The Admiral Elmo R. ("Bud") Zumwalt, Jr. Mesothelioma Treatment and Research Center(s)

Background Information

This is a proposal to create a national treatment and research center, The Admiral Elmo R. Zumwalt, Jr. Mesothelioma Treatment and Research Center ("EZ" Mesothelioma Center) for U.S. veterans who have suspected or diagnosed asbestos-related diseases, such as malignant pleural mesothelioma and asbestosis. During service to our country, our service men and women have knowingly placed themselves in "harm's way." They have willingly laid their life on the line to serve and protect the United States of America and all of us--its citizens. In recognition of that fact, the U.S. Department of Veterans Affairs has been charged with fulfilling President Lincoln's promise "To care for him who shall have borne the battle, and for his widow, and his orphan" by serving and honoring the men and women who are America's veterans. To provide veterans the world-class medical benefits and services they have earned - and to do so by adhering to the highest standards of compassion, commitment, excellence, professionalism, integrity, accountability, and stewardship and by commitment to the core values of integrity, commitment, advocacy, respect, and excellence.

During their service to our country, veterans have been exposed to dangers that most of us can never imagine. Many of the dangers can have life-long consequences. Some of these hazards have been prominently recognized and documented, such as agent orange exposure, Gulf War Syndrome, and post-traumatic stress disorder (PTSD). Yet, many of our service men and women, in every branch of the military, were exposed over decades to the toxic substance generically referred to as "asbestos." To date, however, no special programs exist for those suffering from the diseases caused by this exposure. In fact, the difficulty of treating diseases, such as malignant pleural mesothelioma and asbestosis, has been magnified by the lack of special recognition of asbestos-related diseases within the VHA. Currently, veterans medical records include specific designations for "service connected," combat related (Combat Vet), agent orange, ionizing radiation, "Southwest Asia," "shipboard hazard and defense," MST, and head and/or neck cancer conditions, but there is no specific designation to recognize the thousands of veterans suffering from asbestos-related cancers and conditions. Granted many of our Navy veterans could be included under "shipboard hazards" but the exposure to asbestos was more ubiquitous, occurring in airplane mechanics, electricians, plumbers, insulators, and even enlisted men and women, officers and *family members* in every branch of the Department of Defense.

The U.S. Navy, of course, is the most well-known branch of the military associated with asbestos exposure. As many as one-third of all cases of malignant pleural mesothelioma are diagnosed in veterans, particularly Marine and Navy veterans. In fact, asbestos exposure during military service has claimed the lives of notable Americans, including actor Steven McQueen (Marines) and the 19th Chief of Naval Operations, Admiral Elmo R. Zumwalt, Jr on January 2, 2000; and there are thousands of others.

The current state of treatment for mesothelioma, in particular, is not much more than supportive care—physicians literally watch our veterans die, while only really being able to barely help to minimize their suffering. While claims have been made about successful therapies, including radical surgery, radiation, and chemotherapy (trimodality therapy), in reality, nothing has been proven with certainty (level I evidence) except that chemotherapy minimally prolongs life by less than 3 months (12.1 mos versus 9.3 mos) with only 42% of patients even responding. To state that our knowledge and resources to treat this disease is meager is an understatement. Many veterans who have symptoms suggestive of mesothelioma are not aggressively and systematically evaluated in order to establish a prompt diagnosis. Others are told by misinformed physicians that it's a "slow growing" tumor and are advised not to undergo any treatment because they feel well at the time of diagnosis. Most veterans don't even know they are at risk because no one has assessed their exposure level and counseled them about being monitored, something that labor unions and trade groups have provided their civilian members who are at risk for decades. Perhaps the most

significant lapse in our commitment to our veterans is the total absence of any preventive programs. The latency time between exposure and the development of this fatal disease is between 15 and 50 years. With its group of exposed veterans and its national healthcare system, the VHA is the ideal "battleground" to wage war with this disease demon. Clinical trials with potential anti-inflammatory drugs (the etiology of asbestos-induced cancer is likely chronic inflammation) are waiting for such an opportunity to be tested.

