Multiple institutions’ research findings using the National Mesothelioma Virtual Bank [version 1; peer review: awaiting peer review]

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Abstract
Mesothelioma remains an under-researched cancerous disease due to the lack of high-quality patient samples and clinical information especially outcomes and asbestos exposure data. The National Mesothelioma Virtual Bank (NMVB) is a biobank in which mesothelioma annotated biospecimens can be made widely available to the research community. Here, we summarized the significant research findings from 20 publications that utilized the NMVB samples for novel biomarker and therapeutic discoveries. The results showed that the use of the NMVB resource was dispersed among a variety of basic science topics including, but not limited to, biomarkers, abnormal gene expression, and potential therapeutic targets. Positive biomarkers included several miRNAs and antibodies, HMGB1, ATG5, PIAS3, pancytokeratin and GATA3. Genes that had mutations or high/low levels of expression were BAP1, a human control gene of importance in this disease, as well as various cytokines, and checkpoint inhibitors TM4SF1, PKM2, ARHGDIA, COBLL1, WT1, FOXM1, and CD30. Treatments investigated include thiostrepton, interferon- gene, and Brentuximab. Publications reviewed indicated a significant impact of the NMVB resource utilized in significant studies focusing on biomarker and therapeutic discoveries, which can act as a model for rare diseases, especially in oncology.

Keywords
National Mesothelioma Virtual Bank, Translational Research, Biomarker, Informatics, Rare Disease Biobank, Patient Registries
Introduction
Mesothelioma is commonly a cancerous tumor lining pleural and peritoneal surfaces. Environmental exposure to asbestos, a naturally occurring silicate mineral, is the leading cause of mesothelioma. Other mineral fibers (e.g., erionite, antigorite, actinolite) are known to be carcinogenic as well. Asbestos and these other mineral fibers are thought to directly interfere with the cell spindle during human mesothelial cell division, leading to mutations and increased pathogenicity. The most common symptoms include breathlessness, chest pain, difficulty swallowing, and pleural fluid accumulation; as disease worsens, it leads to death. Because mesothelioma is aggressive and fatal (approximately 8–14 months survival after diagnosis), reduction in exposure and early diagnosis are essential. Biomarkers, especially mesothelin, have been proven useful in malignant pleural mesothelioma (MPM) diagnoses. Furthermore, sampling measures (pleural fluid), staging, immunohistochemistry (IHC), histology (epithelial, biphasic, and sarcomatoid) and imaging (chest radiography, CT imaging, PET-CT) can be used as distinguishers between diagnosis and progression of the MPM, as well as among MPM subtypes. There are both surgical and non-surgical treatment options available to prolong the survival of patients such as chemotherapy, radiotherapy, targeted therapy, surgery, trimodality (consists of surgery, chemotherapy and radiotherapy), and multimodality. Researchers must uncover and improve treatment options rapidly in order to benefit patients.

It’s challenging and sometimes impossible for biomedical researchers to obtain a sufficient number of mesothelioma patients’ high-quality samples and comprehensive clinical information for analysis. As tissue banking informatics becomes increasingly widespread and improved in collection and storage of human biospecimens, researchers can obtain important results in basic and clinical science research that contribute toward personalized medical approaches in a clinical setting. The National Mesothelioma Virtual Bank (NMVB) (https://mesotissue.org/, last accessed on Oct 17th, 2022) is the largest US mesothelioma patient registry and offers pleural and peritoneal mesothelioma biospecimens with high-quality data that are critical for effective biomarker identification discovery and personalized medicine research. The NMVB database captures robust clinical data including patient demographics, epidemiology, health assessment survey, pathology, treatment, and outcomes (collecting tissue and blood products for various types of molecular analysis). Researchers can access statistical data for public view (https://data.mesotissue.org/data-page.html), or search the collection of mesothelioma biospecimens via the request fulfilment process (https://mesotissue.org/specimens). As a result, the NMVB serves as a leading resource for mesothelioma biospecimens by providing a sufficient number of mesothelioma cases, standardizing the data and specimen collection method, facilitating the sharing of information through the NMVB database, and addressing the issues of constraint through confidentiality and de-identification.

