AWARD NUMBER: W81XWH-16-1-0357

TITLE: Preclinical Development of TVAX: An Advanced Multiantigen Vaccine for Therapy and Prevention of Malignant Mesothelioma

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REPORT DATE: September 2018

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;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2018	Annual	15 Aug 2017- 14 Aug 2018

4. TITLE AND SUBTITLE

Preclinical Development of TVAX: An Advanced Multiantigen Vaccine for Therapy and Prevention of Malignant Mesothelioma

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0357

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 Hawaii
SYSTEMS 2425 CAMPUS RD
SINCLAIR LIBRARY RM 1 HONOLULU
HI 96822-2247

8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Materiel 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

We proposed to evaluate the efficacy of multi-antigen vaccines for the treatment of malignant mesothelioma (MM) in mice. In the 1st year of this projects, we developed different immunotherapies using viral vector-based vaccines as MVA or Fowlpox, as well as peptide-based vaccines. For the first prototypes of these vaccines, Tvax and Tvax 2.0, we have included antigens previously demonstrated to be highly expressed in human tumors. Unexpectedly, these vaccines resulted ineffective in reducing MM in mice and displayed signs of autoimmunity. We hypothesized that these negative results were caused by a reduced expression in mouse MM of the antigens included in Tvax vaccines. A whole transcriptome analysis to compare antigen expression between MM and normal tissues confirmed our assumption. This analysis also allowed us to choose a new set of antigens that presented more effective anti-cancer responses in our experiments, without generating auto-immunity. During the 2nd year of this project, we focused in evaluating the anti-cancer efficacy of Tvax 3.0 vaccines, which include this new set of antigens. We also characterized the antigen-specific immune responses generated by Tvax 3.0 and analyzed immune cell infiltrates in tumors from vaccinated mice. All these data were incorporated in a manuscript that will be submitted for publication in the following weeks.

15. SUBJECT TERMS

Malignant Mesothelioma, anti-cancer vaccines, T cell-epitope, multi-epitope vaccines, T regulatory cells, tregitopes.

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

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INTRODUCTION:

Malignant Mesothelioma (MM) is an aggressive form of cancer that typically originates in the pleural cavity, but can also occur in the peritoneum, pericardium and around the testes. Asbestos exposure is the only established risk factor for MM (1).

Even if MM is a rare cancer, a significant number of MM deaths occur among U.S. navy sailors and military personnel that were heavily exposed to asbestos because they worked in shipyards or in their proximity (2). Since there are no effective treatments for MM and the median survival is less than 1 year from diagnosis, there is an urgent medical need to develop novel approaches to treat this understudied disease.

Our purpose is to use advanced anti-cancer vaccines to generate effective immune responses against MM cells. In clinical trials, conventional anti-cancer vaccines have shown to be safe and to induce tumor-specific T cell responses, although increase in survival has been achieved in a limited number of patients. Most of the vaccines utilized in clinical trials, as well in pre-clinical studies usually target a single cancer antigen. Our data obtained with survivin vaccine FP-surv suggest that vaccination with this single antigen was effective against survivin-positive cells (3). However, eradication of survivin-positive cells was followed by an expansion of cancer cell clones with reduced or undetectable survivin expression. These clones elude survivin-specific cytotoxic T cells and maintain the ability to grow uncontrolled. For this project, we developed a novel Tvax vaccine designed to activate antigen-specific T cells against multiple targets and produce stronger anti-cancer responses than single-antigen vaccines.

The scope of this research is to evaluate the therapeutic efficacy of Tvax and its activity on cancer-specific T cells in mouse MM models. We also proposed to develop a clinical version of Tvax (hTvax) and evaluate its efficacy in activating human T cells from healthy donors.

KEYWORDS:

Malignant Mesothelioma, anti-cancer vaccines, T cell-epitope, multi-epitope vaccines, T regulatory cells, tregitopes.

ACCOMPLISHMENTS:

What were the major goals of the project?

Major Tasks for Year 2 as stated in the SOW:

Specific Aim 1, Major Task 2. Identify the most efficacious vaccine by comparing different versions of Tvax in combination with OX86 antibodies to induce mesothelioma (MM)-specific T cells in BALB/c mice. Timeline: Months 6-15

Milestone Achieved: The most effective vaccination to induce MM-specific T cells is identified.

Specific Aim 1, Major Task 3. Evaluate the efficacy of different versions of Tvax vaccines in subcutaneous tumor model of MM progression. Timeline: Months 9-15

Milestone Achieved: The most effective vaccination to reduce MM subcutaneous tumors is identified.

Specific Aim 1, Major Task 4. Evaluate the efficacy of the most effective Tvax vaccine in eradicating late-stage tumors. Timeline: Months 15-18

Milestone not Achieved: Tvax vaccines were ineffective in eradicating late-stage tumors.

Specific Aim 1, Major Task 5. Evaluate the efficacy of Tvax vaccines in intraperitoneal tumor model of MM progression. Timeline: Months 15-18

Milestone Achieved: The most effective vaccination to reduce MM intraperitoneal tumors is identified.

Specific Aim 1, Major Task 6. Prepare and submit manuscript. Timeline: Months 16-18

Task 90% achieved.

Specific Aim 2, Major Task 7. Determine the immunostimulatory capacities of the iVax-predicted peptides in human DC-T cell co-cultures. Timeline: Months 16-26

Task 10% achieved.