Sample VHA Case Study

A 68 year old active veteran mountain biker with a medical history notable only for a history of hypetension and prostate cancer noticed increasing dyspnea on exertion while biking in February, 2010. This progressively worsened by May, 2010 when he initially went to the Las Vegas VA where he was referred for a pulmonary evaluation after he was noted to have a left pleural effusion, possibly suspicious for malignancy (pulmonary consult note 5/19/2010). Thoracenteses were performed on 5/20/2010 (2000 cc yellowish fluid) and 6/3/2010 and were consistent with an exudative process but no specific diagnosis was found. After he was admitted to another hospital for a possible "TIA" he returned to the VA and it was noted on 6/2/2010 that his effusion had rapidly returned, and again there was concern for a malignancy (***at this point recurrent exudative pleural effusions in otherwise healthy individuals demands a thorascopic evaluation***). Apparently no subsequent follow up was performed and when the veteran became even more short of breath he underwent two additional thoracenteses in August, 2010 even after two ing One center on each coast would provide geographic coverage for the entire nation similar to that provided by specialized

Basic Proposal Components

The basic outline of the proposal is to establish ***two national EZ Mesothelioma Centers***. The first would be at the West Los Angeles VA Medical Center where currently there is an expert team already engaged in the care of these patients and in research in the field. A second center logically could be established within the Thoracic Oncology Program of the Surgery Branch at the National Cancer Institute (NIH). One center on each coast would provide geographic coverage for the entire nation similar to that provided by specialized centers for organ transplantation within the VHA. Each center would contribute experts to a ***National VHA Advisory Pane***l to help guide VHA policy in terms of current treatment protocols, clinical trials, and basic science research strategy. In addition, and ***Extramural Advisory Panel*** would be established to help provide creative input and feedback. An ***Annual Mesothelioma Clinical and Basic Science Research Symposium*** would be held alternating at one center or the other and quarterly meetings would be held with advisory panel members via conference calls.

Clinical Program

The EZ Mesothelioma Clinical Program initially would establish a clinical pathway for the evaluation and treatment of all veterans with suspected or diagnosed malignant pleural mesothelioma. This evidence-based guideline/pathway (EBG) would be supported, as much as possible, by medical literature, acknowledging that little level I data exists; yet simultaneously supporting evidence-based individual decision making (EBID). All patients would be placed into a ***VHA EZ Mesothelioma Registry*** and all appropriate candidates would be encouraged to participate in a variety of clinical trials to be conducted. In order to develop and maintain the necessary expertise in the specialized area of mesothelioma, the following "core" resources would be established at each center with representatives from each core to participate in the ***National VHA Advisory Panel***.

> ***Surgery Core.*** This core would consist preferably of two designated general thoracic surgeons at each center with documented experience (ie., >50 cases or one mentor surgeon with >50 cases and a junior surgeon) in complex surgical procedures for malignant pleural mesothelioma and thoracic surgical oncology. Each surgeon would be required to participate in reporting all morbidity and mortality, in providing tissue for a ***VHA National Mesothelioma Tissue Bank*** and to participate in jointly planned and agreed upon clinical trials.

Pathology Core. This core would consist preferably of two to three designated pathologist at each center with documented interest and experience in evaluating pathologic mesothelioma specimens. The differentiation between the two key components, sarcomatoid and epithelioid cells, and all staging criteria would be mandatory.

Radiology/Imaging Core. This core would consist of preferably two designated thoracic radiologists and nuclear medicine physicians with experience in reading thoracic imaging studies, including whole body PET-CT scans. PET-CT scans, by protocol, would be required to be performed in a designated and dedicated scanner for both scans to be done simultaneously and with i.v. and oral contrast. CT scans with contrast will be used for fused images in anatomic evaluation, which should be depicted and read on a high resolution color monitors with acquisition of 1 mm slices merged into 3 mm scans in 3 dimensions. Non-contrast CT scans, as standard practice, obtained at the same time will be used for attenuation correction.

Radiation Oncology Core. This core would consist of one or two designated radiation oncologists with documented experience in all relevant and current techniques for delivering radiation therapy in thoracic patients, including standard external beam radiation, brachytherapy, IMRT, and SBRT. All radiation oncologists would be expected to follow standardized treatment protocols in all patients.

Medical Oncology Core. This core would consist of one or two designated medical oncologists with expressed interest in the compassionate care of mesothelioma patients. The oncologists would be required to follow treatment protocols which would be developed separately for each cell subtype, treating the predominant cell type (ie., >50% representation) as the determining factor. The medical oncologists would be required to treat sarcomatoid predominant tumors as a primary sarcoma and epithelioid predominant tumors with more standard pemetrexed/cisplatin based regimens as well as any experimental regimen the group would propose.