Starting from 2008, the NMVB collected over 2,000 archived mesothelioma and prospective mesothelioma biospecimens that have been accrued from surgical resections and biopsies, including fresh frozen and blood products. Retrospective collections include clinically collected specimens for diagnostic purposes from surgical and diagnostic biopsies, like paraffin tissue samples. Prospective collections are obtained from clinical visits in which physicians obtain permission for each NMVB study via e-informed consent. These researchers have used novel technologies, such as sequencing techniques, staining techniques (such as fluorescence), and DNA/gene expression analyses, to study potential mesothelioma inhibitors, activators, and therapies.

This manuscript aims to summarize the important research findings of key published studies that have utilized NMVB resources and discuss the future direction of the NMVB. The innovative work discussed in this paper was conducted by a total of 320 scholars from 99 institutions or departments.

Biomarker studies related to mesothelioma
In NMVB-related biomedical studies, there are biomarkers that show substantial evidence of mesothelioma and cancer detection in tumor samples. The expression of MicroRNAs as a biomarker can be utilized to determine stages of tumor progression, as well as to categorize cancer types (lung adenocarcinoma versus mesothelioma). The subset of RNA through seven major types (miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205, miR-429) can reduce protein expression (MYC, JUN, VANG1, RH0A, ROCK2, WNT5A, or PLCB1), thereby reducing the likelihood of disease. In prior studies, SV40 has been suggested to contribute to malignant mesothelioma because of its viral capabilities. A 2010 study obtained tissues from several institutions, including the NMVB, to observe SV40 miRNA expression within these cells and detected low expression of SV40 miRNAs, indicating that SV40 may not contribute to mesothelioma tumorigenesis. Another 2013 study further indicated that microRNAs can be investigated in order to understand the change from non-cancerous to cancerous cell. This study found that within several mesothelioma cells, three miRNAs were under expressed (miR-1, miR-206, and miR-133b). Specifically, miR-1 acted as an active malignant pleural mesothelioma tumor suppressor.

Tissue and serum samples were tested in order to establish autoantibodies that could provide accurate recognition of malignant mesothelioma. Although not an all-inclusive list, nine autoantibody biomarkers (PDIA6, MEG3, SDCCAG3,
mesothelioma (MM) biopsies (embedded tissue slides) in this research, BAP1 was mutated in 60% of the specimens.15 Another publication16 focuses on the varying levels of the human control gene in mesothelioma tissues. Out of the immunostaining as an accurate diagnosis predictor between the two cancer forms. Overall, there was a greater lack of lioma patients tissues. In 2020, researchers have studied the Bloom Syndrome (BLM) gene through multiple experiments in mesothelioma cancerous cells. There has been a transition to studies regarding biomarkers (e.g., PIAS3 and HMGB1) that have a role in regula- tion of gene expression in malignant mesothelioma.4,14,15 Out of 70 malignant An important factor of mesothelioma and other cancer types is the modification or increase/decrease of gene expression. Abnormal gene expression in mesothelioma variations in the type of mesothelioma and differences between mesothelioma and other cancers of the lung. 

Interestingly, extracellular vesicles particle (EVP) derived biomarkers are able to distinguish various cancer types. EVP proteins, HSPA8, and CD63 are commonly seen in EVPs. Two other EVP proteins, THBS1 and VCAN, and other less significant biomarkers, such as metabolic enzymes, have the ability to discern between cancer and non-cancer cells.12 Specific EVP proteomes can aid in the classification of 16 cancer types including but not limited to: breast, lung, pancreatic carcinoma, etc.12 In a BAP1 study,4 researchers found that the most specific marker for MM, adenocarcinoma, and SCC was WT1 nuclear positivity, TTF-1 and Napsin A, and p63 and p40, respectively. Another research study15 verified a six-peptide biomarker signature (intercellular adhesion molecule 1, basement membrane-specific heparan sulfate proteoglycan core protein, serum paraoxonase/arylesterase 1, mesothelin, hypoxia up-regulated protein 1, thrombospondin-1) that can be used to detect MPM. Since MPM has a poor prognosis, the tool has the potential to decrease the risk of false negatives when diagnosing individuals. The MPM signature has a higher sensitivity than the SMRP ELISA test.13 A case report14 dealing with a deceased sarcomatoid mesothelioma patient uncovered a loss of p16 cyclin-dependent kinase inhibitor 2A, which is a prominent feature of desmoplastic malignant mesothelioma. Additionally, CK7 and CK5/6 expression is essential in the diagnosis of sarcomatoid mesothelioma. Calretinin, D2-40, and WT-1 are likely elevated in certain central locations (especially the lung). Diffuse sarcomatoid mesothelioma is sensitive for GATA3 expression, but it is improbable that this mesothelioma type will show large levels of TTF-1 and carcinoembryonic antigen. Pleural-based sarcomas are commonly seen to have a loss of pancytokeratin and CD31, a vascular biomarker.

