BREATH OF HOPE

Summer 2016

a publication by the Mesothelioma Applied Research Foundation

THE HUMAN SIDE OF CLINICAL TRIALS

Read more on page 12

INSIDE: In-depth coverage of 2016 clinical trials, treatments, collaborations, opinions, and more!

Photo courtesy of Jenna Daniel

H. Richard Alexander
University of Maryland School of Medicine

Chair, Board of Directors
Mesothelioma Applied Research Foundation

Melinda Kotzian
Mesothelioma Applied Research Foundation

Chief Executive Officer

MESSAGE FROM THE CEO AND THE CHAIR OF THE BOARD OF DIRECTORS

Dear friend of the Meso Foundation,

We are proud to present to you the Summer 2016 issue of the Breath of Hope newsletter. Although progress in the research of a cancer like mesothelioma can never move fast enough, the mesothelioma treatment landscape has changed dramatically in recent years. Despite Alimta/Cisplatin still being the only FDA-approved treatment, today's patients have a lot to consider when choosing a treatment.

With that mind, we have reached out to several experts and have asked them to help us shed light on some of the most frequently discussed questions and concepts currently seen in clinical trials. We hope you find this information useful.

As we, as an organization, continue funding research and continue our focus on accelerating the development of effective treatments, patients and their families remain front and center in our work. Depicted in our cover story is one such family that generously shared their moving story with us and our readers.

In addition to the in-depth coverage of clinical trials, this newsletter also includes information about our upcoming events such as Mesothelioma Awareness Day on September 26, our San Francisco and Chicago conferences on September 16 and October 7, respectively, and our Symposium in March of next year. Please consider participating as much as you can.

With that, we wish to thank you for the opportunity to serve you and look forward to continuing the important work of this foundation.

With much appreciation,

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Published by the Mesothelioma Applied Research Foundation

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Board of Directors Chair: H. Richard Alexander, MD
Science Advisory Board Chair: Tobias Peikert, MD

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Layout: Maja Belamaric

Cover photo courtesy: Jenna Daniel, the Kocis Family.

FOUNDATION'S SCIENCE ADVISORY BOARD'S GOALS

The new chair of the Meso Foundation's Science Advisory Board shares his vision for the future of the board and the future of the organization's research efforts.

By Tobias Peikert, MD
Mayo Clinic

My name is Dr. Tobias Peikert. I am a pulmonary specialist at Mayo Clinic in Rochester MN. My clinical interests are thoracic malignancies and more specifically mesothelioma. I currently serve as the chair of the multidisciplinary Mayo Clinic Mesothelioma Interest Group. I am a clinical investigator focused on translational research in tumor immunology and viro-immunotherapy in mesothelioma and lung cancer. I am very honored to serve as the chair of the Scientific Advisory Board (SAB) of the Meso Foundation.

With the help and support of all members of the SAB, we will strive to continue to provide expert scientific support to the foundation during the grant review process of the Meso Foundation's Research Grant Program. We will maintain a fair, ethical and unbiased grant review process to identify the most scientifically sound application with the highest clinical relevance for mesothelioma patients for consideration of funding by the foundation. We are also planning to provide constructive scientific feedback to all applicants, which will hopefully result in advances in mesothelioma research beyond the funded research projects.

Furthermore, I expect for the SAB to provide scientific expertise to the Meso Foundation's efforts to organize high quality annual scientific meetings to enhance collaborations between international and national young and established investigators in the field of mesothelioma while fostering also an active exchange between patients with mesothelioma and their family members and mesothelioma researchers. In this context, we will also provide the scientific expertise to the Foundation's efforts to provide up to date information about all medical aspects of mesothelioma through the foundation website.

In light of the rapidly evolving advances in cancer therapeutics across various malignancies, I am envisioning that the SAB can help guide the Meso Foundation's efforts to promote clinical research collaborations between international centers of excellence in the field of mesothelioma to facilitate the rapid translation of mesothelioma relevant exciting advances into multi-site clinical trials, support continued advances in the Staging system and development of predictive biomarkers to strive towards stratified care for mesothelioma patients.

In summary, I am very honored to serve as the chair of the SAB and hope that our team will continue to scientifically support the efforts of the Meso Foundation to cure this devastating disease.

WHAT CLINICAL TRIALS ARE CURRENTLY AVAILABLE AND HOW DO THEY ATTACK MESOTHELIOMA?

With only one FDA-approved treatment, mesothelioma patients rely on clinical trials for treatment. Currently, there are a number of promising therapies being tested in a clinical trial setting, offering mesothelioma patients choice, but also difficult decisions.

By Mary Hesdorffer, NP
Mesothelioma Applied Research Foundation

There are many promising therapies under investigation in malignant mesothelioma, and here we will introduce you to some of the strategies being used. Our own personal cancer moonshot is underway with more drug trials than ever before and with unexpected responses being observed in a subset of the mesothelioma population.

At this point, the only Food and Drug Administration (FDA) approved treatment regimen for mesothelioma is a combination of pemetrexed and cisplatin. Today, many clinical trials are testing new drugs in combination with the approved regimen.

A randomized controlled trial of 448 newly diagnosed pleural mesothelioma patients demonstrated a statistically significant increase in overall survival when bevacuzimab was added to pemetrexed and cisplatin. Bevacuzimab is a vascular endothelial growth inhibitor (VEGF inhibitor) that prevents angiogenesis, which is the formation of new blood vessels used to feed tumors the nutrients they need for continued growth. Thus, VEGF inhibitors starve tumors of these nutrients.

Unfortunately, since this trial was conducted in Europe, the approval process in the United States is a bit more complicated. Though not currently approved by the FDA, the National Comprehensive Cancer Network (NCCN) has added this combination to its guidelines for malignant mesothelioma. This is important, as most insurance companies follow these guidelines when reimbursing for cancer care.

Another drug in this class is nintedanib, an oral drug that inhibits VEGF, platelet derived growth factor (PGDFR), and fibroblast growth factor (FGFR). These three factors are thought to be responsible for sustaining tumors, tumor growth, and the cancer's ability to metastasize. A randomized placebo controlled global trial is currently underway to determine if adding nintedanib to the current first line approved combination of pemetrexed and cisplatin is superior to pemetrexed and cisplatin plus a placebo.

Checkpoint inhibitors

Other current trials are testing the use of checkpoint inhibitors as a form of immunotherapy. Such cancer immunotherapy strategies tested in the clinic have typically been aimed at stimulating a T-cell response against specific tumor antigens. There are two types of T-cells. Killer T-cells are able to see inside our bodies own cells simply by scanning their surface. This mechanism allows killer T-cells to hunt down and destroy cells that are infected with germs or that have become cancerous. The other main type of T-cells is called helper T-cells. Helper T-cells orchestrate an immune response and play important roles in all arms of immunity.

