

A. COVER PAGE

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| Project Title: National Mesothelioma Virtual Bank, Continued Innovation | |
| Grant Number: 5U24OH009077 | Project/Grant Period: 09/01/2016 - 08/31/2021 |
| Reporting Period: 09/01/2016 - 08/31/2021 | Date Submitted: 11/20/2021 |
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| Change of Contact PD/PI: N/A | |
| Human Subjects: Yes HS Exempt: No Exemption Number: Phase III Clinical Trial: | Vertebrate Animals: No |
| hESC: No | Inventions/Patents: No |

B. ACCOMPLISHMENTS

B.1. What are the major goals of the project?

National Mesothelioma Virtual Bank (NMVB) collects pleural and peritoneal malignant mesothelioma biospecimens from retrospective and prospectively consented patients from its collaborative sites. The NMVB database stores de-identified biospecimen information and makes it searchable to the mesothelioma research community to support novel biomarker and therapeutic research studies. NMVB is the largest mesothelioma biospecimens resource in the country and is comprised of five healthcare academic collection sites including University of Pittsburgh/UPMC (Pitt), New York University (NYU), University of Pennsylvania (U. Penn), Roswell Park Cancer Institute (RPCI) and University of Maryland (U Md). Our specific aims or goals are as follow:

Specific Aim (Goal) 1: (Ongoing Aim) Continue to serve the translational research needs of the mesothelioma cancer research community.

Specific Aim (Goal) 2: (Expansion Aim) Expand the NMVB to include new collections and sites.

Specific Aim (Goal) 3: (Continued Innovation) Annotation of biospecimens by extraction of clinical, outcomes and pathology data from electronic health records and cancer registry systems.

B.2. What did you accomplish under these goals?

Goal 1: We enrolled prospectively consented malignant mesothelioma pleural and peritoneal cases at all NMVB collection sites. In the funding period we have enrolled 472 retrospectives and prospective consented malignant mesothelioma biospecimens bringing the current total of cases to 1675. We had set a goal of 500 new cases and nearly hit that target. This is despite the 2020 and 2021 impact of COVID which shut down many of our network collection sites due to halts in non-therapeutic clinical trials.

Goal 2: The University of Maryland (U Md) joined NMVB in 2016 and accrued 154 cases. 53 of these are consented prospective cases and 101 of these are retrospective cases. Our goal was to add 150 cases at this site and this was accomplished despite COVID shutdowns

Goal 3: Continued annotation of biospecimens continued through out the funding period including the adoption of the REDCap (Realtime Electronic Data Capture) and all sites were trained on the system and are currently using it for their data annotation and biospecimen management.

Overall Goals:

Biospecimens Fulfilled from Letters of Intent: The purpose of NMVB is to serve the mesothelioma research community with clinical and outcomes data and biospecimens to facilitate translational research focused on biomarker discovery and therapeutic innovation towards the eventual halt of progression and death from this disease. We fulfilled 26 Letters of Intent in the current funding period which was impacted by COVID research shutdowns in 2020. This has nicely rebounded in 2021 where there are currently 8 LOIs either fulfilled or in the process of being completed.

B.3. Competitive Revisions/Administrative Supplements

There are no competitive revisions or administrative supplement in the current reporting period:

B.4. What opportunities for training and professional development did the project provide?

The NMVB does not have a training or professional development goal in the current reporting period:

B.5. How did you disseminate the results to communities of interest?

The NMVB marketing and outreach strategies targeted to the mesothelioma research community: 1) publicized the availability of the NMVB to prospective researchers, 2) solicits input from the research community about how to maximize the effectiveness of the NMVB, and 3) informs the research community of advances facilitated by the NMVB. Additionally, members of NMVB (Taylor and Ganapathiraju) are board of director members and scientific advisors of the Meso Fdn who will help promote this resource. We will continue to market the resource broadly to the scientific community by:

- a) Participating in no fewer than two annual scientific symposia (Meso Fdn Annual Meeting/International Mesothelioma Interest Group and/or other meetings on a rotating basis)
- b) Publishing marketing materials annually, including bookmarks, binder inserts, and tri-fold mailers
- c) Sending quarterly email notification of the NMVB to appropriate published and funded researchers
- d) Continuing our NMVB website presence and maintaining and updating the public query tool and the database