Previously, miRNAs were an essential component of determining the progression of non-cancerous cells to mesothelioma cancerous cells. There has been a transition to studies regarding biomarkers (e.g., PIAS3 and HMGB1) that have a major or minor role in mesothelioma expansion and proliferation. Other biomarkers may be useful in determining variations in the type of mesothelioma and differences between mesothelioma and other cancers of the lung.

Abnormal gene expression in mesothelioma

An important factor of mesothelioma and other cancer types is the modification or increase/decrease of gene expression. BAP1 plays a pivotal role in regulating gene expression in malignant mesothelioma.5,14,15 Out of 70 malignant mesothelioma (MM) biopsies (embedded tissue slides) in this research, BAP1 was mutated in 60% of the specimens.15 Not surprisingly, there is a loss of BAP1 expression in 50% of biphasic mesotheliomas and 25% of sarcomatoid mesotheliomas.14 In addition, BAP1 can be utilized in order to distinguish between non-small lung carcinoma and malignant mesothelioma (MM).14 Due to prior records of immunohistochemical (IHC) differentiation causing difficulty when discriminating between non-small lung carcinoma and MM, this specific study4 aimed to investigate BAP1 immunostaining as an accurate diagnosis predictor between the two cancer forms. Overall, there was a greater lack of BAP1 nuclear staining in MM as compared to non-small lung carcinomas (in which it was extremely rare).

Another publication16 focuses on the varying levels of the human control gene in mesothelioma tissues. Out of the 45 independent mesothelioma samples from the NMVB, 42 tissues were observed to have high levels of this particular gene. In contrast, Merkel cell polyomavirus (MCPyV) was either never seen or detected at extremely low levels in all tissues. In 2020, researchers have studied the Bloom Syndrome (BLM) gene through multiple experiments in mesothelioma patients’ samples and animal models.17 BLM is a helicase enzyme that aids in DNA replication and the repair of DNA damage. There are two BLM mutations: biallelic BLM mutations and inactivating germline BLM heterozygous mutations. Biallelic mutations of the Bloom Syndrome gene cause Bloom Syndrome, leading to the risk of developing cancer because of chromosomal instability, the disruption of cell-cycle processes, and decreased p53-mediated apoptosis. Heterozygous BLM mutations lead to a truncated BLM protein. In a few experiments, the researchers found that some mesothelioma patients contained harmful BLM mutations. Another experiment regarding BLM-silencing human mesothelial cells found reduced caspase-3 levels, and therefore, reduced apoptosis in human mesothelial (HM) cells and reduced levels of phosphorylated histone γ-H2A.X involved in DNA repair. The researchers further conducted a mice experiment and observed an increase in M1 macrophages and levels of TNF-α, IL-1β, IL-3, IL-10, and IL-12(p70) for BLM heterozygous mutated mice compared to WT mice. These cytokines are linked to carcinogenesis.
A gene expression test study developed a potential molecular algorithm that could replace the current MPM staging system (which has issues of validity and comprehension). In this examination, samples undergo clinical tests that assess the expression of genes. Utilizing MPM-matched frozen and formalin-fixed, paraffin-embedded (FFPE) samples, a gene expression score (GES) was confirmed to provide prognostic information about different patient conditions. The expression of four genes (TM4SF1, PKM2, ARHGDIA, and COBLL1) and three ratios (TM4SF1/PKM2, TM4SF1/ARHGDIA, and COBLL1/ARHGDIA) are used in this score, which can allow for a more accurate reading in addition to current staging systems. Cells contain complicated interactions between cell surface receptors and transcriptional factors, leading to gene expressions that dictate the cell’s specific and wide-ranging functions. A SPaRTAN model is utilized to decipher the connections between cell surface receptors and transcriptional factors, which are then used as predictions for future transcriptional factor (TF) activity. The model includes a bilinear regression algorithm that learns an interaction matrix. SPaRTAN was applied to malignant peritoneal (MPeM) and pleural mesothelioma (MPM) tumors to obtain and analyze the regulatory states of CD8+ T cells. A portion of the MPeM CD8+ T cell population that was tested had high PD-1, TIM3, and TOGIT (checkpoint inhibitors) expression. A portion of the MPM CD8+ T cell population had the same results, indicating exhausted CD8+ T cells in these tumors. BCL3 activity was found in MPeM CD8+ T cells when PD-1 was present, but not in MPeM CD8+ T cells.