One reason these prior approaches, including therapeutic cancer vaccines, have not generally been successful is that T-cells have "checkpoints," such as PD-1 and CTLA-4, to guard against autoimmunity and to protect tissues from damage by an overly enthusiastic immune response. We are now testing PD1/PDL1 and CTLA-4 inhibitors to stop the immune system from protecting cancer cells, essentially taking the brakes off the immune system.

Some such agents, including pembrolizumab, avelumab, atezolizumab, tremeluminab and ipilimumab, are currently in testing or have recently been tested in malignant mesothelioma. Though some studies have not reported favorable results, these immunotherapies will continue to be tested in clinic as we continue to gain further understanding of how best to use them. We may see them used in the newly diagnosed, after surgery to prevent the return of cancer, in the metastatic setting, and/or combined with others in this class of drugs, such as CTLA-4 plus PDL1, CTLA-4 plus a MTOR inhibitor (LY3023414), or even in conjunction with chemotherapy.

Mesothelin Directed Therapy

There are also clinical trials designed to target mesothelin. Mesothelin is a protein found on the outside of epithelial mesothelioma cells, which was discovered at the National Cancer Institute and developed by a team of scientists, including our past Science Advisory Board Chair Dr. Raffit Hassan. This has been an exciting breakthrough in mesothelioma, resulting in a number of clinical trials being developed to exploit mesothelin as a target.

Immunotoxins use mesothelin to gain access to mesothelioma cells and deliver a toxin directly into the tumor, thus sparing many of the systemic side effects observed in traditional chemotherapy. SS1P, pioneered at the NCI, has demonstrated activity in mesothelioma and a new trial has been launched to build upon the knowledge acquired in the earlier clinical trials.

Amatuximab, a monoclonal drug antibody that targets mesothelin, is now being tested in a randomized global clinical trial that is testing pemetrexed and cisplatin plus amatuximab vs. pemetrexed and cisplatin plus a placebo. The purpose of this trial is to determine if adding amatuximab to our current FDA approved regimen is better than the standard treatment.

Anetumab ravtansine, an antibody drug conjugate that targets mesothelin, is also being tested in clinical trials. The design is a randomized trial of vinorelbine vs. anetumab. The results of this trial, if positive, could bring about an approval for anetumab in the second line setting for mesothelioma. BMS-986148 is another antibody drug conjugate that targets mesothelin and it is currently in a Phase I/II trial for solid tumors (there are a number of additional cancers which express mesothelin).

Vaccines are also being developed to target mesothelin. For example, CRS 207 is a vaccine that utilizes a modified version of the listeria virus to kill mesothelioma tumors. It has demonstrated activity when used in conjunction with pemetrexed and cisplatin in newly diagnosed pleural mesothelioma patients.

There are also a number of trials that modify the patients' own immune cells (T-cells) to recognize and attack mesothelioma tumors by targeting mesothelin. In this case, a patient's cells are collected and modified in the lab and then infused back into the patient. There have been some dramatic results reported in a number of tumors.

We hope this article is helpful to you, but we understand this information is by no means meant to be complete. If you have any questions or are considering enrolling in a clinical trial, please contact the Meso Foundation.

> ***Our own personal cancer moonshot is underway with more drug trials than ever before and with unexpected responses being observed in a subset of the mesothelioma population.***

About the Author
Mary Hesdorffer, NP, is the executive director of the Mesothelioma Applied Research Foundation. Ms. Hesdorffer is fully credentialed as a nurse practitioner and has spent nearly 20 years actively treating patients with mesothelioma.

UPCOMING BENCH TO BEDSIDE CLINICAL TRIALS

By Marjorie G. Zauderer, MD, MS, FACP

Despite the recent negative results of the large tremelimumab trial, DETERMINE, which were presented at the American Society of Clinical Oncology Annual Meeting in June 2016, many exciting novel therapies for mesothelioma are currently in development. Mimicking success in other malignancies, new drugs are being designed to target and exploit the underlying biology of mesothelioma. By capitalizing on laboratory discoveries, rational treatments are identified and tested so that advances are made more rapidly. In particular, three translational advances with upcoming clinical trials address some of the most common molecular alterations/features in mesothelioma – BAP1, NF2, and WT1.

BAP1: BAP1 alterations in mesothelioma were first reported in 2011 by Dr. Ladanyi's research group. Working in Dr. Ross Levine's leukemia research lab, Dr. LaFave discovered that BAP1 mutant cancers (both leukemia and mesothelioma) are very dependent on another protein EZH2 which influences the expression of a variety of genes. In the laboratory, Dr. LaFave showed that using an EZH2 inhibitor causes cancer cell death, most pronounced in cells with altered or absent BAP1. Luckily, an EZH2 inhibitor already exists and a dose has been established. Therefore, a phase II study of the EZH2 inhibitor tazemetostat in BAP1 mutant mesothelioma is planned to open in the summer of 2016 for patients with pleural or peritoneal mesothelioma who have previously had chemotherapy.

NF2: While NF2 mutations were identified in mesothelioma many years ago, interventions targeting the pathways involved with NF2 signaling have yielded disappointing results to date. Dr. Giancotti's research group, however, recently discovered an additional anti-cancer function of the NF2 pathway that occurs in the nucleus of cells. With NF2 mutations, there is an important dependence on the NEDD8-activating enzyme to carry out abnormal pro-growth signaling. In the laboratory, inhibition of the NEDD8-activating enzyme was particularly lethal in NF2 mutant cancer cells. As with EZH2 inhibitors, a NEDD8-activating enzyme inhibitor already exists and a dose has been established. A clinical trial with this inhibitor is soon to follow.

WT1: WT1 is commonly expressed on the surface of mesothelioma cells but is not expressed on normal tissues. Because of the selective expression of WT1 on malignant cells, Dr. Scheinberg created a peptide (protein) vaccine for WT1 to trigger people's own immune systems to selective target and destroy cells expressing WT1. After creating and optimizing the vaccine in the laboratory, a safety study was conducted. Once proven safe, a phase II study of the WT1 vaccine, now called SLS-001, was conducted in patients with pleural mesothelioma who completed multimodality treatment. Based on the encouraging results of this small clinical trial, a larger international study is planned.