NMVB uses a variety of advertising approaches to engage the research community:

- 1) The NMVB website: It is designed and hosted by the Pitt team with input from the CDC, NIOSH and the NMVB Steering Committee. The website includes general information about the mesothelioma resource, information about the types of specimens available, a searchable Web Portal Query Tool of the cases, and forms for applying for biospecimen requests and handling all inquiries by researchers. Google Analytics is used to provide access statistics for the NMVB website. The website has been

engineered with Google Analytics code to log each page that is accessed and provides continuous tracking of usage, including statistical information and graphical reports.

2) Mass mailings to potential users: The e-mail addresses of mesothelioma investigators are acquired from PubMed, member organization websites and the NIH Reporter database. E-mail addresses are shared with NMVB marketing team (MPIs and Pitt PM) by the Meso Fndn which includes their pilot grant program applicants as well as their lifetime list of their national meeting attendees. An “opt out/unsubscribe” option is offered to each e-mail NMVB e-mail list recipient. We actively update these lists and provide quarterly e-mails marketing the NMVB.

3) Posters and podium presentations: NMVB maintains a regular presence at relevant research meetings (e.g. Meso Fndn Symposia, International Mesothelioma Interest Group and other translational cancer research meetings).

4) Marketing booth: NMVB distributes brochures, bookmarks, descriptive publications and an “Intro to NMVB – User Guide” at research meetings outlined above.

Outreach to Patients: Together with CDC NIOSH, the NMVB (and the new Mesothelioma Patient Registry at U Md), working in collaboration with the Meso Fndn will continue to publicize the availability of this resource to prospective patients afflicted by mesothelioma and the research community that serves them. The Meso Fndn is the nation’s primary advocacy group for mesothelioma patients and families, and the NMVB team is strongly represented at the Meso Fndn meetings, which allows NMVB to communicate effectively about the NMVB to the scientific and advocacy community. Additionally, the individual sites will discuss the importance of this research directly with the patients who are often members of the Meso Fndn.

B.6 - What do you plan to do during the next reporting period to accomplish the goals?

The NMVB will continue to innovate in developing research resources for this rare but deadly asbestos related cancer. The NMVB will expand to a new US geographic site (Baylor College of Medicine) and add a number of new biospecimen from a diverse patient population which includes African Americans, Asian, Hispanic and native/Pacific Islander patients. In addition, we will add new data types (imaging and proteo-genomic data) from both peritoneal and pleural mesotheliomas across the network. We will remain focused on the development of biomarkers and therapeutic innovations for this uniformly fatal disease.

C. PRODUCTS

C.1. Publications, conference papers, and presentations

Publications from NMVB: In the current funding period we have enhanced our tracking by developing an NMVB Google Scholar tracking page (see https://scholar.google.com/citations?hl=en&user=SDBimbQI7okC&view_op=list_works&sortby=pubdate) which lists all NMVB publications since 2009. For the 2016-21 period NMVB published 28 publications. More importantly, as measured by total citations (since 2016 and as of 11/28/21), the NMVB has generated 3117 citations and has an h-index of 15 and an i10-index of 41 for the past funding period. More importantly, NMVB citations peaked in 2021 to an all time high passing all previous years. NMVB published articles in the American Journal of Industrial Medicine, American Journal of Pathology, Cancer Cytopathology, Cancer discovery, Cancer Epidemiology and Prevention Biomarkers, Cancers (Basel), Cell, Human Pathology, Modern Pathology, Journal of Molecular Diagnostics, Journal of Thoracic Oncology, Oncotarget and Proceedings of the National Academy of Sciences.