What was accomplished under these goals?

During the 1st year of this project we developed different multi-antigen Tvax vaccines to treat MM in mice and performed experiments to compare their specific immune responses and anti-MM efficacy. Among these vaccines, Tvax 3.0 generated the most robust immune responses and significant anti-MM efficacy, without showing any sign of autoimmunity. In year 2, we used Tvax 3.0 to complete all the Major Tasks in Specific Aim 1. The results of these experiments are included in a manuscript that will be submitted for publication in the following days.

We have chosen the antigens for Tvax 3.0 by analyzing the entire transcriptome of two different MM tumors (CRH5 and EOH6) and two normal tissues (lung and kidneys) using a Clariom S gene array. We compared the expression of 40,000 mRNA and, together with the Bioinformatics core at our institution, we calculated tumor vs. normal fold changes in expression for each mRNA. The antigens that showed higher fold changes for both CRH5 and EOH6 MM tumors were those included in Tvax 3.0 vaccines. The expression levels of these antigens in normal and tumor tissues are showed in Figure 1.

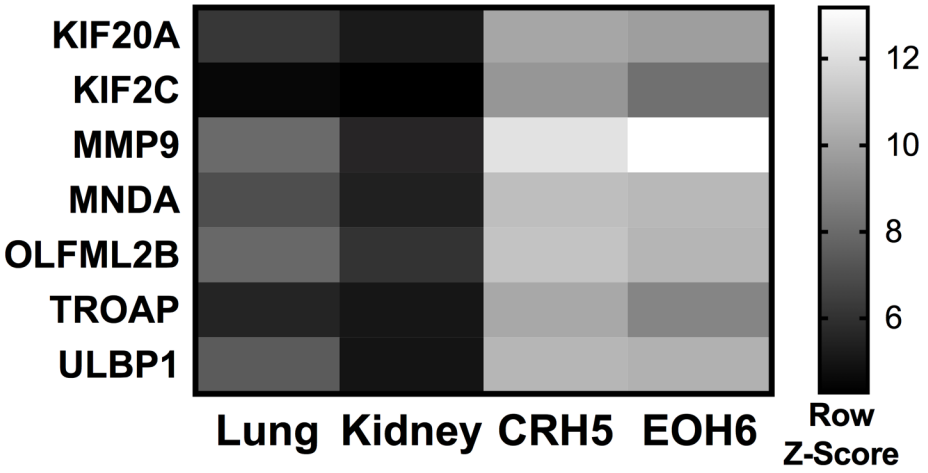


Figure 1. MM tumors overexpress the antigens included in Tvax 3.0. Whole transcriptome analysis was performed on two MM mouse tumors (CRH5 and EOH6) and two normal tissues (kidney and lung). mRNA levels are indicated by Row Z-Score colors in a heat map.

Immune stimulatory epitopes were then identified for each antigen using the informatic tools provided by our collaborator EpiVax Inc., and included in peptide-based vaccines (p-Tvax) or viral vector-based vaccines (MVA-Tvax). The p-Tvax vaccine includes a total of 7 peptides, one for each antigen, and is injected subcutaneously together with CpG as adjuvant. MVA-Tvax codifies multiple epitopes for each antigen for a total of 56, and is injected intramuscularly. The list of the epitopes included in p-Tvax are showed in Table 1.

Table 1. p-Tvax 3.0 Epitopes

N.	Antigen	Start position	Peptide	Length
1	KIF20A	860	Ac-SSTDSSPYARILRSRHSPLLK-amide	21
2	KIF2C	356	GDLSGKSQNASKGIYAMASRDVFLLKN-amide	27
3	MMP9	594	RVFFFSGRQMWVYTGKTVLGPRSLDKLGL-amide	29
4	MNDA	298	Ac-NETSSVLEAAPKQMIEVPNCITRN -amide	24
5	OLFML2B	50	DNQENVLSQLLGDYDKVKAVSEGSD-amide	25
6	TROAP	156	Ac-KGGTTQRGQSARSSAYLAPRIPTH-amide	24
7	ULBP1	56	Ac-LNRQPLFVYKDKKCHAIGAHRNSMNATKI- -amide	29

When we performed experiments to evaluate the anti-MM efficacy of Tvax 3.0 vaccines, we observed significant delay in tumor growth and improved survival in mice carrying subcutaneous CRH5 tumors treated with p-Tvax alone or in combination with OX86 immune stimulatory antibodies. In intraperitoneal MM models using EOH6 cells, we also observed delay in tumor growth and improved survival following p-Tvax vaccination, but only in combination with OX86. Interestingly, in a different intraperitoneal model with AB12 cells, we observed delay in tumor growth using p-Tvax alone or in combination with OX86, but survival improvement was obtained only using both p-Tvax and OX86 (Figure 2).

It is important to emphasize that we did not know the transcriptome of AB12 MM cells. In these experiments, our purpose was to assess if anti-cancer vaccines designed to express antigens commonly expressed by different MM tumors, can be also used to treat MMs in which the antigen expression profile is unknown, but hypothetically express the common antigens discovered in other MM tumors.