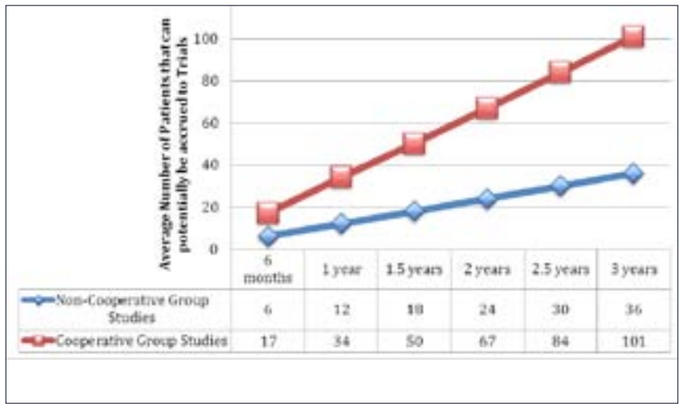
These three areas of investigation are a partial snap shot of the provocative translational research taking place in mesothelioma, and they exemplify the promise of the bench to bedside process.

About the author
Marjorie G. Zauderer, MD, MS, FACP, is a medical oncologist specializing in the care of patients with lung cancer and mesothelioma at Memorial Sloan Kettering Cancer Center.

COLLABORATIVE MESOTHELIOMA RESEARCH: DESIGNING A RENAISSANCE

By Kanwal Raghav, MD and Anne Tsao, MD

Mesothelioma is an archetype of a rare cancer. Unfortunately, the rarity of the disease does not diminish the impact of this malady on the lives of the rare few that are afflicted by it. With the exception of few successes, such as the EMPHACIS trial, there has been a scarcity of adequately powered and randomized trials in this orphan cancer. Consequently, despite key advances in therapy, the prognosis for mesothelioma has not improved greatly over the past few decades and the median survival of unresectable disease is dismal. While, there is a large unmet need to develop novel therapies in mesothelioma to improve patient outcomes, the paucity of patients at any single center will always be the foremost limitation to performing large and efficient studies.



	6 months	1 year	1.5 years	2 years	2.5 years	3 years
Non-Cooperative Group Studies	6	12	18	24	30	36
Cooperative Group Studies	17	34	50	67	84	101

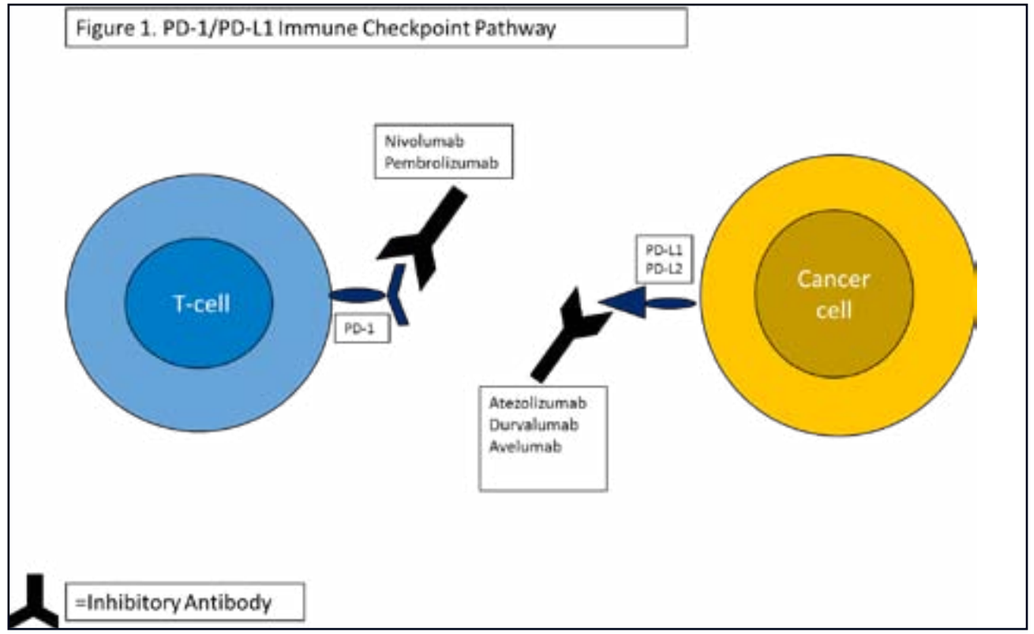
The International Rare Cancers Initiative (IRCI) established in 2011 is a testament to the realization that rare cancers need collaborative large scale efforts to enhance progress. In the United States, the cooperative groups sponsored by the National Cancer Institute (NCI) present to us a unique opportunity, already existent, for such endeavors. Their achievements in pediatric cancers are evidence enough that these collaborative approaches are valuable and can impact patient care in rather uncommon malignancies. The cooperative group collaborations extend across the United States and also internationally allowing for not only faster but also more pervasive research. The existing shared infrastructure and centralized resources of cooperative groups allows faster accrual with lower shared executive costs. This is critical to mesothelioma since traditionally there has been a lack of interest and financial backing of industry in developing novel therapeutics in this disease.

We surveyed clinical trials on mesothelioma published on PubMed and found 59 studies published in the last 10 years, 20 of which were done in the United States. Of these 40% were done through the cooperative groups. Notably, cooperative group studies accrued patients at a significantly higher rate (approximately an average of 3 patients per month) than other studies (1 patient per month). Figure 1 shows the expected size of studies that can be accomplished using a cooperative group network in the United States compared to non-cooperative group studies. This analysis compellingly demonstrates that cooperative group studies are more efficient and accrue patients at a higher rate than non-cooperative group studies, making larger and more robust studies feasible.

Despite organizational, regulatory and operational challenges associated with cooperative groups, the benefit of a more widespread access to patients is expected to overcome these limitations. The ability to complete large trials rapidly can be instrumental in bringing innovative interventions to patients in a timely fashion in an effort to improve their outcomes. Integration of innovative trial designs within a cooperative group network may lead to increased pace of discovery in mesothelioma and deliver practice-changing results.

The present circumstances are reminiscent of a little fable from the Panchatantra. The tale begins with a trap, set by a hunter with grains strewn under a tree. A flock of doves swoop down to eat the grains and are instantly trapped in the hunter's net. As the huntsman approached, the doves flapped their wings individually in a desperate bid to escape. After several futile attempts they realize that the net was "too big" for any one of them to lift individually, but if they all, "together" flew upwards synchronously, they could lift the snare and carry it far away from the hunter. It is time for all of us to recognize that the problem of this orphan disease is "too big" and will be best resolved with a cooperative and organized research undertaking. We believe that this cultural shift is vital to the future of mesothelioma research and what's more is that we owe this to our patients who look towards us for answers and hope.