Examples of NMVB-facilitated discoveries from the current funding period include:

- 1) Drs. Becich/Dhir (Pitt), Feldman (U Penn), Melamed/Pass (NYU) contributed 63 NMVB fresh frozen and consented mesothelioma samples to The Cancer Genome Atlas (TCGA) initiative. The results of this effort and analysis of the genomic sequencing of pleural mesotheliomas, led by NMVB team members Harvey Pass (NYU) and Hatice Osmanbeyoglu (Pitt) were published in 2018 in Cancer Discovery as “Integrative Molecular Characterization of Malignant Pleural Mesothelioma” and to date has been cited 257 times.
- 2) Drs. A Hoshino, HS Kim, L Bojmar, KE Gyan, M Cioffi, J Hernandez, et al published “Extracellular vesicle and particle biomarkers define multiple human cancers” in Cell in 2018 and this paper has been cited 192 times.
- 3) Dr. Carbone (NMVB REP), D Shimizu, A Napolitano, M Tanji, HI Pass (NMVB Site PI), H Yang, et al published “Positive nuclear BAP1 immunostaining helps differentiate non-small cell lung carcinomas from malignant mesothelioma” in 2016 in Oncotarget which has been cited 53 times
- 4) Drs. Bartlett (formerly Pitt NMVB co-I) and Pingpank (current Pitt NMVB co-I) published in 2017 “The prognostic significance of BAP1, NF2, and CDKN2A in malignant peritoneal mesothelioma” in Modern Pathology which has been cited 102 times.
- 5) Drs. De Rienzo and Bueno (Harvard, Dana Farber Cancer Center) in collaboration with Castle Biosciences (Houston, TX) published “Validation of a Gene Expression Test for Mesothelioma Prognosis in Formalin-Fixed Paraffin-Embedded Tissues.” The 2018 study confirms that a proprietary gene-ratio test for predicting malignant pleural mesothelioma (MPM) post-surgical outcome is a robust and clinically feasible assay that can be performed using fresh-frozen or FFPE tissue with equal prognostic accuracy. The test effectively stratifies low-, intermediate-, and high-risk patients and is a powerful tool for guiding treatment decisions when managing patients with MPM. Drs. Becich (NMVB PI) and Feldman (Penn site PI) are co-authors of this study.
- 6) Drs. Becich (Pitt PI) and Ganapathiraju (Pitt co-I) published “Mesothelioma Interactome with 367 Novel Protein-Protein Interactions” in Cancers which now expands the NMVB to protein-protein interaction data sharing. This first publication focused on the pleural mesothelioma interactome and a second publication focused on the peritoneal mesothelioma interactome is being submitted for publication.

C.2. Website(s) or other Internet site(s) – include URL(s)

The NMVB's main website is at <https://mesotissue.org/> and includes an innovative cohort (biospecimen and clinical data including outcomes) discovery tool at <https://data.mesotissue.org//data-page.html>. We have also launched a protein-protein interaction discovery tool at <https://hagrid.dbmi.pitt.edu/wiki-MPM/> which is linked off the the "Interactome" tab on the main website.

C.3. Technologies or techniques

The NMVB uses novel technology to share with the mesothelioma research community including the data discovery tool at <https://data.mesotissue.org//data-page.html> and the protein-protein interactome tool at <https://hagrid.dbmi.pitt.edu/wiki-MPM/> which is linked off the the "Interactome" tab on the main website at <https://mesotissue.org/>.

C.4. Inventions, patent applications, and/or licenses

The NMVB has no intellectual property to report as we are a research resource and not discovery science.

C.5. Other products and resource sharing

The NMVB openly shares its biospecimens and clinical data as well as software tools and workflows with the research community.

D. PARTICIPANTS**D.1. What individuals have worked on the project?** Please include calendar, academic, and summer months.