Overall, BAP1 plays an essential role in affecting malignant mesothelioma – showing a reduction in gene expression in these BAPI studies. Similarly, abnormal expression levels of certain genes (e.g., human control gene and BLM gene) may be indicators of mesothelioma. Researchers have constructed systems, such as the SPaRTAN and GES score, to understand cell activity.

Therapeutic targets for mesothelioma treatment
Researchers have determined numerous therapeutic targets and potential inhibitory substances or molecules that could aid in the treatment of mesothelioma. There are two therapeutic targets, FOXM1 protein and CD30, that can decrease cell growth. Researchers observed that Forkhead box M1 (FOXM1) was present in the majority of human malignant mesothelioma cells (>50%). The protein, FOXM1, controls gene expression in the cell cycle (specifically S phase entry to mitosis), which assists in cell progression. CD30 is a cytokine receptor that aids in the regulation of apoptosis, which means that the presence of the gene in mesothelioma cells should be high. To counter tumor progression, researchers utilized thiostrepton (TS) to inhibit this specific protein. TS disables peroxiredoxin 3 (PRX3) by increasing mitochondrial oxidant production, leading to the decrease of the FOXM1 protein and CD30 that cause cell death. As a result, FOXM1 and CD30 have the capability of being a therapeutic target and TS could be a therapeutic strategy. Researchers, in 2015, observed the intensity of immunostaining using tissue microarray slides from the NMVB and applied brentuximab vedotin to target CD30 antigens. After subsequent analyses, CD30 mRNA expression was abnormally high in mesothelioma tissues, giving further evidence that the receptor could be a therapeutic target in the future. And brentuximab Vedotin does impact the activity of CD30, leading to decreased cell growth and survivability.

Furthermore, there are two widely known non-surgical treatments, chemotherapy and radiation therapy, that are involved in decreasing size and morbidity with MPM. Unfortunately, studies have shown that malignant pleural mesothelioma is not as affective. A University of Pennsylvania Medical Center study hypothesized that a vesicular stomatitis virus (VSV) vector that incorporated an Interferon-β gene could effectively prevent the growth of lysis mesothelioma cells because the virus is normally an oncolytic agent. Forty-eight mesothelioma tumors were obtained from the NMVB for various treatments (hIFN-β, IFN-β ELISA, IFN-β bioassay). As presumed, the delivery of genes results in a decrease of lysis activity and an increase in antitumor immune responses.

These studies have established FOXM1 and CD30 as therapeutic targets, and thiostrepton and brentuximab vedotin as therapeutic strategies that decrease cell stability. Additionally, the treatment of VSV vectors containing the Interferon-β gene serves as a cell progression inhibitor, as well.

Cases in which the usage of tumor samples aided in the determination of potential biomarkers, gene expression, and therapeutic factors for general mesothelioma and/or differentiating mesothelioma subtypes are summarized in Table 1.