About the authors
Kanwal Raghav, MD is the Assistant Professor in the Department of Gastrointestinal (GI) Medical Oncology at The University of Texas MD Anderson Cancer Center.
Anne Tsao, MD, is the Associate Professor in the Department of Thoracic/Head and Neck Medical Oncology and the Director of the Mesothelioma Program at The University of Texas MD Anderson Cancer Center.



PD-1 AND PD-L1: WHAT ARE THEY AND HOW DO THEY DIFFER?

Recently, immune checkpoint inhibitors have been the focus of much discussion.

By Kristen A. Marrone, MD

There has been a lot of recent interest in the use of immunotherapy in the treatment of many cancer types, including mesothelioma. The use of immunotherapy is the idea of using the body's own immune system (the system that recognizes and tries to kill 'foreign' insults, such as infections or cancers) to fight your cancer. Scientists continue to work to understand the ways our body's immune system interacts with cancer cells in our bodies. One of the relatively recent findings has been the discovery of how cancer cells can use 'immune checkpoints' to evade healthy immune systems.

Immune checkpoints are proteins our immune system cells use to tell the difference between 'foreign' cells and 'self' cells. Some of these checkpoints are like red lights, telling the immune system not to attack a specific cell. Other checkpoints are like green lights, telling the immune system to attack a specific cell. PD-1 is an immune checkpoint found on an immune cell called a T-cell, and inhibits (stops) normal T-cell function when it is turned on by another immune checkpoint protein called PD-L1 (Figure 1). PD-L1 has been found on many different kinds of cancer cells, including mesothelioma, and is thought to be one way that these cancer cells can turn off the normal immune response that would otherwise harm them.

What are immune checkpoint inhibitors?

Immune checkpoint inhibitors are a new class of cancer therapy drugs that work on these protein pathways to 'switch back on' the normal immune system response against cancer. These immune checkpoint inhibitors are antibodies against PD-1 and PD-L1, and block the usual binding of these two proteins. By blocking this interaction, the immune system response gets turned back on by 'taking off the PD-1/PD-L1 brakes.' There are many immune checkpoint inhibitors being studied in clinical trials for many cancer types.

These immune checkpoint inhibitors are commonly well-tolerated, with less side effects than classic chemotherapy. However, because they turn on your immune system, they can cause unique side effects related to auto-immune diseases, where your immune system can attack your normal tissue/organs. Immune checkpoint inhibitors are given intravenously every 2-4 weeks in an oncology office.

How are PD-1, PD-L1 and immune checkpoint inhibitors related to my mesothelioma?

The preliminary results of a clinical trial (KEYNOTE-028) using a PD-1 immune checkpoint inhibitor, called pembrolizumab, in malignant pleural mesothelioma were recently discussed at a cancer research meeting. This study found that for previously treated patients whose mesothelioma tumor cells had PD-L1 on their surface, giving pembrolizumab resulted in a modest response rate (24%), high rate of disease control (76%) and was well tolerated.

The preliminary results of another clinical trial (JAVELIN) using a PD-L1 immune checkpoint inhibitor, called avelumab, in previously treated malignant mesothelioma was presented at a different research meeting. These patients were not picked based on their mesothelioma cells expressing PD-L1. This study found a modest response rate (9.5%) and disease control rate (57%), and was again well tolerated in terms of side effects.

What are the next steps in understanding how to use this information in mesothelioma treatment?

This study shows promising results for the use of immune checkpoint inhibitors in mesothelioma patients. Physicians and scientists continue to work to understand how and when to give these medications to provide maximum benefit with minimum side effects. Therefore, more work is being done to understand if these medications can be given to patients with non-metastatic disease, patients who haven't received chemotherapy before (treatment naïve), given in combination with other agents like chemotherapy or radiation. Understanding how best to identify those patients who will be most likely to benefit from these agents, and how to monitor response to therapy is also being investigated at this time. While immune checkpoint inhibitors are currently only in use in a clinical trial setting, if results continue to be promising they may soon be considered a standard therapy for the treatment of mesothelioma.

About the author

Kristen A. Marrone, MD, is a medical oncology fellow at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins Hospital. She works under the leadership of Julie R. Brahmer, MD, associate professor of oncology and interim director of the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins Hospital.

NEW MESOTHELIOMA TASK FORCE TAKES SHAPE

by Shakun Malik, MD

On November 9-10, 2015, the International Conference on Mesothelioma was held at the University of Hawaii Cancer Center, Honolulu, HI. The meeting was co-sponsored by the International Association for the Study of Lung Cancer (IASLC) and the agenda was designed with significant input from staff at the US National Cancer Institute (NCI) and National Institute of Environmental Health Sciences (NIEHS).

The clinical session concluded with the consensus that due to the relative rarity of the disease, multidisciplinary international efforts are needed to conduct and complete randomized clinical trials with clinically meaningful endpoints.

NCI is currently working on submitting a request for funding a mesothelioma trials planning meeting that has been endorsed by the NCI Thoracic Malignancy Steering committee. The meeting is planned for March 2017.

This meeting is a collaborative effort of the NCI, International Association for the Study of Lung Cancer (IASLC) and the Mesothelioma Association Research Foundation. International participation of the surgical, medical and radiation oncologists, environmentalists' and pathologists' who are experts in the field is expected.

Expected outcomes of the meeting will be 2-3 trials that are feasible, statistically robust and clinically meaningful in this rare disease that lacks randomized trials.

Most of the available clinical information about early-stage pleural mesothelioma treatment is derived from retrospective single-center series and thus there is no consensus as to the optimal treatment. The combination of pemetrexed and platinum is the only FDA approved regimen for patients with malignant pleural mesothelioma who are either unresectable or are not otherwise candidates for surgery.

Patient advocacy efforts supported by the Mesothelioma Applied Research Foundation (Meso Foundation) have resulted in the introduction in the US Congress of a bill to establish a mesothelioma patient registry. High-quality information from such a registry is essential in providing data to evaluate patient outcomes, quality of life and follow-up information, calculate survival rates, analyze referral patterns, allocate resources at regional or state level, report cancer incidence, and identify unmet mesothelioma research needs.

About the author

Dr. Shakun Malik joined the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program in November 2013 as the head of thoracic oncology therapeutics. Her goal is to facilitate lung cancer research. Prior to joining CTEP, Dr. Malik worked at the U.S. Food and Drug Administration (FDA), where she gained valuable experience in understanding the regulatory pathways that make drugs available to patients.

