AWARD NUMBER: W81XWH-19-1-0189

TITLE: Characterization of Novel Vaccine Targeting Follicle-Stimulating Hormone Receptor in Ovarian Cancer

PRINCIPAL INVESTIGATOR: David Weiner, Ph.D.

CONTRACTING ORGANIZATION: The Wistar Institute of Anatomy & Biology

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
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Philadelphia, PA 19104-4265

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14. ABSTRACT

Ovarian cancer initially responds well to treatment but returns in a high number of patients. The time after treatment when there is no disease provides a great opportunity for vaccinating against the tumor to prevent a return. An active immune system against the tumor has several advantages. It is associated with longer survival of ovarian cancer patients and it allows other immunotherapy (i.e. Keytruda) treatments to work. This immunotherapy has shown impressive results in other tumors as melanoma, but not in ovarian cancer because the immune system is poorly active against it. The follicle-stimulating hormone receptor (FSHR) is a protein expressed only in the ovaries (which are removed by surgery) and in 50-70% of ovarian cancer. We have generated a vaccine against FSHR and know that it activates the immune system in mice and improves survival in mouse ovarian cancer.

Our objective is to improve survival of patients with ovarian cancer by 1) Testing the FSHR vaccine in mice with human immune system and against human ovarian tumors. 2) Combining the vaccine with immunotherapy to attempt to make ovarian cancer more sensitive to this revolutionary treatment.

15.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. **INTRODUCTION:**
The follicle-stimulating hormone receptor (FSHR) is an antigen that is selectively expressed in women in the ovarian granulosa cells(18) and at low levels in the ovarian endothelium(19). Most importantly, this protein is expressed in 50-70% of ovarian carcinomas(20-26). Given that oophorectomy is a standard procedure in the treatment of ovarian cancer, targeting the FSHR should not cause damage to healthy tissues. Therefore, **FSHR could be an ideal vaccine target to prevent recurrence of against ovarian cancer**. ***Our central hypothesis is that the SynCon FSHR DNA vaccine will be able to synergize with checkpoint inhibitors in immunocompetent mice and increase survival in humanized ovarian cancer models***, so that this therapy can be translated to ovarian cancer patients in subsequent clinical trials. This work will pave the way for subsequent testing of SynCon FSHR DNA vaccine against FSHR+ ovarian cancers in the clinic. We will establish the effectiveness of the combination of SynCon FSHR vaccine with checkpoint inhibitors in a variety of preclinical models including relevant humanized mice harboring human immune systems and ovarian tumors. Our results will provide a mechanistic rationale for the testing of this ovarian cancer targeted DNA vaccine as a potential "game-changer" against this lethal disease.

2. **KEYWORDS:** Ovarian cancer, FSHR, checkpoint, immunotherapy, DNA vaccine

3. **ACCOMPLISHMENTS:** Local and independent IACUC approval for initiation of these studies was received in January 2020.

What were the major goals of the project?

Goal(s)	**Anticipated completion time**	**Complete (Y (date) or N)**
Specific Aim 1. Determine whether SynCon FSHR DNA vaccine synergizes with combination therapy with checkpoint inhibitors.		
Major Task 1. Investigate the effect of combination strategies between SynCon FSHR vaccine & checkpoint inhibitors. *Site IACUC is still under review by Wistar IACUC as of 3-11-2019. We will forward it to ACURO once it is approved. Animal work is not initiated until approved Wistar IACUC is also approved by ACURO.*	Months	1-9
Local IRB/IACUC Approval	1-2	**Yes** Wistar IACUC protocol #201326 approved 1/17/2020
Subtask 1. Submit IACUC approval documentation.	1-2	**Yes**
Subtask 2. Study the combination of SynCon FSHR vaccine with checkpoints in maintenance cohort (follow survival).	2-6	No

Groups: 1) SynConFHSR+IgGcontrol, 2) SynConFHSR+anti-PD-1, 3) SynConFHSR+anti-CTLA4, 4) empty vector+IgGcontrol, 5) empty vector+anti-PD-1, 6) empty vector+anti-CTLA4. 10 mice per group		
Subtask 3. Study the combination of SynCon FSHR vaccine with checkpoint inhibitors in unresectable disease cohort (measure tumor growth). Groups: 1) SynConFHSR+IgGcontrol, 2) SynConFHSR+anti-PD-1, 3) SynConFHSR+anti-CTLA4, 4) empty vector+IgGcontrol, 5) empty vector+anti-PD-1, 6) empty vector+anti-CTLA4. 10 mice per group.	3-8	No
Subtask 4. Study the effect of the combination of SynCon vaccine-checkpoint inhibitors in tumor microenvironment of unresectable cohort (same groups as Subtask 2). 10 mice per group. Resection of tumor and spleen.	9-10	No
Specific Aim 2. Determine the effectiveness of human SynCon FSHR DNA vaccine against human ovarian cancer in humanized mice. *Animal work is not initiated until approved Wistar IACUC is also approved by ACURO.*		No
Major Task 2. Demonstrate immunogenicity of SynCon FSHR in humanized mice.	8-18	
Major Task 3. Demonstrate anti-tumor effectiveness SynCon FSHR in humanized mice.	24-29	

What was accomplished under these goals?
In this first year of the award we completed both local IACUC approval and Acuro IACUC approval. Unfortunately, our laboratory and institute were impacted by the COVID-19 pandemic and non-COVID based animal studies were halted by the Wistar Institute from February-June 2020. With reopening beginning now, we are excited to resume these studies as planned.