Biomedical informatics research in NMVB
Through the process of continuously enriching the research cohort of mesothelioma patients and providing samples and research data to external institutions, the NMVB team has also been upgrading NMVB infrastructure using state-of-art informatics techniques and sharing our experience in peer-reviewed articles. We developed a multidisciplinary approach to conduct honest broker service efficiently and effectively, sharing our practical experience in Ref. Using mesothelioma as an example, we have developed and deployed common data elements for tissue banks for translational research in cancer, which is generalizable to other types of cancers.
| Category                          | Research samples used in the study (not limited to samples from NMVB, may include samples from other resources)                                                                 | Research findings                                                                                                                                                                                                 | Publication |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| **Biomarkers in tumor samples**  | 100 mesothelioma tumor samples: 77 mesothelioma tumor samples (NMVB) and 23 (Brigham and Women’s hospital) 32 adenocarcinoma tumor samples (National Disease Research Interchange) | Specifically, these 7 major types of microRNA, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205, miR-429, can lead to the reduction of MYC, JUN, VANGL1, RHQ2, ROCK2, WNT5A, or PLCB1 expression that is commonly found in mesothelioma. | 6           |
|                                  | 28 nonmalignant biopsies, 20 pleural biopsies from lung adenocarcinoma patients and 94 mesothelioma tumor samples (made up of 42 epithelioid, 18 biphasic, 10 sarcomatoid, and 24 non-histologically defined mesothelioma patients) | SV40 is not a useful biomarker of mesothelioma.                                                                                                                                                                                                                     | 7           |
|                                  | (unknown number) tumor samples from NMVB, 28 tumors (University of Minnesota Cancer Center), 6 patient’s normal parietal pleura without malignancies of any kind (Tissue Bank at Stanford Center), MPM cell lines (epithelial and sarcomatoid) (National Caner Institute) | miR-1 acts as an active MPM tumor suppressor.                                                                                                                                                                                                                     | 8           |
|                                  | 5 tissue and 215 serum samples (NMVB)                                                                                                                                                                                                                                                                                                                                                           | 9           |
|                                  | 9 autoantibody biomarkers (PDIJ6, MEG3, SDCCAG3, IGHG3, NADH dehydrogenase 1, BACRP11-484D18, CH507-528H12, RP11-413M2) in tissue and serum samples within the phage library (T7 MM) could provide accurate recognition of malignant mesothelioma |                                                                                                                                                                                                                                                                   |             |
|                                  | NMVB tissue microarray slides (does not state the exact amount)                                                                                                                                                                                                                                                                                                                                    | 10          |
|                                  | Low PIAS3 expression in MM cells. PIAS3 prevents mesothelioma growth through the inhibition of STAT3 activity.                                                                                                                                                                                                                       |             |
|                                  | 29 serum samples from individuals with 4+ years of continuous exposure to asbestos fibers and mesothelial HMGB1-cKO mice                                                                                                                                                                                                                                                                          | 11          |
|                                  | HMGB1 and ATG5 are biomarkers likely to cause carcinogenesis.                                                                                                                                                                                                                                                                          |             |
|                                  | 497 normal and cancer-associated human and murine-derived samples                                                                                                                                                                                                                                                                                                                                 | 12          |
|                                  | Extracellular vesicle and particle biomarkers are able to distinguish various cancer types through two main proteins (HSPA8 and CD63) and other less expressed proteins (such as THBS1 and VCAN).                                                                                                                                                                                                                   |             |
|                                  | 213 MPM patients and 189 Asbestos-exposed patients                                                                                                                                                                                                                                                                                                                                               | 13          |
|                                  | Intercellular adhesion molecule 1, basement membrane-specific heparan sulfate proteoglycan core protein, serum paraoxonase/arylesterase 1, mesothelin, hypoxia up-regulated protein 1, and thrombospondin-1 are biomarkers that can detect MPM.                                                                                                                                                  |             |
|                                  | 1 sarcomatoid mesothelioma patient                                                                                                                                                                                                                                                                                                                                                              | 14          |
|                                  | There was positivity for pancytokeratin and GATA3. Additionally, there was a loss of CDKN2A and negativity for calretilalin, D2-40, HBME and WT-1.                                                                                                                                                                                                 |             |
Furthermore, the NMVB team has been using NMVB data to conduct internal scientific research. We explored the potential of using automated image analysis in the evaluation of mesothelioma tissue microarray, which matched the performance of manual scoring by pathologists. This result indicates that an automated image analysis approach may be a reproducible, objective, and accurate way for the immunohistochemical assessment of biomarker expression. In a cancer history classification study, we applied Natural Language Processing (NLP), a modern Artificial Intelligence technique, to automatically classify personal and family history from free-text medical reports of mesothelioma patients, with a high accuracy. In another study, we conducted a retrospective review of the NMVB cohort, and identified factors influencing malignant mesothelioma survival, including age (younger than 45), gender (female), epithelioid histological subtype, staging (I), peritoneal occurrence, and having the combined treatment of surgical therapy with chemotherapy. Moreover, for malignant pleural mesothelioma, we developed a novel computational algorithm that automatically discovered 364 potential protein-protein interactions, of which five interactions (BAP1-PARP3, KDR-ALB, PDGFRA-)