THE FUTURE DIRECTION OF SURGERY FOR MALIGNANT PLEURAL MESOTHELIOMA

By Melissa Culligan, RN, MS and Joseph S. Friedberg, MD

Surgery has a clear and well-defined role in diagnosing and palliating patients with malignant pleural mesothelioma (MPM), but the use of surgery as a therapeutic modality remains controversial. While there is no current level I evidence establishing a beneficial role for surgery over nonsurgical treatments, the evidence is compelling that some patients benefit more from a surgery-based approach than would be reasonably expected without surgery. Some recently reported trials of highly selected patients yielded subset cohorts with overall survivals measured in years, not months. It is possible these patients might have had the same results without surgery, but critical analysis would suggest that was unlikely. It does appear, therefore, that some patients will benefit from surgery but who those patients are, what operation they should have, what adjuvants they should receive – that's the rub.

Here are the obstacles that stand in the way of defining the role of surgery in the treatment of MPM patients:

- The current staging system, while incorporating nodal status, distant metastases and, to some degree, invasive characteristics of the cancer that might adversely affect surgical resection, still includes patients who are defined as having early stage disease but will likely not derive benefit from surgery. Prognosticators such as pain, platelet count, tumor bulk and, especially, pathologic subtype are currently used by experienced surgeons to complement the formal staging and select patients more likely to benefit from surgery - truly epitomizing the art of medicine. Ultimately, as current science suggests, molecular genetics may become part of a staging system that will more accurately predict which patients will benefit from surgery and, ideally, what adjuvants (perhaps individualized) should be combined with surgery. The future direction of surgery must, and will, include revisions of the staging system that allow for better patient selection.

- While the goal of surgery, a macroscopic complete resection, is generally agreed upon, the operative approach remains controversial. The two techniques, lung sacrificing and lung-sparing, are widely practiced throughout the world, with proponents and detractors of both. Both have advantages and disadvantages. Lung-sacrificing surgery, extrapleural pneumonectomy, has the advantages of being highly standardized and serving as a platform by which the effect of adjuvant therapies could likely be assessed in a properly structured study. The obvious disadvantages are those associated with having one lung. Lung-sparing surgery (pleurectomy) has the advantage of leaving the patient with two lungs, but the operation is more time consuming, almost certainly leaves behind more microscopic disease and is far from standardized. The future direction of surgery must, and will, yield a standardized technique for lung sparing surgery and better definition of which patients are best served by which operation.

- MPM is a rare disease with an extraordinarily diverse number of presentations and surgically encountered challenges/ scenarios. These are inherent and immutable obstacles that, combined with the multitude of surgery/adjuvant permutations that are being reported as treatments, make it extremely challenging to rigorously compare results, the typical pathway of incremental progress. The future direction of surgery must, and will, include more collaborative trials between centers of excellence that will allow valid comparisons of interventions and selection of what should be adopted and what should be abandoned.

- Surgery for MPM is, arguably, the largest palliative operation known to man. Within this context, until such time that surgery is part of a predictably curative treatment, we owe it to our patients to elevate post surgical quality of life to an equal footing with overall survival. The future direction of surgery must, and will, include a greater emphasis on quality of life, allowing patients to give true informed consent for their operation and allowing researchers to design treatment strategies in a way that addresses what patients truly want.

The future direction of surgery, therefore, must focus on: better patient section, more standardized and situationally defined surgical approaches, better collaboration between researchers and greater emphasis on quality, not just quantity, of life. These achievable objectives, in combination with the exciting emergence of immunotherapies, suggests that we could be on the verge of a new era where surgery could assume a role in the treatment of MPM analogous to non-small cell lung cancer – an accepted treatment with quantified quality of life impact for a predictable survival benefit in a clearly defined subset of patients with the disease.

About the authors
Melissa Culligan, RN, MS, is Program Administrator of the Division of Thoracic Surgery Director of Clinical Research, Division of Thoracic Surgery Nurse Navigator at the University of Maryland Mesothelioma and Thoracic Oncology Treatment and Research Center. Ms. Culligan is also a member of the Board of Directors of the Mesothelioma Applied Research Foundation.
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NIH TISSUE PROCUREMENT AND NATURAL HISTORY STUDY OF PATIENTS WITH MALIGNANT MESOTHELIOMA

By Anish Thomas, MD

Malignant mesothelioma is a tumor arising from the mesothelial cells of the pleura, peritoneum, pericardium, or tunica vaginalis. Malignant pleural mesothelioma is the most common of these, comprising of 80% of the cases. Each year over 2500 new patients are diagnosed with pleural mesothelioma. The majority of these patients present with advanced stages of disease. Patients with mesothelioma have few well-studied treatment options due in large part to the rarity of the disease. One of the most effective tools to study any disease is tumor and other body fluid samples from patients with detailed annotation of the clinical course of each patient i.e. how were they diagnosed and how well did they do on specific treatments etc.

The overall goal of the NIH Tissue Procurement and Natural History Study is to collect systematically annotated tumor and other bio-specimens from patients with all types of mesothelioma. The objectives of this study are to conduct cellular, molecular, and genetic analysis to find new ways to treat this disease as well as to identify new methods to detect it early and to monitor patients who are in treatment for response. Additional objectives are to improve our understanding of rare forms of mesothelioma (such as pericardial and tunica vaginalis mesothelioma) in terms of their natural history and effectiveness of various treatments.

The eligibility for the trial are broad and essentially any one with mesothelioma who is 2 years or older without any major illness is eligible. The trial involves a one-time visit to the mesothelioma clinic at the Center for Cancer Research, Bethesda, MD. Prior to your visit, your local oncologist will be contacted to obtain details of previous treatment, copies of your CT scans (or other imaging studies) and tumor from the previous surgery or diagnostic procedure. During the visit, an NIH medical oncologist with expertise in mesothelioma will evaluate the patient and review the clinical course. Blood, urine, and abnormal body fluids (pleural fluid or ascetic fluid) will be collected for research purposes. Usually, all the testing and consultation can be completed during the course of a day. Studies which may be performed on collected material include genetic and genomic studies, establishment of cell cultures and immunologic studies. The study opened in September 2013 and as of December 2015 had enrolled 175 patients. Preliminary findings including the development of a dedicated database to collect data for this study were presented at the International Mesothelioma Interest Group meeting in 2016.

About the author
Anish Thomas, MD, is the Staff Clinician at the Thoracic and Gastrointestinal Oncology Branch of the National Cancer Institute.