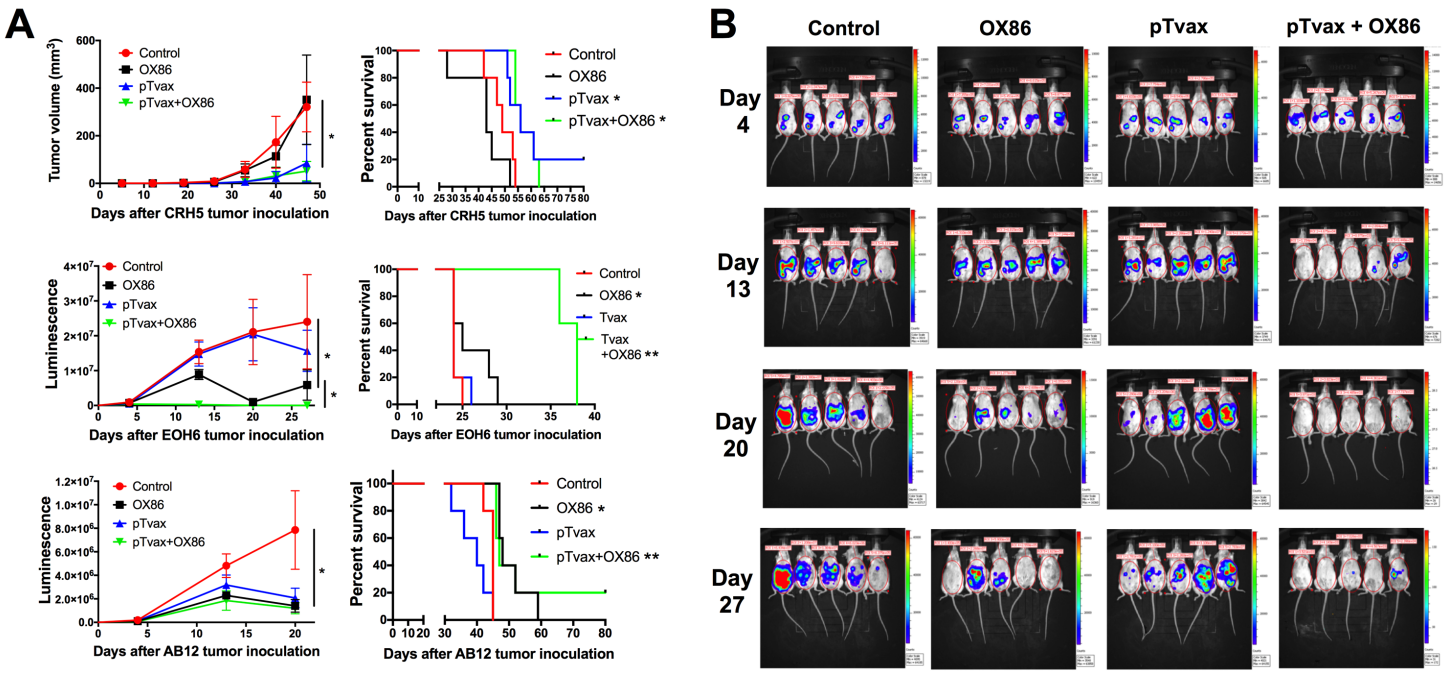


Figure 2. Vaccination with p-Tvax delays tumor growth and improves survival in subcutaneous and intraperitoneal mouse models of MM. A) BALB/c mice were injected subcutaneously with 100.000 CRH5 cells, or intraperitoneally with 50.000 of either EOH6 or AB12 cells, both expressing a luciferase gene. 7 and 14 days after tumor injection, mice were vaccinated with a subcutaneous injection of p-Tvax peptides plus CpG adjuvant. 200μg of OX86 were injected at day 9 and 14. Tumor volumes and animal survivals are shown for injection with three different cell lines: CRH5 (Top), EOH6 (Middle) and AB12 (Bottom). Tumors were measured weekly with a caliper for subcutaneous tumor. Intraperitoneal MM dimensions were instead assessed by measuring luciferase activity with IVIS imaging following injection with luciferin substrate. Statistical significance vs. Control or Single treatment was determined by ANOVA followed by Bonferroni test (*$p<0.05$). For survival, mice were followed until subcutaneous CRH5 tumors reached volumes of 300 mm^3 and were then sacrificed. In intraperitoneal models injected with EOH6 or AB12 MM cells, survival was assessed by euthanizing the mice at first sign of morbidity. Log-rank analysis was used to determine significance vs. Control (*) or vs. single treatment (**) ($p<0.05$). B) Representative images from IVIS imaging of mice carrying EOH6 tumors, vaccinated with the different immunotherapies.

Experiments using viral vector-based vaccines as MVA-Tvax, failed in providing MM growth delay or improved survival when used alone or in combination with either OX86 antibodies or with p-Tvax (Figure 3). The development of Fowlpox vectors carrying the Tvax 3.0 antigens has been instead delayed for technical reasons. We will perform experiments using this vaccine to assess its anti-cancer activity in the next weeks.