What opportunities for training and professional development has the project provided?
Nothing to report

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

What do you plan to do during the next reporting period to accomplish the goals?
In the next reporting period, we plan to complete major task 1, including subtasks 1-4.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report.

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.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
The COVID-19 pandemic significantly impacted all work at The Wistar Institute from February-June 2020. These impacts included restricted access to the worksite, decreased animal facility and IACUC staff, and an interruption to mouse orders except for studies focused on SARS-CoV-2. These necessary interruptions were critical to the safety of Wistar employees but had significant impact on our ability to achieve the goals outlined in the SOW for this period of the award. With work resumed, we anticipate rapid return to focus on these studies.

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.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  Nothing to report

  Journal publications
  Nothing to report

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

Other publications, conference papers and presentations.
Nothing to report

- **Website(s) or other Internet site(s)**
  Nothing to report

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Nothing to report

- **Other Products**
  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	**David B. Weiner, PhD**
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-2232-8512
Nearest person month worked:	1 person month
Contribution to Project:	P.I. providing overall supervision and guidance
Funding Support:	This award

Name:	**Kar Muthumani, PhD**
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-6807-2065
Nearest person month worked:	1 person month
Contribution to Project:	Generation of humanized mice and evaluate immune responses and the effectiveness of FSHR DNA vaccine in humanized mice tumor model.
Funding Support:	This award

Name:	**Ebony N. Gary, PhD**
Project Role:	Postdoctoral Fellow
Researcher Identifier	0000-0002-2928-1120

(e.g. ORCID ID):	
Nearest person month worked:	1 person month
Contribution to Project:	Performs experiments including mouse immunization, tissue collection and processing, and data analysis
Funding Support:	This award

Name:	**Pratik Bhojnagarwala**
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-9403-5276
Nearest person month worked:	10 person months
Contribution to Project:	Performs experiments
Funding Support:	This award

Name:	**Devivasha Bordoloi**
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-3485-8369
Nearest person month worked:	3 person months
Contribution to Project:	Performs experiments
Funding Support:	This award

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Yes, see below changes to Dr. Weiner's active support:

Termination of "Immediate and Persistent Protection against EBOLA Zaire"
Termination "Effect of Immunization Route and Prior Immunity for a Live Attenuated Varicella AIDS Vaccine"
Termination of "Phase I/II Trial of a Therapeutic DNA Vaccine for Chronic Hepatitis C Virus (HCV) Infection"
Activation of "Prometheus: A Platform for Rapid Development of Human Antibody Based Therapeutics and Prophylactics Against Emerging Viral Threats (CORE B)"
Activation of "DNA/EP to Evaluate the Vaccinal Effect"
Activation of "Synthetic DNA-encoded antigens targeting gastric cancer-specific antigens"
Activation of "Multi-Networked T Cell Epitope Vaccine for Global HIV Prevention and Therapy"
Activation of "Novel DNA encoded monoclonal antibodies (DMABs) for control of Antimicrobial Resistant (AMR) Pseudomonas aeruginosa"
Activation of "Collaborative Influenza Vaccine Innovation Centers (CIVICs) Component A: Vaccine Center"

Activation of "Design, synthesis and evaluation of optimized dIgA targeting VP4 protein of Rotavirus"
Activation of "CEPI Translational Platform Program encompassing cGMP manufacturing and clinical development of DNA vaccine candidates against both LASSA virus and MERS coronavirus"

What other organizations were involved as partners?
Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

AWARD CHARTS:
The Award Chart (available on https://ebrap.org/eBRAP/public/Program.htm) must be submitted at time of award is included in the Appendix.

9. APPENDICES: *Award Chart attached.*

OC180118: Characterization of Novel Vaccine Targeting Follicle-Stimulating Hormone Receptor in Ovarian Cancer

PI: David Weiner, The Wistar Institute, PA

Budget: $781,699

Topic Area: Ovarian Cancer

Mechanism: OCRP-IIRA

Research Area(s): 0806 - Therapeutic Vaccines, 0502 - Tumor Immunology

Award Status: 5/15/19-5/14/22

Study Goals:

Major Task 1. Investigate the effect of combination strategies between SynCon FSHR vaccine & checkpoint inhibitors.
Major Task 2. Demonstrate immunogenicity of SynCon FSHR in humanized mice.
Major Task 3. Demonstrate anti-tumor effectiveness SynCon FSHR in humanized mice.

Specific Aims:

Specific Aim 1. Determine whether SynCon FSHR DNA vaccine synergizes with combination therapy with checkpoint inhibitors.

Specific Aim 2. Determine the effectiveness of human SynCon FSHR DNA vaccine against human ovarian cancer in humanized mice.

Key Accomplishments and Outcomes

Wistar and Acuro IACUC approval- January 2020

Publications: none to date
Patents: none to date
Funding Obtained: none to date