TRIALS WITH TRIALS

Emily Brown Kocis' brave journey with peritoneal mesothelioma and clinical trials.

By Jessica Blackford-Cleeton

In July of 2014, at the age of 25, Emily Brown Kocis was enjoying motherhood in South Carolina. Eight months earlier she gave birth to her beautiful daughter, Ellie. It was in July of that year that she noticed her abdomen was swelling rapidly.

"In late July 2014, my belly became extremely swollen (what I later found out was ascites). I went to my OB-GYN thinking I was possibly pregnant again," Mrs. Kocis remembered.

During that appointment, her OB-GYN ran some tests. A subsequent CT scan showed that Mrs. Kocis had up to four masses on or around her ovaries. She was sent to an OB-GYN oncologist for surgery. Four softball size tumors were removed from her abdomen. Mrs. Kocis also learned that cancer was in surrounding areas of her abdomen, including her diaphragm. After tumor samples were sent to MD Anderson and the Mayo Clinic, Mrs. Kocis learned she has peritoneal mesothelioma.

"At first, I was truly and honestly in denial that I had cancer," Mrs. Kocis stated. "I was recovering from major abdominal surgery and just couldn't believe that after that long surgery and horrible recovery that there was still cancer in my body. Plus, I had a baby to care for and moms with infants just don't get cancer, right?!"

After Mrs. Kocis' diagnosis of peritoneal mesothelioma, she was treated locally with two cycles of cisplatin and pemetrexed chemotherapy. Unfortunately, another CT scan showed the cancer in her abdomen and on her diaphragm was growing rapidly. In October of 2014, Mrs. Kocis headed to Memorial Sloan Kettering for cytoreductive surgery which included a warm water bath.

According to Mrs. Kocis, "This one was over 10 hours long. My surgeon was able to remove all the visible cancer by scraping my organs, including the diaphragm, and removing my gall bladder, uterus and ovaries, and a portion of my intestines (resulting in a temporary ileostomy)".

Two weeks after the surgery, Mrs. Kocis started receiving cisplatin and mitomycin chemotherapy through an intraperitoneal port. The cisplatin made her feel nauseous and fatigued for 7-10 days after infusion. She completed six full cycles in February 2015. Her next scan was local and she received amazing news; the surgery and subsequent chemotherapy had worked. The scan was clean. Unfortunately, the celebration was short lived:

"Heartbreak came one week later when my disk of CT images was read by my team at Memorial Sloan Kettering who DID see concerning lesions throughout my abdomen. At this point, my team advised me to seek a clinical trial."

Emily Brown Kocis with her husband and daughter.

Mary Hesdorffer of the Mesothelioma Applied Research Foundation helped Mrs. Kocis find a clinical trial. Her first was at the University of Chicago in July, 2015. She was placed in a trial for Keytruda. Regrettably, the trial didn't work.

> *I hope that by participating in clinical trials, the research data collected will help future patients beat this disease quickly, even if I cannot.*

"My midpoint scan showed the drug was working - visible necrosis in the tumors is how the news was delivered. After round 4, the scan showed that those tumors were no longer dead; blood flow had returned to the tumors, and I would no longer be able to stay on the trial. We were back to square one and back in touch with the Foundation for help," Mrs. Kocis stated.

In December of 2015, Mrs. Kocis went to the National Institutes of Health in Maryland for pre-trial screening and testing. She was still eligible for SS1P and pentostatin plus cyclophosphamide for mesothelioma. The schedule was intense in terms of travel and hospitalization. Every third week she was hospitalized for 7-10 days to receive the experimental drug. Mrs. Kocis did as much research as she could on the side effects of each drug.

"I was very well aware that it could cause pain and nausea/vomiting. What I didn't realize until half way through the protocol was how extremely homesick and depressed I would be in the hospital, away from my baby, getting poked and prodded around the clock, getting little sleep each night, with no guarantee," Mrs. Kocis remembered.

Mrs. Kocis powered through all four cycles, though her end treatment scan showed continued growth. In her own words, she was back to "square one".

Mrs. Kocis is now beginning another trial at the National Institute of Health entitled topotecan with VX-970. Although this trial is not typically given to those with mesothelioma (it's usually for those with small cell lung cancer), it comes with hope that it will halt tumor growth.

"The good news is that this trial, though less desirable travel/duration of time away from home-wise, is outpatient so I get to stay at the hotel with my husband and come in daily for treatment (as opposed to staying in the hospital all week)", said Mrs. Kocis.

As for now, Mrs. Kocis is dealing with the daily struggles of life with cancer.

"Some days I feel generally okay. We go about living life like no one is sick; we spend time at the beach, pool, shopping, etc. Some days I just can't get off the couch (I'm tired, extremely nauseous, achey, etc.) and my husband or mom have to step in to fill in where I can't," Mrs. Kocis explained. "The most difficult thing for me right now is that I can't provide for most of my daughter's needs like I used to. Now I can't believe I ever once complained about all the needs of a child. Every night I ask the Lord to let me do those tasks again. And to do them for years to come."

As Mrs. Kocis begins her third trial, she has some words of wisdom for newly diagnosed mesothelioma patients:

"Do not stop with your local oncologist. Find an expert in the field. The best thing I did was seek a specialist who knew the disease well and knew how to properly treat my disease. I've seen too many patients stop with their local doctors and miss the opportunity to rid their cancer by a specialist."

Mrs. Kocis is not just a cancer patient. She is a mother, daughter, wife, and most importantly, a fighter. Her never ending quest to participate in clinical trials shows not only that she is strong, but willing to try any means necessary to beat mesothelioma:

"I hope that by participating in clinical trials, the research data collected will help future patients beat this disease quickly, even if I cannot".

Emily in September 2015, during a round of treatment.

PAINT THE WORLD IN MESOTHELIOMA AWARENESS!

Mesothelioma Awareness Day, established by Meso Foundation volunteers in 2004, has been the driving force behind the movement to bring more attention and funding to this cancer.

In the last ten years, through various activities, the Meso Foundation and its volunteers have been able to obtain "National Mesothelioma Awareness Day" proclamations by both the U. S. Senate and the House of Representatives, have raised over a million dollars, have received local government proclamations in their states and localities, and have generated media coverage for their stories, events, and activities. This year, we invite you to wear blue, share photos and videos of yourself in blue on social media, and organize or attend a fundraising event. More information is available at:

curemeso.org/awarenessday.

WEAR BLUE!

Any blue will do, but you can also purchase blue shirts in the Meso Foundation's store at curemeso.org/store.