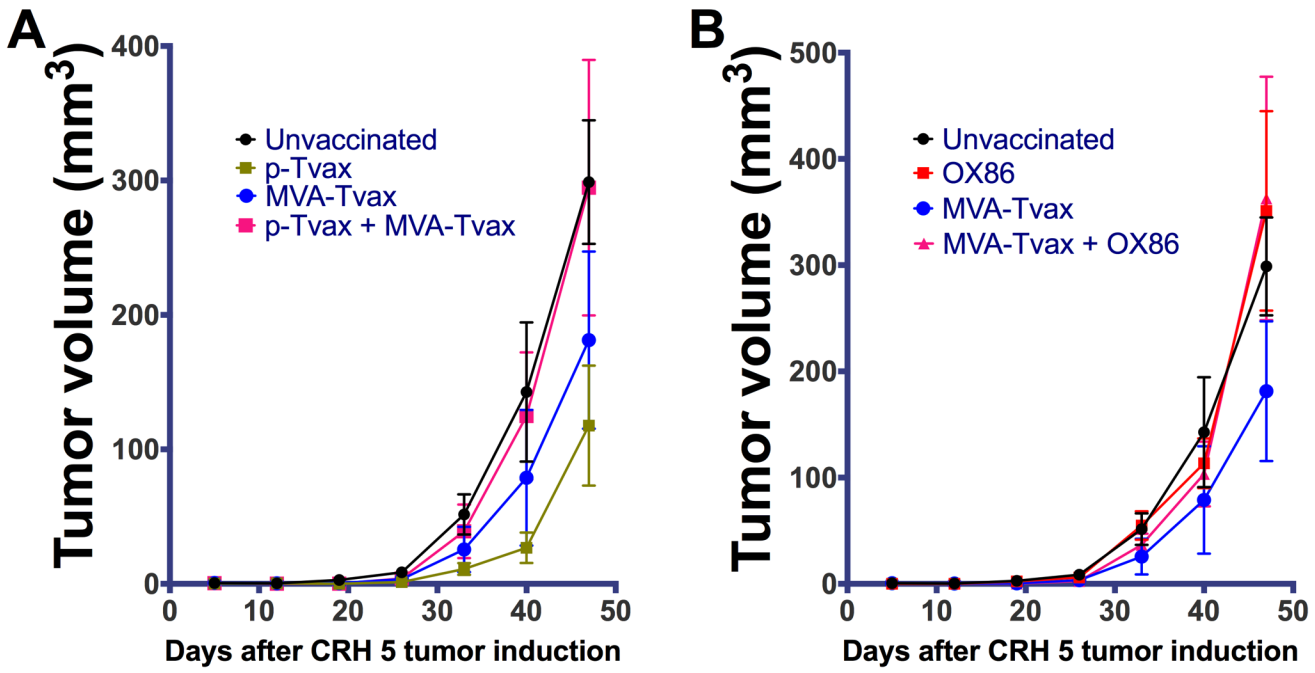
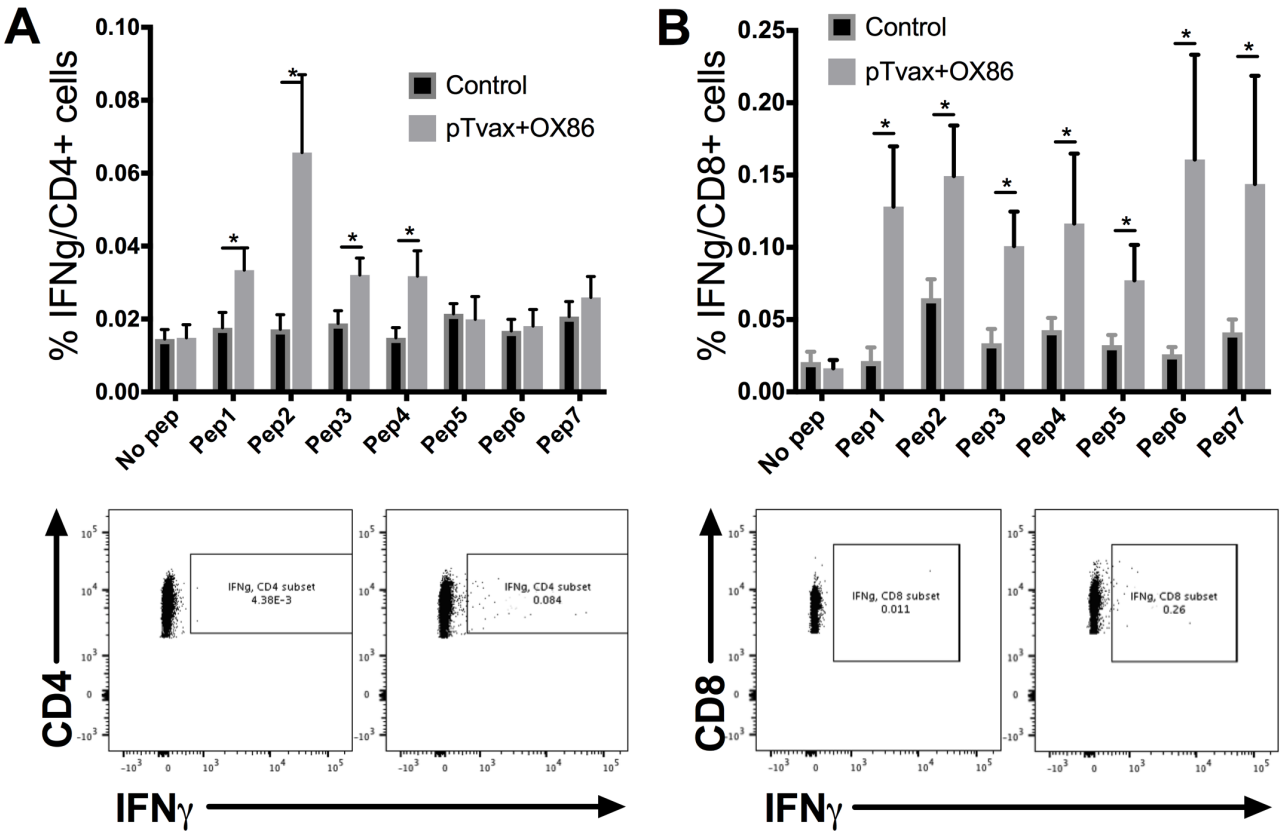