<table>
<thead>
<tr>
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<th>Research findings</th>
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<tr>
<td>Changes of gene expression</td>
<td>32 primary lung adenocarcinomas, 13 primary lung SCC and 35 MM biopsies (20 epithelial, 8 biphasic, and 7 sarcomatoid)</td>
<td>MM has a lack of nuclear staining for BAP1 and non-small lung carcinoma has a positive BAP1 staining. The most specific marker for MM, adenocarcinoma, and SCC was WT1 nuclear positivity, TTF-1 &amp; Napsin A, and p63 and p40, respectively.</td>
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<td>70 MM biopsies (embedded tissues slides)</td>
<td>BAP1 is mutated in 60% of the specimens, playing a pivotal role in regulating gene expression.</td>
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<td>45 independent mesothelioma samples</td>
<td>42 tissues were observed to have high levels of the human control gene. In contrast, merkel cell polyomavirus was either never seen or detected at extremely low levels in all tissues.</td>
<td>16</td>
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<td>122 pleural and peritoneal mesothelioma patients and germline DNA of 10 patients with mesothelioma</td>
<td>The cytokines, TNF-α, IL-1β, IL-3, IL-10, and IL-12(p70) are linked to carcinogenesis. BLM mutations can impact processes of the cell and proteins leading to cell death.</td>
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<td>73 patients with FFPE biopsy specimens and clinically documented evidence of surgical resection of the tumor with diagnosis of histologic subtype</td>
<td>As part of the GES system, the expression of four genes (TM4SF1, PKM2, ARHGDIA, and COBLL1) and three-ratios (TM4SF1/PKM2, TM4SF1/ARHGDIA, and COBLL1/ARHGDIA) are used for a more accurate patient condition reading.</td>
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<td>Therapeutic targets and potential inhibitory substances</td>
<td>Tissue microarrays (included duplicate paraffin-embedded sections for 46 tumors)</td>
<td>FOXM1 allows for cell progression. In turn, thiostrepton can be used to interfere with PRX3 in FOXM1 protein and cause cell death.</td>
<td>20</td>
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<td>83 mesothelioma specimens</td>
<td>CD30 levels are high in mesothelioma cells. Brentuximab vedotin targets CD30 antigens.</td>
<td>21</td>
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<td>48 mesothelioma tumors</td>
<td>Interferon-β prevents the lysis of mesothelioma cells when incorporated into a VSV vector, which is a virus that is normally an oncolytic agent.</td>
<td>22</td>
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**ALB, CUTA-HMGB1, and CUTA-CLPS** were validated experimentally; our comparative transcriptome analysis identified five potentially repurposable drugs targeting the interactome proteins (cabazitaxel, primaquine, pyrimethamine, trimethoprim, and gliclazide). To share our findings with the whole research community, we make the discovered interactions publicly available through Wiki-MPM (https://hagrid.dbmi.pitt.edu/wiki-MPM/, last accessed on July 31th, 2022). Realizing the computational approach may be more needed by rare types, we further applied similar techniques on malignant peritoneal mesothelioma and identified 417 novel protein-protein interactions.