SHARE

As you cover the world in blue awareness, document it with photos, videos, and anything else that can be shared on social media. Then, share it with a #curemeso tag!

FUNDRAISE

Organize/attend a fundraising event. See our supporters'events listed on page 19.

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INTRAPLEURAL MEASLES VIRUS THERAPY FOR PLEURAL MESOTHELIOMA

By Tobias Peikert, MD
Mayo Clinic

Pleural mesothelioma remains a difficult disease to treat and new therapies are urgently needed. The use of viruses to selectively infect and kill tumor cells (oncolysis) and perhaps trigger an effective anti-tumor immune response represents an interesting new treatment option. Close contact of the tumor to the pleural space (space between the outside of the lung and the inside of the chest wall) provides an opportunity to administer cancer therapies, including viruses, near the tumor for patients with pleural mesothelioma. Within the last few years, several viruses have been and are currently being evaluated in pleural mesothelioma. These include Adenoviruses, Vaccinia Virus (GL-ONC1), Herpes Virus (HSV1716) and Measles Virus.

The interest in using the Measles virus for cancer therapy was triggered by several patients whose hematological malignancies (lymphomas) disappeared after suffering through a measles virus infection in the absence of any specific therapy for their cancer. In contrast to the natural measles infection with the wild-type measles virus which represents a potentially life-threatening disease, the administration of attenuated vaccine strain measles viruses has an excellent safety record.

Vaccine strain measles virus enters cells predominantly using a receptor called "CD46" which is present in larger amounts on the cell surface of various tumors, including mesothelioma, but only in very low levels in normal cells. This phenomenon allows the virus to specifically target and infect tumor cells while avoiding normal cells. Pre-clinical experimental data suggests that the modified vaccine stain measles virus (MV-NIS) very effectively kills mesothelioma tumor cells in cell culture and animal models. In addition, the measles virus has been shown to stimulate the immune system and activate the immune system to target the tumor.

MV-NIS is currently being evaluated as a cancer treatment in a number of clinical trials across various malignancies including: ovarian cancer, multiple myeloma and pleural mesothelioma. Several patients with multiple myeloma have experienced dramatic responses including one patient who accomplished a complete disease response after measles virus therapy. (http://www.mayoclinicproceedings.org/article/S0025-6196(14)00332-2/fulltext)

We have recently completed a first in human (Phase I) study investigating the intrapleural administration of the measles virus (MV-NIS) in patients with pleural mesothelioma. In this study MV-NIS was delivered directly into the pleural space using an intrapleural catheter. We have treated a total of 12 patients receiving 4 different doses of MV-NIS for up to 6 treatment cycles. The treatment was safe and well tolerated. The highest dose, 9 x 10^9 viral particles (enough measles virus to vaccinate 1-10 million individuals), was found to be safe (maximal tolerated dose). In this small study we observed clinical stabilization of the disease after MV-NIS treatment in most patients and the preliminary data suggests a promising overall survival of 15 months. We also detected the emergence of new anti-tumor antibodies. Unresolved challenges include limited MV-NIS infection of and viral replication within the tumor and the boosting of measles virus antibody responses in the patients following MV-NIS therapy.

The preliminary results from other ongoing studies investigating the intrapleural administration of the vaccinia virus – GL-ONC1 (NCT01766739) and the herpes simplex virus – (HSV1716) have also demonstrated safety and similar disease responses to MV-NIS in patients with pleural mesothelioma.

Our study currently continues with a maximal tolerated dose expansion cohort (NCT01503177) and we are seeking to recruit an additional 20 patients with pleural mesothelioma. In addition, combination approaches such as cell carriers for the virus, intra-tumoral delivery of the virus, combination of the virus with immune checkpoint inhibitors and transient removal of anti-measles antibodies by plasmapheresis to address the remaining challenges of measles virus therapy in pleural mesothelioma are being explored.

DID YOU KNOW?

Charity Navigator, America's largest and most-utilized independent evaluator of charities, has awarded the Mesothelioma Applied Research Foundation (Meso Foundation) the prestigious 4-star rating for good governance, sound fiscal management and commitment to accountability and transparency.

MESO FOUNDATION BY THE NUMBERS

$9.4 million in mesothelioma research grants funded

99 studies fundeed through the research grant program

$11.9 million in government funding directed to mesothelioma research

$0.86 cents of every dollar donated goes to programs

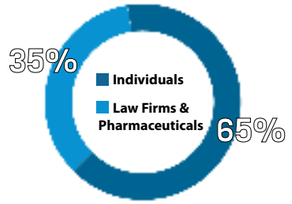
600 people helped every month, including patients, caregivers, and bereaved

488 proposals submitted to the research grant program

204 articles resulted from Meso Foundation funding

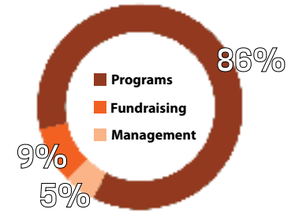
83 journals published research funded by the Meso Foundation

WHERE THE MONEY COMES FROM



The Meso Foundation receives 65% of its donations from individual donors and 35% from law firms and pharmaceutical companies.

HOW THE MONEY IS USED



The Meso Foundation uses 86% of donations received to support its programs, 9% on fundraising, and 5% on management.

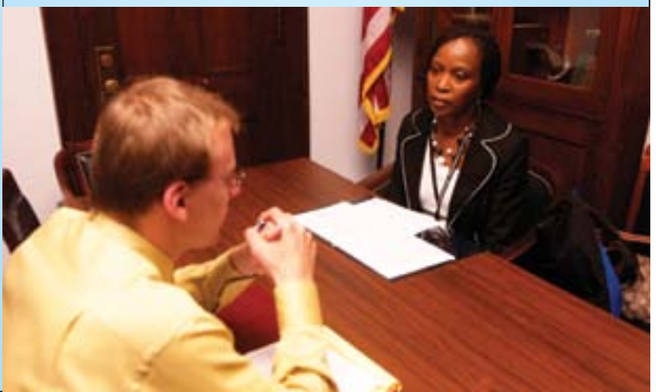
YOUR ADVOCACY MATTERS

Thanks to your advocacy, in July 2015, the Mary Jo Lawyer Spano Mesothelioma Patient Registry Act of 2015 was introduced in Congress. The profound impact of patient registries has been demonstrated in other diseases such as gastrointestinal stromal tumors, Gaucher's disease, newborn screening for inborn errors of metabolism, interstitial pulmonary fibrosis, muscular dystrophy and many others; which, following their implementation, have seen an acceleration in treatment development and acceleration toward cures.