Figure 3. MVA-Tvax did not delay MM growth nor improved survival when used alone or in combination with either OX86 antibodies or with p-Tvax. BALB/c mice were injected subcutaneously with 100.000 CRH5 cells. 7 and 14 days after tumor injection, mice were vaccinated with either subcutaneous injection of p-Tvax peptides plus CpG adjuvant, or with an intramuscular injection of MVA-Tvax. 200μg of OX86 were injected at day 9 and 14. Tumors were measured weekly with a caliper.

Once we identified p-Tvax as the most effective and safe vaccine, we proceeded by analyzing the specific immune responses for each single peptide antigen. In these experiments, we discovered that peptides n.1, 2, 3 and 4 were able to stimulate both antigen-specific $CD4^+$ and $CD8^+$ T cells, while peptides n. 5, 6 and 7 stimulated only $CD8^+$ T cells. In other experiments, we evaluated if splenocytes from vaccinated mice, stimulated with all the Tvax peptides, secrete granzyme B when interact with MM cells. The results demonstrated that T cells from vaccinated mice can recognize and attack all the MM cells involved in this study (AB12, CRH5 and EOH6) as shown in Figure 4.


A
% IFNg/CD4+ cells
0.10
0.08
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Control
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No pep
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Control
pTvax+OX86
No pep
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Pep5
Pep6
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CD4
IFNγ
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IFNγ
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IFNg, CD8 subset
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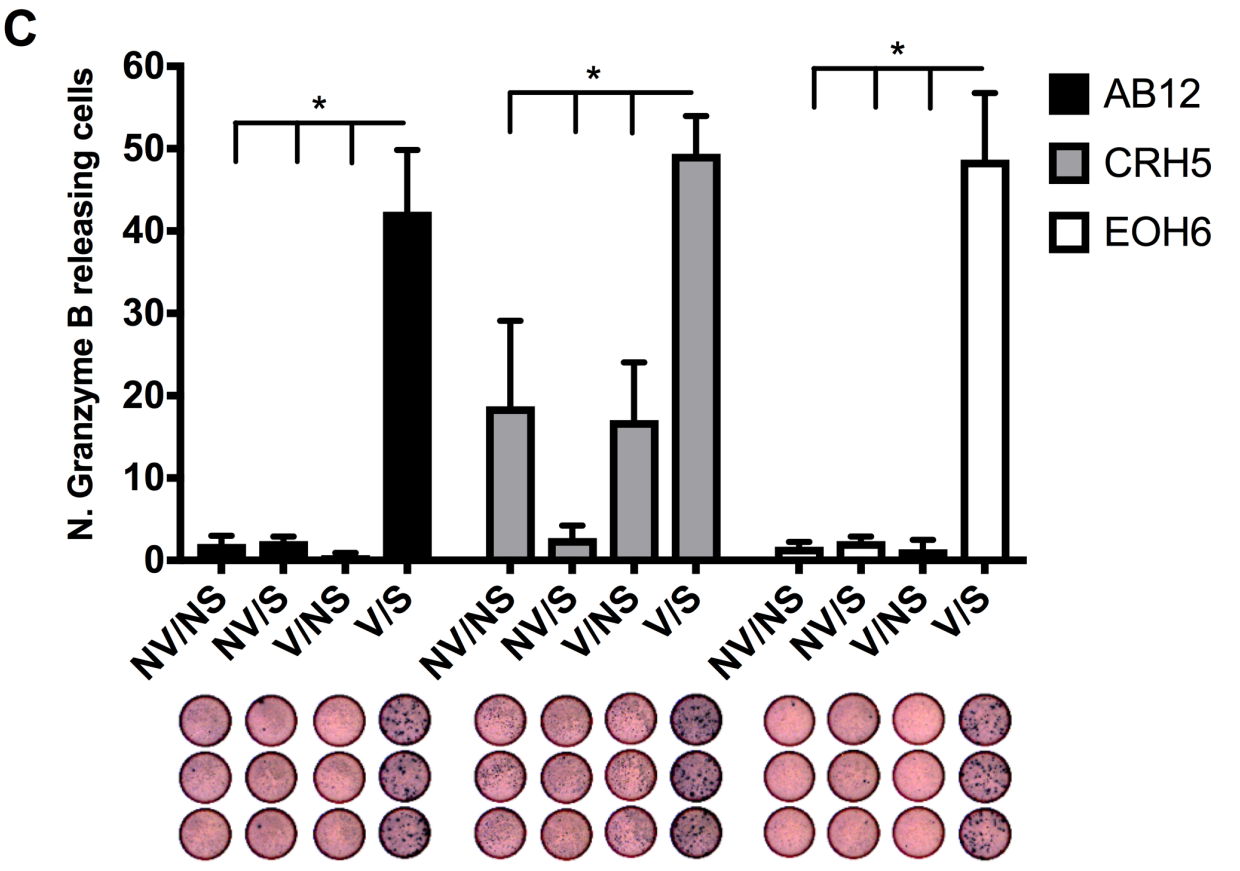
C
N. Granzyme B releasing cells
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Figure 4. Induction of IFN-γ secreting T lymphocytes by p-Tvax vaccination. BALB/c mice were vaccinated with two subcutaneous injections of Tvax peptides +CpG (one week apart). Control mice were left untreated. Five days after the last vaccination spleen cells were isolated and enumerated for assays. A) Intracellular IFN-γ in $CD4^+$ T cells was evaluated by flow cytometric ICC analyses of spleen cells cultured with or without p-Tvax peptides. Percentage of IFN-γ expressing $CD4^+$ T cells are presented as mean ± S.E. Statistical significance vs. Control was determined by ANOVA followed by Bonferroni test (*p<0.05). Bottom Panel: Representative data from flow cytometric analysis of p-Tvax-vaccinated and control mice. Lymphocytes were either not stimulated (NP) or stimulated with peptide n.2. $CD4^+$ T cells were distinguished using a marker gate in the CD3 vs. CD4 dot plot. B) Data are showed for intracellular IFN-γ in $CD8^+$ T cells. C) Secretion of Granzyme B was evaluated by ELISPOT assay. Spleen cells from vaccinated mice (V) or unvaccinated (NV) were activated with p-Tvax peptides in the presence of 5 IU/mL IL-2 for 5 days (S) or incubated with no peptide (NS). Following 4 hours incubation with different MM cells, the number of as spot-forming cells per 10^5 cells was evaluated and results represented as mean ± S.E. Statistical differences between vaccinated mice, stimulated with peptides (V/S) and other conditions were evaluated by ANOVA followed by Bonferroni test (*p<0.05).