| Commons ID | S/K | Name | Degrees(s) | Role | Cal | Aca | Sum | Foreign | Country | SS |
|---------------|-----|--------------------------|-------------|--------------------|-----|-----|-----|---------|---------|----|
| BECICH | Y | Becich, Michael John | BS,PHD,MD | PD/PI | 4.8 | 0 | 0 | | | |
| MADHAVI | Y | Ganapathiraju, Madhavi K | PHD,MOTH,BS | Co-I | 5.3 | 0 | 0 | | | |
| HARTMANDJ | Y | Hartman, Douglas Joseph | | Co-I | 1.8 | 0 | 0 | | | |
| APENNATHUR1 | Y | Pennathur, Arjun | MD | Co-I | 1.2 | 0 | 0 | | | |
| JCSILVERSTEIN | Y | Silverstein, Jonathan C. | BS, MD, MS | Co-I | 1.2 | 0 | 0 | | | |
| | N | Schwenk, Melissa | | Data/Web Manager | 3.6 | 0 | 0 | | | |
| | N | Stewart, Karla | | Honest Broker | 1.1 | 0 | 0 | | | |
| | N | Wiehagen, Luke | | Project Manager | 3.0 | 0 | 0 | | | |
| | N | Ma, Congrong | | Tissue Coordinator | 1.2 | 0 | 0 | | | |
| | N | Culligan, Melissa | | Research Nurse | 1.0 | 0 | 0 | | | |
| | N | Dube, Emily | | Technician | 3.0 | 0 | 0 | | | |
| | N | Khashab, Tamara | | Data Manager | 4.0 | 0 | 0 | | | |
| GOPARC01 | N | Goparaju, Chandra | | Staff Scientist | 1.0 | 0 | 0 | | | |

D.2 Personnel updates

- a. **Level of Effort:** No
- b. **New Senior/Key Personnel:** No
- c. **Changes in Other Support:** Yes, attached.
- d. **New Other Significant Contributors:** No

E. IMPACT**E.1 - What is the impact on the development of human resources, if applicable?**

N/A

E.2 - What is the impact the Public Health Relevance and Impact? The investigator should address how the findings of the project relate beyond the immediate study to improved practices, prevention or intervention techniques, legislation, policy, or use of technology in public health.

The NMVB is coordinated by the University of Pittsburgh/UPMC (Pitt) and is located in Pennsylvania, which is one of six states in the US that have asbestos-related death rates at 50-100% above the national average. From 1999 to 2017 New York and Pennsylvania had 32,922 deaths from asbestos related disease with the preponderance of mortality from malignant mesothelioma. Despite recent advances in therapy, including immunotherapy, median survivals are consistently 18 months or less. Experts once thought that the worldwide incidence in mesothelioma was expected to flatten in 2020 but unfortunately, that death toll has continued to rise. Even though the link between malignant mesothelioma and asbestos is well known, over 100 million people continue to be exposed in the workplace every year. In the US, approximately 72,000 new cases are expected by 2031. To date, there is no cure for mesothelioma and effective treatments are limited. NMVB aims to support research efforts in the discovery of methods to prevent, diagnose earlier, and more effectively treat this deadly disease by providing a cohort of biospecimens with clinical, pathology and outcome data (as well as proteogenomic and imaging data to the translational research community).

F. CHANGES**F.1 – Changes in approach and reasons for change, including changes that have a significant impact on expenditures**

The NMVB did not experience changes in approach or experience impact on expenditure outside of those imposed by COVID in 2020-21.

F.2 - Actual or anticipated challenges or delays and actions or plans to resolve them

The NMVB did experience COVID related delays which are no longer of concern (except no face to face meeting or travel due to health/safety concerns).

F.3 - Significant changes to human subjects, vertebrate animals, biohazards, and/or select agents

The NMVB did not have any significant changes to report in this funding period.

G. Special Reporting Requirements**G.1 Special Notice of Award Terms and Funding Opportunities Announcement Reporting Requirements**

Attached are the signed certifications and assurances documents.

G.2 Responsible Conduct of Research (RCR)

The NMVB make sure all key personnel receive annual training on RCR

G.3 Mentor's Research Report or Sponsor Comments

N/A

G.4 Human Subjects**G.4.a Does the project involve human subjects?**

Yes. The NMVB does include human subjects as we collect questionnaires, clinical data from electronic health records and well as biospecimens and blood/DNA samples.

G.4.b Inclusion Enrollment Data

The NMVB enrollment table is included below:

| Racial Categories | Ethnic Categories | | | | | | | | | Total |
|---|------------------------|-------------|----------------------|--------------------|-----------|----------------------|--------------------------------|------------|----------------------|-------------|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | |
| | Female | Male | Unknown/Not Reported | Female | Male | Unknown/Not Reported | Female | Male | Unknown/Not Reported | |
| American Indian/ Alaska Native | 2 | 1 | | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Asian | 5 | 8 | | 0 | 1 | 0 | 1 | 1 | 0 | 16 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Black or African American | 16 | 19 | | 1 | 1 | 0 | 3 | 1 | 0 | 41 |
| White | 317 | 1032 | 2 | 6 | 9 | 0 | 24 | 49 | 0 | 1439 |
| Multiple Races | 3 | 4 | | 1 | 6 | 0 | 2 | 0 | 0 | 16 |
| Unknown or Not Reported | 2 | 6 | 1 | 0 | 2 | 0 | 35 | 81 | 59 | 186 |
| Total | 345 | 1070 | 3 | 8 | 19 | 0 | 65 | 132 | 60 | 1702 |