**Discussion**

With regard to research findings using NMVB, there was a high number of publications that investigated and examined specific genes’ roles in mesothelioma, such as IFN-β, BAP1, and PIAS3, and pre-existing or current cancer/mesothelioma therapies, such as HDACi panobinostat, CRS, and HIPEC. In addition, there were publications related solely to the development and utilization of NMVB as a significant resource. Many publications had some positive scientific findings that allowed for possible therapies to aid in mesothelioma or cancer treatment including (but not limited to) delivery of type I IFNs, curcumin, brentuximab vedotin, panobinostat, and CRS/HIPEC. There were also gene markers that were not related to or did not provide enough information for lung inflammation, cancer, or mesothelioma, such as MCPyV DNA and CRP. When comparing mesothelioma and lung adenocarcinoma, there were certain miRNA traits that varied, indicating that miRNAs can act as potential biomarkers. The NMVB has been proven to a robust biobanking resource to support the fundamental domain of biomedical science, including molecular and genetic epidemiology, molecular pathology and pharmacogenomics.

The NMVB was cited in 879 publications in 2021 compared to 676 publications in 2020 (a nearly 30% increase). NMVB is on track for over 1000 citations in CY2022, establishing that the bank is important in sharing genomic data and specimens. There are many NMVB publications from the users of the resource that focus on biomarker development, of which some are previously discussed in this publication.

The NMVB plans to improve its system on including which specimen types and related annotation by taking mesothelioma researchers’ feedback and expand the reach of its database in the upcoming years. Currently, there are nine collaborating institutions that are a part of the NMVB, including New York University, University of Pittsburgh/UPMC, University of Pennsylvania, Roswell Park Cancer Institute, Mount Sinai School of Medicine (currently inactive), Baylor College of Medicine, Fox Chase Cancer Center, Temple University and University of Maryland (https://mesotissue.org/about/, last accessed on July 31th, 2022). Additionally, NMVB hopes to make use of international networks like MesoNet (France), the United Kingdom Biobank and the Italian Mesothelioma Biobank to obtain far-reaching and increased data from mesothelioma patients that can be accessed by researchers.

The NMVB is making efforts with the CDC and MedMorph to create advanced infrastructure and refined tools that can enhance data extraction of asbestos exposure and occupational health data. With so many years of practical experience, the team leaders of NMVB actively joined a nationwide workshop discussing the potential usefulness and feasibility of national mesothelioma registry. Moving forward, the NMVB is working with an epidemiology and occupational health expert and gain knowledge through the CDC NIOSH to enhance the investigation of occupational history and the exposure that may contribute to mesothelioma.

Lastly, the NMVB utilizes a communications plan involving the NMVB website, mass mailings to users, and presentations at national meetings. The NMVB website contains links to the CTSA, NIH, NCI, Office of Biospecimen and Biorepository Research, National Center for Biotechnology Information, the Cancer Genome Atlas Project and dozens of other biorepository and relevant organizational websites. These supply information about mesothelioma, biospecimens, and other specimens via a searchable database. Letters and/or e-mails are sent to investigators and their cancer research coordinators that have published articles in mesothelioma research in the recent past as well as investigators that have received or applied for Mesothelioma Foundation research grant funding. NMVB is always present and markets the resource especially at the Mesothelioma Applied Research Foundation’s annual symposium, the International Mesothelioma Interest Group’s every other year meeting, the AACR meeting and other research meetings. The NMVB will have outreach efforts, such as increasing the awareness of the NMVB resource, increasing education about the function NMVB and how it is operated, providing information about scientific advances facilitated by NMVB, and learning from the affected communities about the disease especially through active participation at the International Symposium on Malignant Mesothelioma (Mesothelioma Foundation sponsored annual meeting).

**Conclusions**

The NMVB has aided in biomarker, gene expression, and therapeutic target studies. NMVB plans to improve its resources and system allowing for future researchers to make widespread use of the data and specimens within the
database. It is essential that the NMVB dataset continues to expand and play a pivotal role in cancer research, especially for possible treatments/phenomena that target NMVB specimens and aid in inhibiting tumor growth in certain cells.

Data availability
No data are associated with this article.

Acknowledgements
We thank Schwenk, Melissa Dawn for setting up the NMVB research paper Google scholar webpage: https://scholar.google.com/.

References


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