We also analyzed the phenotype of tumor-infiltrating lymphocytes in mice vaccinated with p-Tvax peptides alone or in combination with OX86 immune stimulatory antibodies. In these assays, we observed that p-Tvax significantly increases the number of $CD4^+$ T cells, while OX86 increases the number of $CD8^+$ T cells when are both compared with controls. OX86 also reduced the number of $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory cells in tumors from OX86-treated mice. When p-Tvax and OX86 were used in combination, we observed higher percentages of both $CD4^+$ and $CD8^+$T cells and statistically significant reduction of T regulatory cells (Figure 5). In tumors from mice treated with the different immunotherapy, we also analyzed the level of inflammatory cytokines as TNF-α, IFN-γ, IL-2, IL-4, IL-5, without detecting any difference among conditions.

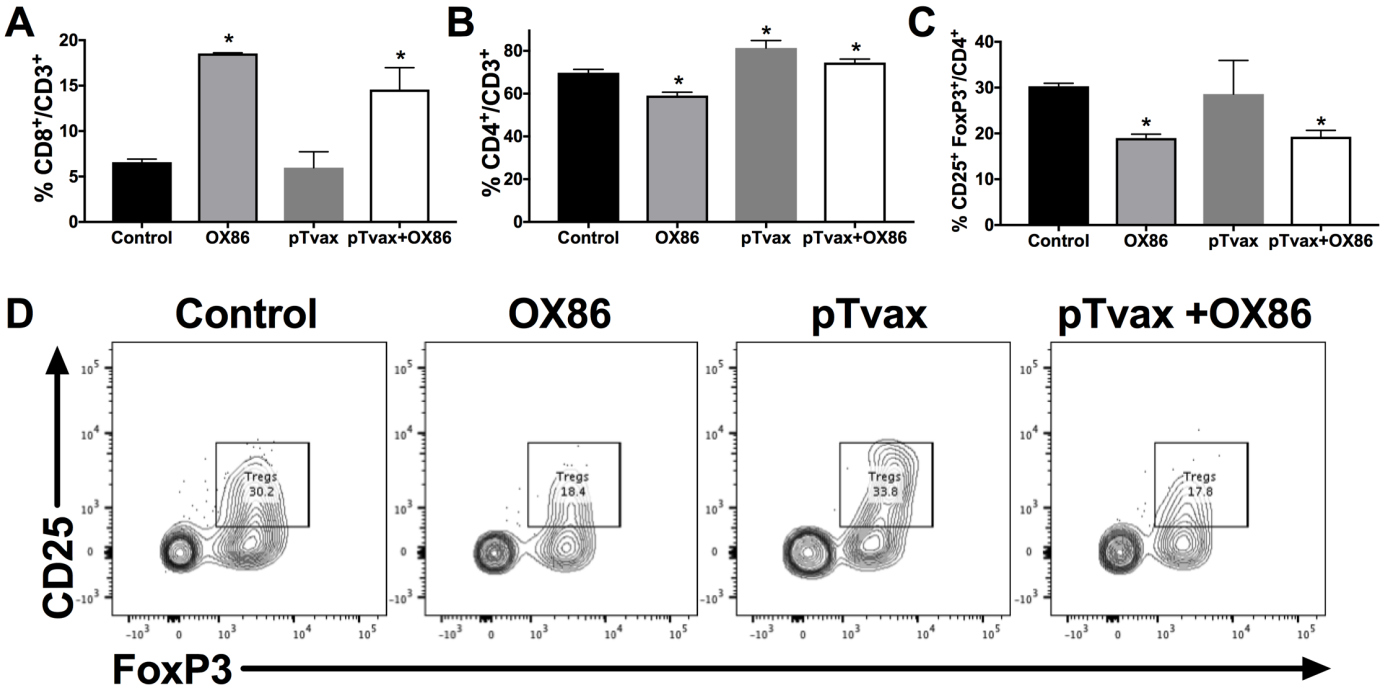

Figure 5. p-Tvax in combination with OX86 antibodies induce CD8$^+$ and CD4$^+$ T cell tumor infiltration while reducing T regulatory cells. Tumors from controls or from mice treated with either p-Tvax or OX86, or with a combination of the two, were collected and enzyme-digested. Staining was performed using anti-mouse CD8, CD4, CD25 and FoxP3 antibodies with live cells distinguished from debris using LIVE/DEAD® cell viability dye. A) Percentage of CD8$^+$ T cells in CRH5 tumors from treated and control mice. Results represent mean ± S.E. with means of each group compared using ANOVA followed by Bonferroni test. Data for CD4$^+$ T cells and T regulatory cells are showed respectively in (B) and (C). D) Representative data from flow cytometric analysis of CRH5 tumors in treated and control mice (*$p<0.05$).

We incorporated all these results obtained with p-Tvax and OX86 in a manuscript that will be submitted for publication in the following days to complete all the tasks included in Specific Aim 1.

For specific Aim 2, we proposed to develop a clinical version of Tvax (hTvax) and evaluate its efficacy in activating human T cells from healthy donors. In the original proposal we presented a first version of Tvax that included 7 antigens that were discovered to be overexpressed in the majority of human cancers (Survivin, Metastasin, Midkine, Wilms Tumor-1, Brachyury, Fibroblast Activation Protein and Vascular Endothelial Growth Factor Receptor 2). With the experiments performed during the 1st year of this project we realized that these antigens may not be the most expressed in human MM tumors. Therefore, we have chosen new MM-specific antigens for the human version of Tvax by analyzing the data from recently published studies in which whole gene expression profiling was performed in MM tumors from human patients (4). In these days, with the support of our collaborator Dr. Moise from EpiVax, we are analyzing these antigens to identify highly immunogenic T cell epitopes to perform the experiments listed in Specific Aim 2 (5).

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

A career development plan for myself, the PI of this project, was included in the proposal for this DoD grant. During this reporting period, I had weekly one-on-one meetings with my mentor, Dr. Hoffmann, to discuss analyses of data and the ongoing planning of this project. I also met once a month with my secondary mentor Dr. Carbone to analyze the histological samples obtained from the mouse studies and discuss the future direction of my researches.