Since the introduction, we have seen a huge outpouring of support from the scientific community, as well as a number of health organizations. We have also seen at least 500 of our own supporters email and call their elected officials asking them to support the bill.

Behind the scenes, we have continued working with our allies on Capitol Hill, and expect to see the bill brought to the floor of Congress for a vote in the next few months. To learn more, and to find out if your congressional representative has signed on as a supporter, visit curemeso.org/advocacy.

Contact mkotzian@curemeso.org if you have any questions.



WISH TO DONATE?

As you can see, individual support is critical to continuing our fight to eradicate this devastating disease. Here, every dollar has the ability to make the difference by funding ground-breaking research, patient support programs like counseling, support groups and travel grants, advocacy efforts on Capitol Hill and so much more.

Help us continue our fight against mesothelioma by using the enclosed envelope to make your gift today, or by visiting us at curemeso.org/donate.

LET US APPRECIATE YOU!

LET US APPRECIATE YOU! THANK YOU!

New in 2016, our Meso Foundation Giving Societies aim to appreciate our most generous and loyal donors. Your participation is a great way to fund the important work of the Meso Foundation, while enjoying exclusive benefits at each level. Make your gift today to be part of our inaugural appreciation ceremonies at the 2017 International Symposium, March 27-29, 2017 in Washington, DC.

CONTACT
Maureen Devine-Ahl, Director of Development
mdevine@curemeso.org
(703) 879-3823

DISTINGUISHED BENEFACTOR SOCIETY

Our Distinguished Benefactor Society recognizes donors who have personally donated $100,000 or more to the Meso Foundation in the course of their lifetime. To qualify, donors must achieve $100,000 in personal giving to the Meso Foundation, excluding fundraising event revenue, sponsorships, grants, corporate support or other types of revenue.

Donors will be honored and inducted into our Distinguished Benefactor Society at our International Symposium in Washington, DC and listed each year as part of our annual report.

LEGACY SOCIETY

The Legacy Society recognizes donors who have listed the Meso Foundation as a beneficiary in their will or estate. A written statement in your will that specific assets, a set dollar amount or a percentage of the estate's value will be left to the Meso Foundation is an easy way to leave a lasting impact.

Legacy Society donors receive recognition on our website and in our annual report. If you have included the Meso Foundation in your estate planning, please notify us so we may add your name to the list of Legacy donors.

CIRCLE OF HOPE SOCIETY

The Mesothelioma Applied Research Foundation's Circle of Hope Society recognizes total individual giving from January 1 – December 31. Individual giving is defined as personal giving to the Meso Foundation, and does not include fundraising event revenue, sponsorships, grants, corporate support or other types of revenue.

Bronze $1,000 - $2,499: Benefits include recognition in annual report, invite to Symposium VIP reception.

Silver $2,500 - $4,999: Benefits include recognition in annual report, invite to Symposium VIP reception, update calls with chairs of BOD and SAB.

Gold $5,000 - $9,999: Benefits include recognition in annual report, invite to Symposium VIP reception, update calls with chairs of BOD and SAB, reduced registration fees to Foundation events.

Platinum $10,000 - $24,999: Benefits include recognition in annual report, invite to Symposium VIP reception, update calls with chairs of BOD and SAB, reduced registration fees to Foundation events, individual recognition at Symposium, personal update with Foundation's executive director.

Diamond $25,000+: Benefits include recognition in annual report, invite to Symposium VIP reception, update calls with chairs of BOD and SAB, reduced registration fees to Foundation events, individual recognition at Symposium, personal update with Foundation's executive director, opportunity to name/sponsor a session at a Meso Foundation special event.

UPCOMING COMMUNITY FUNDRAISING EVENTS

JULY 24

Dining with Donnie Cookbook in honor of Donald E. Smitley

This event will take place on Sunday, July 24 in Saint Marys, Pennsylvania. Contact Jennifer Gelsick at jennifer.gelsick@hotmail.com for more information.

AUG 12

13th Annual George W. Snyder Memorial Golf Outing hosted by the Insulators and Allied Workers Local #24

This event will be held on Friday, August 12 in Pasadena, Maryland. Contact Lino Cressotti at 301-725-2400 for more information.

AUG 20

Music For Meso in memory of James Dunbar "Dun" Stockwell

This event will be held on Saturday, August 20 in Baton Rouge, Louisiana. Contact Natalie Stockwell at natly877@aol.com for more information.

SEPT 10

Kayaking 4 Meso in honor of Linda Wells

This event will begin at 9:30AM on Saturday, Setpember 10 at Halfmoon Lighthouse Park in Waterford, New York. Contact Mark Wells at markwells@kayaking4meso.org or visit www.kayaking4meso.org to learn more.

SEPT 17

Oktoberfest

This event will be held on Saturday, September 17 from 8am to 11pm in Edwardsville, Illinois. Contact Caitlin Lagemann at Gori Julian & Associates, PC, at caitlin@gorijulianlaw.com for more information.

SEPT 18

Bruce A. Waite Miles for Meso 5K

This event will be held on Sunday, September 18 at Ontario High school at 457 Shelby-Ontario Rd, Ontario, Ohio 44906. Registration opens at 1:00PM and the race starts at 2:00PM. The registration fee is $20 until September 9 and then it will be $25. For more information, visit www.brucewaite5k.com.

UPCOMING MESO FOUNDATION EVENTS

SEPT 16

International Symposium on Malignant Mesothelioma: San Francisco

This one-day conference will feature top mesothelioma experts, professionally-moderated support sessions, and a number of opportunities for socialization. Learn more and register at curemeso.org/symposium.

SEPT 17

Celebration of Life: San Francisco

This private ceremony will bring together members of the bereaved community to connect with one another and honor those who have passed on from mesothelioma. Learn more at curemeso.org/celebrationoflife.

SEPT 26

Mesothelioma Awareness Day

Established by Meso Foundation volunteers in 2004, this day has been the driving force behind the movement to bring more attention and funding to this cancer. Learn more at curemeso.org/awareness.

OCT 7

International Symposium on Malignant Mesothelioma: Chicago

This one-day conference will feature top mesothelioma experts, professionally-moderated support sessions, and a number of opportunities for socialization. Learn more and register at curemeso.org/symposium.

MARCH 27-29, 2017

2017 International Symposium on Malignant Mesothelioma

Save the date to join us for the 2017 Symposium, which will be held in collaboration with the National Cancer Institute on March 27-29th at the National Institutes of Health in Bethesda, Maryland. Learn more at curemeso.org/symposium.

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