G.4.c ClinicalTrials.gov

No

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

No

G.5 Human Subject Education Requirement

Are there personnel on this project who are newly involved in the design or conduct of human subject's research?

No

G.6 Human Embryonic Stem Cells (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 Vertebrate Animals

Does this project involve vertebrate animals?

No

G.8 Project/Performance Sites

| Organization Name: | DUNS | Congressional District | Address |
|--|-----------|------------------------|---|
| Primary: UNIVERSITY OF PITTSBURGH AT PITTSBURGH | 004514360 | PA-018 | UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH PA 152132303 |
| University of Pittsburgh | 004514360 | PA-018 | The Offices at Baum 5607 Baum Blvd Pittsburgh PA 152063701 |
| New York University | 121911077 | NY-012 | 550 First Avenue New York NY 100166481 |
| University of Maryland | 790934285 | MD-005 | 3112 Lee Building, 7809 Regents Drive College Park MD 100166481 |
| University of Pennsylvania | 042250712 | PA-002 | 3451 Walnut Street, Room P221 Philadelphia PA 191046205 |
| Roswell Park Cancer Institute | 824771034 | NY-026 | Elm and Carlton Streets Buffalo NY 142630001 |

G.9 Foreign Component

No foreign component

G.10 Estimated Unobligated Balance

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes, \$272,781.13. This balance exists due to the loss of UPenn as a site for much of the final budget period as well as the unexpected departure due to medical reasons at the start of 2021 of the replacement project manager, after the departure of Joyce Zelnis, who had been hired for the NMVB project. As it was due to medical reasons, the position had to remain 'filled' per University policy even though we were not paying this person's salary. The person formally resigned in August 2021 and we have since hired a senior person to fill this role in Year 15.

G.11 Program Income

Is program income anticipated during the next budget period?

No

G.12 F&A Costs

Is there a change in performance sites that will affect F&A costs?

N/A

I. OUTCOMES

I. Provide a concise summary of the outcomes or findings of the award, written for the general public in clear and comprehensible language, without including any proprietary, confidential information or trade secrets

Note: project outcome information will be made public in NIH RePORTER

The National Mesothelioma Virtual Bank (NMVB) is a translational research resource for a rare asbestos related cancer which affects the lining cells (mesothelium) of the pleural (lung) and peritoneal (abdomen) cavities of the affected patients. The NMVB collects biospecimens, clinical/outcomes data derived from electronic medical records and asbestos occupational/exposure questionnaires from patients with mesothelioma and shares them with cancer researchers to develop biomarkers which help prevent and treat this nearly uniformly fatal cancer. In the last funding period (2016-21), NMVB added 472 cases to the nearly 1700 cases it shares with the research community to help develop insights toward halting the progression and death from this deadly cancer. In addition, NMVB supplied biospecimens and data to 26 research teams nationally and internationally despite the downturn in research in 2020 and 2021 during COVID. The NMVB supported 28 publications during this funding period resulting in a record number of citations in both 2020 and 2021 and an h-index of 15 and an i10-index of 41 which is remarkable for a rare disease. NMVB contributed to The Cancer Genome Atlas program 63 cases of pleural (lung) mesothelioma which expanded the impact of this CDC NIOSH funded resource resulting in a Cancer Discovery publication in 2018 that has been cited 257 times (as of 11/29/21). The discovery of the BAP1 gene related to mesothelioma was also a major discovery facilitated by this resource with contributions from both the research community and key personnel of NMVB. Finally, to expand the impact of NMVB, we have added protein-protein interaction data from public data sources to NMVB as part of the quest for continued innovation for the novel biospecimen and clinical/outcomes data resource.