I participated in the weekly seminars hosted by the Cancer Center and the Medical School at the University of Hawaii. I also attended some of the webinars organized by Epivax and the Institute of Immunology and Informatics at the University of Rhode Island.

To improve my experience in teaching, I presented lectures for the courses in “Cell and Molecular Biology” (CMB 622) and “Infection and Immunity” (TRMD 610) at the University of Hawaii.

How were the results disseminated to communities of interest?

Nothing to report

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

For the next reporting period, I plan to perform experiment to assess the immunogenicity of hTvax peptides in DC-T cell cocultures using human blood derived cells. Also, the cytotoxicity activity of human T cells stimulated with DC loaded with the hTvax peptides will be also evaluated.

Viral vector vaccines as Fowlpox or MVA will not be developed for human immunization, since these vectors did not provide the expected anti-cancer activities in our experiments in mouse models. Moreover, the high number of T cell epitopes included in these vaccines may stimulate auto-immune T cells, as observed in our experiments performed in both year 1 and 2 of this project.

IMPACT:

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

The main goal of this translation proposal is to test innovative vaccines in animal models of MM progression to identify new therapeutic and preventive interventions. In the therapeutic setting, Tvax vaccines may be used to induce tumor regression in patients with MM at the early stages of disease. In the case of most late-state tumors, chemotherapy or surgery can be used to reduce tumor burden. In these patients, immunotherapy with Tvax vaccines can be used post-treatment to stimulate the immune system in killing remaining cancer cells and increase post-cancer survival. Our studies would also provide the framework for developing vaccines to prevent cancer development in people exposed to asbestos and/or genetically predisposed who are at high risk for developing MM in the future. Investigators at the University of Hawaii Cancer Center have recently discovered germline Bap1 mutations in families with high incidence of MM. In addition, two biomarkers, Soluble Mesothelin Related Peptides (SMRP) and Osteopontin (OPN) have garnered interest in recent years as a means of detecting recurrence of MM. This progress has enabled the use of PCR analysis to detect Bap1 mutations and the use of ELISA to evaluate SMRP and OPN protein levels as a means of identifying patients at high risk of developing MM for early intervention (6).

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

In our original proposal, we planned to develop and evaluate anti-cancer efficacy of different vaccine platforms as DNA, peptide, and viral vectors. Among these vaccines, we expected to obtain the best results from viral vector-based vaccines. Unexpectedly, these vaccines lacked in anti-cancer efficacy and displayed signs of auto-immunity in several experiments performed in both year 1 and 2 of this project. Therefore, we will proceed with our studies using only peptide vaccines as they were the most effective in delaying tumor growth, without inducing auto-immunity.

