

AWARD NUMBER: W81XWH-20-1-0537

TITLE: Improving Mesothelioma Therapy by Boosting Immune Responses to Mutations by Vaccination and by Immunogenic Chemotherapy

PRINCIPAL INVESTIGATOR: Bruce Robinson

CONTRACTING ORGANIZATION: University of Western Australia, Crawley, Australia

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14. ABSTRACT This is the first annual report for award CA190450. The project examines neoantigen immune responses in (a) clinical samples and (b) mouse models. We have been significantly delayed in obtaining approval for human studies. HRPO approval was not obtained until recently (9-Jul-2021) and subsequently no other milestones for clinical aspects of the project have been met. We requested an extension of the award in May to accommodate this. We have successfully obtained ACURO approvals and commenced work on mapping and identifying simple (i.e. SNV) neoantigens in the mouse models. We have demonstrated that 44% of predicted neoantigens elicit T cell immune responses. Unfortunately, COVID related lockdowns have restricted some laboratory based aspects of identifying complex neoantigens. However, this has now been resolved. We are on track to complete Task 3 studies within timelines.									
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1. INTRODUCTION:

Mesothelioma is an aggressive cancer caused by exposure to asbestos. New checkpoint blockade therapies have demonstrated that a person's own immune system can eradicate the tumour. However, this only occurs in the minority of cases. In this project we look at an alternative approach to stimulate the immune system to specifically attack a patient's own tumour by vaccinating against tumour derived mutated new or "neo"-antigens. Our objective is to study neo-antigen immune responses in mesothelioma patients and use mouse model systems to evaluate the most effective neo-antigen vaccination strategy.

2. KEYWORDS:

mesothelioma, neoantigen, chemotherapy, immunotherapy, asbestos, treatment

3. ACCOMPLISHMENTS:

What were the major goals of the project?

AIM 1 To identify candidate mesothelioma neo-antigens and evaluate T cell responses to them

<i>Milestone(s)</i>	<i>Target Date</i>	<i>Completion Date</i>
Local IRB/IACUC Approval	01-Jul-20	100%
HRPO review and approval of IRB protocols	01-Oct-20	09-Jul-20
Recruit 8 patients	01-Jan-21	0%
Recruit 20 patients	01-Jul-21	0%
WGS, and RNAseq (n=20)	01-Jul-21	0%
Proteomic studies (subset of patients estimate 21)	01-Jul-21	0%
Neo-antigen identification	01-Jul-21	0%

AIM 2 To examine the effect of mesothelioma chemotherapy on neo-antigen specific T cell responses (n=30).

<i>Milestone(s)</i>	<i>Target Date</i>	<i>Completion Date</i>
Testing of neo-epitopes from pools	01-Jan-23	0%
Immunogenicity of simple or complex neo-epitopes	01-Jan-23	0%
Responses following chemotherapy	01-Jan-23	0%
Does chemotherapy enhance T-cell activation	01-Jan-23	0%
Does chemotherapy alters T-cell frequency	01-Jan-23	0%
Transcriptional profile of T cells	01-Jul-23	0%
Define clonality of epitope specific T cells	01-Jul-23	0%
Confirm TCR antigen specificity	01-Jul-23	0%

AIM 3 Pre-clinical evaluation of neo-antigen vaccination**Aim 3.1: Neoantigen Discovery in mice**

<i>Milestone(s)</i>	<i>Target Date</i>	<i>Completion Date</i>
Local animal ethics approval	01-Oct-20	05-Oct-20
ACURO review and approval	01-Jan-21	22-Oct-20
Complex-epitope mapping AB1 and AE17	01-Jul-22	10% complete
ID natural tumor induced neoantigen response	01-Jul-22	20% complete
ID vaccine induced neoantigen response	01-Jan-23	20% complete

Aim 3.2: Assessing tumor rejection following neo- antigen vaccination

<i>Milestone</i>	<i>Target Date</i>	<i>Completion Date</i>
Define protective neo-antigens	01-Apr-23	0% complete

Aim 3.3: Assessing tumor rejection following combined neo-antigen vaccination plus chemotherapy or neo-antigen vaccination plus ICPB

<i>Milestone</i>	<i>Target Date</i>	<i>Completion Date</i>
Define optimal peptide type (simple versus complex versus versus proteomically defined) and number to synergize with chemotherapy.	01-Jul-23	0% complete

Aim 3.4: Assessing tumor rejection following combined neo-antigen vaccination plus chemotherapy plus ICPB

<i>Milestone</i>	<i>Target Date</i>	<i>Completion Date</i>
Define optimal peptide type (simple versus complex versus) and number to synergize with ICPB.	01-Jul-23	0% Complete

Task 4:

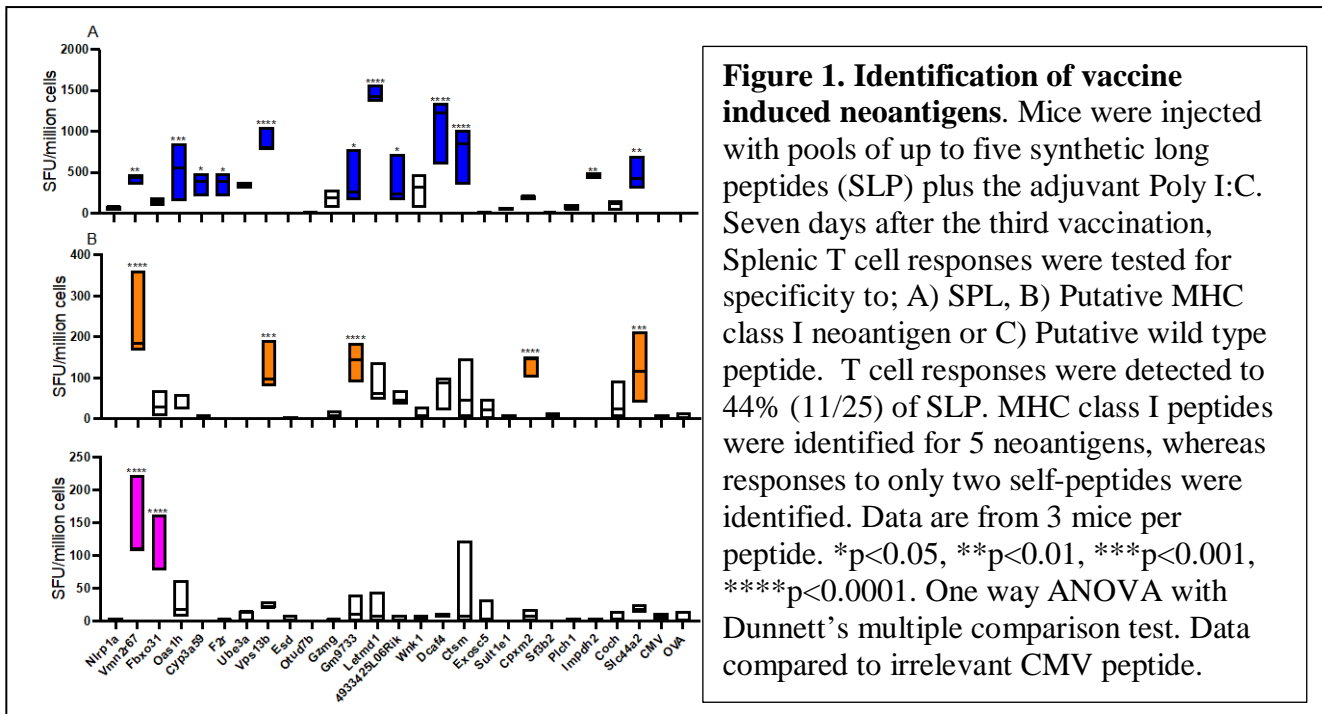
Dissemination of Results	01-Jul-23	0% Complete
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What was accomplished under these goals?

1. HRPO approval was received two weeks ago. No patients have been recruited to the study during this period.

2. We have acquired local animal ethics approval as well as ACURO for these studies within the specified times. In parallel we have performed experiments to identify natural and vaccine induced neoantigen response to simple (SNV) neoantigens in AB1-HA inoculated BALB/c mice. Approximately, 44% of SNV derived neoantigens are capable of inducing vaccine induced T cell responses (Figure 1). Studies will be repeated but results so far are consistent with the literature.

In order to identify complex neoantigens for proteomics and genomic studies mouse tumors are being grown and will be sent to our collaborators soon. Due to COVID-19 related lockdowns our collaborators in Melbourne have been unable to perform wet-laboratory work until recently which has delayed this aspect of the project.



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

The premier meeting for our disease-type, the International Mesothelioma Interest Group Meeting was held virtually in May 2021. The virtual nature of the meeting enabled all members of the team to attend and provided an opportunity for professional development.

Prof Creaney (virtually) attended a bioinformatics workshop (Galaxy Smorgasbord training) in February this year in order to attain greater proficiency in DNA and RNA analysis.

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?

We will perform activities as outlined in the Statement of Work to accomplish Year 2 goals.

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:

As reported previously, delays in obtaining HRPO approval has delayed Tasks 1 and 2. This has been communicated with the grants officials.

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

As discussed we have had delays in obtaining HRPO approval, this has been rectified.

Whilst Australia has not been impacted as significantly by the COVID-19 pandemic as the United States or many other countries, we have experienced periods of lock down (as described above) that have slowed the project. We are also experiencing delays and even difficulty in sourcing some laboratory supplies because of the world-wide impact of the virus on supply chains. We will continue to manage the situation and adapt our research as required, should the situation in Western Australia change, we will inform the US DoD.

Changes that had a significant impact on expenditures

We have had delays in the acquisition of Human ethics approvals which has delayed spending on Aims 1 and 2. This has no effect on the overall cost of the project.

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

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

Publications, conference papers, and presentations

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?

<i>Name</i>	Prof. Bruce Robinson, MBBS, UWA
<i>Project Role</i>	PI
<i>Researcher Identifier</i>	0000-0001-7865-2760
<i>Nearest person month worked</i>	1 month
<i>Contribution to Project:</i>	Oversight of project
<i>Name</i>	Prof. Jenette Creaney, UWA
<i>Project Role</i>	Co- PI
<i>Researcher Identifier</i>	0000-0002-9391-9395
<i>Nearest person month worked</i>	2 months
<i>Contribution to Project:</i>	Facilitating human ethics approvals
<i>Name</i>	Dr Alec Redwood, UWA
<i>Project Role</i>	Co-PD/PI
<i>Researcher Identifier</i>	0000-0001-8601-8292
<i>Nearest person month worked</i>	2 months
<i>Contribution to Project:</i>	Planning, oversight of Aim 3, preparation of all animal ethics applications.
<i>Name</i>	Peter Chaing
<i>Project Role</i>	Research Assistant
<i>Researcher Identifier</i>	
<i>Nearest person month worked</i>	1 month
<i>Contribution to Project:</i>	Performing immunogenicity testing in BALB/c mice. Preparations for human studies.
<i>Name</i>	Tina Firth
<i>Project Role</i>	Clinical research assistant
<i>Researcher Identifier</i>	
<i>Nearest person month worked</i>	1 month
<i>Contribution to Project:</i>	Assistance with human ethics documentation and development of protocols and work processes

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

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS: *updated and submitted with*

9. APPENDICES: