This is part of our "no cost extension" proposal.

Q5. As you have not provided an update in your second annual report for what you plan to accomplish in the in the next reporting period. I would request that you include that now.

A5. We will be performing the following studies in the no-cost extension period:
• Test our vaccine for the spontaneous model of melanoma (B6.Cg-Braf tm1Mmcm Ptentm1Hwu Tg(Tyr-cre/ERT2)) We are performing both prophylactic as well as therapeutic studies.
• As shown above we have constructed a virus that expresses two tumor epitopes (GP100 and TRP2). We are now comparing the efficacy of this new vaccine to other single epitope virus vectors.

Q6. can you please also clarify the AIMS of the SPARK Technology Commercialization Fund award the you received.

A6. The spark award is based on completely different studies unrelated to the DOD award:

C. difficile is a spore forming, gastrointestinal pathogen that is the leading cause of nosocomial infections in developed nations. C. difficile causes antibiotic-associated colitis and intestinal inflammatory disease. The C. difficile pathogen can affect elderly patients in particular during hospitalizations that lead to severe C. difficile associated diarrhea and pseudomembranous colitis with case-fatality rates of up to about 10%. Each year more than 3 million cases of C. difficile-associated diarrhea are reported in the US alone with health care costs exceeding $3 billion annually. Because C. difficile forms spores that are extremely difficult to remove from institutional settings such as hospitals and nursing homes, a source of new infections is nearly always present. It is estimated that 1–3% of all hospitalized patients treated with antibiotics become infected with C. difficile. While the elderly are still most affected, C. difficile associated disease has been reported in what have been considered traditionally “low risk” humans, such as healthy persons in the community, peripartum women and children. Most disturbingly, hyper-virulent and antibiotic–resistant strains have emerged in the last several years that are associated with increased morbidity, mortality and recurrence rates of antibiotic resistant strains of C difficile. Replication-proficient virus-like vesicles (VLVs), a technology recently developed by CaroGen Corporation, offer a transformative platform for the development of novel vaccines. VLVs are lipid-enveloped nanoparticles that can be engineered to express multiple disease antigens and stimulate a powerful humoral and cellular immune response. The platform technology has been validated in the HIV and in chronic hepatitis B virus disease models and will be exploited to develop a vaccine for C. difficile. Specifically in this proposal we seek to test in mice the immunogenicity and efficacy of a panel of recombinant C. difficile candidate we have recently generated in VLVs. These fusion proteins, ranging in size from 50 to 158 kda, are secreted into the culture supernatant. These data suggest that the VLVs are likely to drive strong, conformational-dependent antibody responses.

Thus the specific aims of this project are:
1. To characterize the immune response to VLV vectors in mice
2. To evaluate the efficacy of these vaccines in appropriate mouse challenge model after C. difficile infection.

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

- Tasleem Samjee received training in tumor immunology and molecular biology under this grant.
- The PI is planning on attending the Society of Immunotherapy of Cancer (SITC 2015) meeting in Maryland in November of this year.
- The PI (Kamal Khanna) has been in close touch with Dr. Mary Jo Turk (Dartmouth) who is the designated collaborator. We have discussed the results and future
plans. She has been instrumental in helping us to start the experiments with the mouse model of spontaneous melanoma. Working with this model can be challenging and her help has been critical. She has also advised the PI regarding career issues in the field of Tumor Immunology.

How were the results disseminated to communities of interest?

- Our results were published in an article in Cancer Immunology Research in January 2015.
- Our more recent results in the intradermal model were also disseminated in a research poster at the National MD/PhD Student Conference in July 2015.

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

During the next few months, we will be concluding our experiments using anti-PD-1 and anti-CTLA-4 therapies in combination with MCMVgp100KGP in an intradermal melanoma model. We will also perform these experiments using a model of metastatic melanoma. In addition, in the next few weeks, we will be validating our BAC containing gp100KGP and the modified Trp2 epitope and generating our MCMV expressing both altered gp100 and altered Trp2. Once generated, we will test this combination virus to determine if it is more effective than MCMVgp100KGP.

IMPACT:

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

- In this proposal, we have generated a potential new therapy for melanoma. Our studies have shown that MCMV expressing tumor antigens can generate potent, long-lasting antitumor immunity. In the future, this technology may be applied to human CMV and may be an effective immunotherapy for melanoma and other cancers.

What was the impact on other disciplines?

- Nothing to Report

What was the impact on technology transfer?

- Nothing to Report

What was the impact on society beyond science and technology?

- Nothing to Report

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

PRODUCTS:

Publications, conference papers, and presentations

Journal publications.


Other publications, conference papers, and presentations.

Grenier JM, Qiu Z, Marcin G, Khanna KM. Improving Novel Cytomegalovirus-Based Vaccine for the Treatment of Localized Melanoma. Poster Presentation. 2015 National MD/PhD Student Conference, Keystone, CO.


Website(s) or other Internet site(s)
- Nothing to Report

Technologies or techniques
- Nothing to Report

Inventions, patent applications, and/or licenses
- Nothing to Report

Other Products
- Nothing to Report

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: Kamal Khanna, Ph.D.
Project Role: Principal Investigator
Nearest Person month worked: 4
Funding Support: 10% of Dr. Kamal Khanna’s salary support is provided by the SOM

Name: Tasleem Samji, Ph.D.
Project Role: Posdoctoral Fellow
Nearest personal months: 2
Project Role: Dr. Samji’s role for this project was critical with respect to the design and generation of the new BAC based vector that expresses two modified melanoma tumor antigens (TRP2 and GP100)

Name: Leigh Maher
Project Role: Research Assistant I
Nearest personal months: 2
Contribution to Project: Ms. Maher is the technician in the lab and she has assisted technically in virtually every experiment especially the ones dealing with flow cytometry and processing of tissues for imaging.
Name: Zhijuan Qiu  
Project Role: Graduate Student  
Nearest person month worked: 12  
Contribution to Project: Developed MCMVgp100KGP and performed experiments testing its efficacy.  
Funding Source: Internal School of Medicine Start up Funds

Name: Jeremy Grenier  
Nearest person month worked: 7  
Contribution to Project: Performed MCMVgp100KGP and immune checkpoint blockade experiments. Also, developing MCMVgp100-Trp2.  
Funding Source: Internal Graduate School funds

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

2R01AI043573 (Thrall, PI). Dr. Khanna’s effort on this grant ended 9/29/14.

R21AI109188 (Khanna, PI) awarded 7/11/2014 with 1.2 calendar months effort on this project.

Center on Aging; Internal Funding (Khanna, PI) awarded 1/1/15 with .12 calendar months effort on this project.

U01AI095544 MIST Supplement (Khanna, PI) awarded 7/1/15.

What other organizations were involved as partners?

Nothing to report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Nothing to report

QUAD CHARTS: Nothing to report

APPENDICES N/A