

AWARD NUMBER: W81XWH-15-1-0115

TITLE: Phase 1 Trial of Intratumoral Administration of NIS-Expressing Strain of Measles Virus in Unresectable or Recurrent Malignant Peripheral Nerve Sheath Tumor

PRINCIPAL INVESTIGATOR: Dusica Babovic-Vuksanovic, MD

CONTRACTING ORGANIZATION: Mayo Clinic
Rochester, MN 55905-0002

REPORT DATE: October 2018

TYPE OF REPORT: Annual Report

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE			<i>Form Approved</i> <i>OMB No. 0704-0188</i>		
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2018		2. REPORT TYPE Annual		3. DATES COVERED 15 Sep 2017-14 Sep 2018	
4. TITLE AND SUBTITLE Phase 1 Trial of Intratumoral Administration of NIS-Expressing Strain of Measles Virus in Unresectable or Recurrent Malignant Peripheral Nerve Sheath Tumor			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W81XWH-15-1-0115		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Dusica Babovic-Vuksanovic, MD E-Mail: dbabovic@mayo.edu			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Mayo Clinic 200 First Street SW Rochester, MN 55905-0002			8. PERFORMING ORGANIZATION REPORT		
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 NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Study approved by Mayo IRB on April 18, 2016, and by USAMRMC/ORP/HRPO on May 6, 2016. All study staff completed IRB training. Dose volume charts have been developed to facilitate pharmacy orders. Study opened for enrollment on May 17, 2016. Study coordinators identified and assigned to the study by Mayo Clinic Cancer Center. Three patients have been enrolled in the study. They completed treatment per protocol and continue the follow up. None of the treated patients experienced side effects. With the first 3 patients we have completed the first dose level. One patient has been currently on study after receiving second dose level. So far out of 4 treated patients one died to cancer progression. Others are undergoing follow up. An additional patient is under evaluation for eligibility at this time.					
15. SUBJECT TERMS Neurofibromatosis 1, Malignant Peripheral Nerve Sheath Tumor (MPNST), MV-NIS, Oncolytic Virus, Measles Virus					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF 10	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

1. Introduction	Page 4
2. Keywords	Page 4
3. Accomplishments	Page 4
4. Impact	Page 5
5. Changes/Problems	Page 6
6. Products	Page 7
7. Participants & Other Collaborating Organizations	Page 9
8. Special Reporting Requirements	Page 10
9. Appendices	Page 10

1. INTRODUCTION:

Malignant peripheral nerve sheath tumors (MPNST) is the major complication contributing to early mortality and overall decrease in life expectancy in Neurofibromatosis 1 patients. Oncolytic viruses can selectively infect and destroy tumor cells. Our preliminary data confirm that MPNST cells are highly susceptible to MV-NIS. We are conducting Phase I clinical trial to determine safety of intratumoral administration of MV-NIS. Protocol includes MV-NIS injections under ultrasound or CT guidance, *in vivo* monitoring of distribution and kinetics of virus using SPEC/CT or planar gamma camera imaging after TC-99m administration and assessing changes in tumor size by using WHO criteria. Our correlate studies will explore the time course of viral gene expression, virus elimination and humoral and cellular immune response to the injected virus.

2. KEYWORDS:

Neurofibromatosis 1, malignant peripheral nerve sheath tumor (MPNST), MV-NIS, oncolytic virus, measles virus

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?

Major Task 1: Prepare Protocol for Phase I Clinical Trial --completed
Major Task 2: Coordinate Study Staff for Clinical Trial I--completed
Major Task 2: Conduct Phase I Clinical Trial---study open and recruitment in progress
Major Task 3: Perform Correlate Studies
Subtask 1: Evaluate virus incorporation and persistence in MPNST after injection
Subtask 2: Assess viremia and viral shedding

What was accomplished under these goals?

1. Received Mayo IRB approval on 04/18/2016
2. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, US Army, and USAMRMC human subjects protection requirements. Approval Received on May 6, 2016.
3. All staff completed IRB training
4. Developed drug dose volume chart to facilitate pharmacy orders once patients start enrolling
5. Study opened for patient enrollment on May 17, 2016 to Mayo Clinic in Rochester
6. Study coordinators identified and assigned to the study by Mayo Cancer center
7. Three patients treated per protocol, completed first dose level
8. One patient is on the study at second dose level and another patient is being evaluated for eligibility.

8. Study modification approved by Mayo IRB on April 20, 2017 included administrative changes to the consent and protocol

Protocol Summary

- Clarification of Week 6 imaging assessment only be done if uptake on prior imaging
- Updated time from injection of tracer to imaging to one hour
- Added Heparin tubes for assessment of immune response
- For viral shedding assessments, made Day 15 mandatory and Day 28 and Week 6 contingent upon Day 8 and/or Day 15 results
- Minor text and formatting edits throughout
- Updated the tissue collection at Week 6 to specify that the collection is not dependent on positive SPECT

Consent Summary

- Added to Sections 5 and 6 that patients are to wear masks during clinic visits for 12 days after the injection.
- Removed unneeded exclusion language from Section 6
- Classification added to Section 5

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 goal?

Continue patient accrual and procedures per protocol

4. **IMPACT:** Describe 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?

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

Changes in approach and reasons for change

Nothing to report

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

The study is now open and actively recruiting eligible patients, however, the IRB approval was longer than anticipated due to administrative delays.

First dose level is completed. Second dose level is in progress. Due to initial administration delay of opening study we will request a one year extension of funding. This will be submitted in early 2019.

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**Significant changes in use or care of human subjects**

Received Mayo IRB approval on 04/18/2016.

The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, US Army, and USAMRMC human subjects protection requirements. Approval Received on May 6, 2016.

Annual IRB progress report approved by Mayo IRB 1/11/2017

We are preparing the annual IRB progress report to submit to Mayo Clinic IRB due 12/20/2018.

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:**• Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

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: Dusica Babovic-Vuksanovic

Project role: PI

Person months worked: 34

Contribution to projects: submitted quarterly reviews, coordinated activities needed for study opening for accrual

Funding support: this award

Name: Scott Okuno

Project role: co-PI

Person months worked: 26

Contribution to projects: patient accrual

Funding support: this award

Name: Jennifer Picket

Project role: study coordinator

Person months worked: 2

Contribution to projects: coordination of study procedures

Funding support: this award

Name: Jaclynn Wessling

Project role: study coordinator

Person months worked: 13.5

Contribution to projects: coordination of study procedures

Funding support: this award

Name: Jodi Klocke

Project role: study coordinator

Person months worked: 8

Contribution to projects: coordination of study procedures

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?

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A