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

We spent more time than expected to identify the best immunotherapy among DNA-based, peptide-based and viral-vector vaccines. Therefore, we are in delay of few months in completing the last task included in Specific Aim 1 (Prepare and submit manuscript).

For Specific Aim 2, we are in delay of few months in performing the first subtask of Major Task 7 because we had to select new antigens for the human version of Tvax. However, since we will not produce the viral-vectors included in Major Task 8, we expect to conclude the other experiments listed in the SOW and submit a manuscript for publication on time for the end of this project.

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

PRODUCTS:

Publications, conference papers, and presentations

- **Journal publications.**
    - Marciel MP, Khadka VS, Deng Y, Kilicaslan P, Pham A, **Bertino P**, Lee K, Chen S, Glibetic N, Hoffmann FW, Matter ML, Hoffmann PR. Selenoprotein K deficiency inhibits melanoma by reducing calcium flux required for tumor growth and metastasis. Oncotarget. 2018 Feb 3;9(17):13407-13422. doi: 10.18632/oncotarget.24388. eCollection 2018 Mar 2. Erratum in: Oncotarget. 2018 Jul 20;9(56):30937. PMID: 29568366. Status of publication: published. Acknowledgement of federal support: No.

- Marciel MP, Rose AH, Martinez V, Horio DT, Hashimoto AS, Hoffmann FW, **Bertino P**, Hoffmann PR. Calpain-2 inhibitor treatment preferentially reduces tumor progression for human colon cancer cells expressing highest levels of this enzyme. Cancer Med. 2018 Jan;7(1):175-183. doi: 10.1002/cam4.1260. Epub 2017 Dec 6. PMID: 29210197. Status of publication: published. Acknowledgement of federal support: No.

- **Pietro Bertino**, Thomas A. Premeaux, Brien K. Haun, Michael P. Marciel, Fukun W. Hoffmann, Alan Garcia, Haining Yiang, Sandra Pastorino, Michele Carbone, Toshiro Niki, John Berestecky, Peter R. Hoffmann, Lishomwa C. Ndhlovu. Targeting galectin-9 C-terminus induces mesothelioma apoptosis and M2 macrophages depletion. Cancer Immunol Research. Status of publication: under review. Acknowledgement of federal support: No.

- **Books or other non-periodical, one-time publications.**
  Nothing to Report

- **Other publications, conference papers, and presentations.**
  Some of the data from this project were presented during the "Cancer Biology Winter Retreat" and the "Cancer Immunotherapy Symposium" hosted by the Cancer Center of the University of Hawaii the 8th of December 2017 and the 17th of July 2018 respectively.

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

During this reporting period, we produced DNA-based, peptide-based and viral vector-based vaccines expressing different set of cancer antigen. These vaccines will be available for other research projects performed in my lab or Dr. Hoffmann lab. In case of collaboration, this vaccine can be also shared with other laboratories at the Medical School and/or Cancer Center of the University of Hawaii.

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?

Name: Pietro Bertino

Project Role: PI

Research Identifier (ERA Commons ID): pbertino

Nearest person month worked: 9

Contribution to the project: Dr. Bertino had overall responsibility for all aspects of the project. He conducted experiments and analyzed the data. He also was in charge of preparing regulatory approval requests and progress reports.

Funding Support: This award and bridging funds from the University of Hawaii.

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

Nothing to report

What other organizations were involved as partners?

Nothing to report

SPECIAL REPORTING REQUIREMENTS: Not applicable

APPENDICES:

Bibliography:

1. Noonan CW. Environmental asbestos exposure and risk of mesothelioma. Ann Transl Med. 2017;5(11):234. doi: 10.21037/atm.2017.03.74. PubMed PMID: 28706902; PMCID: PMC5497111.

2. Krstev S1 SP, Rusiecki J, Blair A. Mortality among shipyard Coast Guard workers: a retrospective cohort study. Occup Environ Med. 2007 Oct;64(10):651-8.

3. Bertino P, Panigada M, Soprana E, Bianchi V, Bertilaccio S, Sanvito F, Rose AH, Yang H, Gaudino G, Hoffmann PR, Siccardi A, Carbone M. Fowlpox-based survivin vaccination for malignant mesothelioma therapy. Int J Cancer. 2013;133(3):612-23. doi: 10.1002/ijc.28048. PubMed PMID: 23335100; PMCID: PMC3663911.

4. Barone E, Gemignani F, Landi S.J. Overexpressed genes in malignant pleural mesothelioma: implications in clinical management. Thorac Dis. 2018 Jan;10 (Suppl 2):S369-S382. doi: 10.21037/jtd.2017.10.158. Review. PMID: 29507807.

5. Moise L, Gutierrez A, Kibria F, Martin R, Tassone R, Liu R, Terry F, Martin B, De Groot AS. iVAX: An integrated toolkit for the selection and optimization of antigens and the design of epitope-driven vaccines. Hum Vaccin Immunother. 2015;11(9):2312-21. doi: 10.1080/21645515.2015.1061159. PubMed PMID: 26155959; PMCID: PMC4635942.

6. Chen Z, Gaudino G, Pass HI, Carbone M, Yang H. Diagnostic and prognostic biomarkers for malignant mesothelioma: an update. Transl Lung Cancer Res. 2017;6(3):259-69. doi: 10.21037/tlcr.2017.05.06. PubMed PMID: 28713671; PMCID: PMC5504120.