Anesthesiology Core. This core will be partially covered by dedicated thoracic anesthesiologists and not general anesthesiologist or even cardiac anesthesiologists. Protocols for managing patients undergoing lung-sparing pleurectomy and decortication procedures will be expanded from the already existing thoracic anesthesiology service manned from the UCLA Anesthesiology Service. It will be necessary, however, to expand on this service with increased case volume.

Pulmonary and Critical Care Medicine Core. This core would require the participation of at least two pulmonologists with an interest and experience in treating patients with asbestos-related pulmonary disease. These physicians would be responsible for protocol development for providing perioperative pulmonary care as well as palliation of pulmonary symptoms including dyspnea.

Palliative Care Core. This core would consist of a single palliative care physician and supporting staff who would monitor the administration of palliative care medicine when appropriate. This would including nutritional, respiratory, physical, and other supportive care as well as a prominent role in palliative care of pain.

Nursing Care Core. This core would include at least two nurse practitioners to develop and monitor inpatient as well as outpatient nursing protocols. The nurses will be responsible for frequent follow-up visits (in person and telephonic) as well as coordination of medical care at outside VHA centers.

Supportive Care Core. This core would include at least one member from the nutrition service, respiratory care, pharmacy, operating room, social work, and clinical psychiatry. Each member will be responsible for developing standard procedures for the evaluation and monitoring of patient

health in their area. Emphasis will be placed on the psychological evaluation and support of patients. Furthermore, a clinical coordinator will be exclusively assigned to the mesothelioma program at each center in order to facilitate referrals and coordinate travel arrangements for veterans from outside centers.

Data Management Core. This core will consist of one or two data managers who will primarily capture all data from patient care, including all data associated with clinical trials. This data will be entered into a common database maintained jointly by the two centers and accessible via a secure internet interface.

Statistical Core. This core will consist of one or two statisticians who will be made available for data analysis, particularly in preparation for the ***Annual Mesothelioma Clinical and Basic Science Research Symposium***. The statisticians should also be available for consultation in planning clinical trials as well as in certain circumstances for basic science projects.

Clinical Projects

The EZ Mesothelioma Clinical Program would initiate several clinical projects and clinical trials. These will be designed to document and test current strategies used by many VHA centers around the country but have no level 1supporting evidence. In addition, investigational projects will be established to assess novel therapeutic approaches based on existing basic science evidence. Finally, a correlative science project will help establish a tissue bank for use in future basic science and clinical work.

Project 1. This project would establish a center wide process for accumulating all types of tissue specimens, including blood, urine, tissues, and potentially even buccal smears and breath condensate to create a ***VHA National Mesothelioma Tissue Bank.*** This bank would be jointly maintained by the pathology and surgery cores at both centers. The cost of maintaining such a bank would be covered as part of the center. The ***VHA National Mesothelioma Tissue Bank*** would be established within the guidelines of the NIH for biorepositories and maintained within the VA system. Possible sharing of specimens will be considered with collaborators as outlined below under **Collaboration**.

Project 2. This project would seek to establish the current practice and variations thereof within the VA system for patients with diagnosed malignant pleural mesothelioma. The Data Management Core under the direction of one or more of the senior investigators will identify the distribution and number of patients with the ICD-9 diagnosis codes for malignant pleural mesothelioma (163.X). As a follow-up study, the various treatment approaches and outcome will be investigated. The initial diagnostic code work would be relatively straightforward but the outcomes research would take more work, money, and time. This would establish, however, the baseline as to how veterans are being treated and against which the centers success needs to be measured.

Project 3. This project would plan and initiate clinical trial(s) designed to test "accepted" clinical practices which have no real supporting medical literature. Several questions that may be addressed, if feasible, include the role of surgery, the role of postoperative adjuvant radiation therapy, and role of induction (preoperative) chemotherapy, as well as the strategy of early postoperative adjuvant chemotherapy in high risk patients (T3/N2) versus delayed postoperative adjuvant chemotherapy once measurable disease has returned and response rates can be assessed.

Project 4. This project would seek to initiate a novel therapeutic clinical trial. Initial candidate targeted therapeutic agents include angiogenesis inhibitors, interferon alpha, and PRX321, a novel IL-4 based immunotoxin shown to have particular promise in preclinical testing. This molecule is currently licensed from the NIH by Protox Therapeutics and collaborative IND application would be

filed. Currently, funding for this project is limited from the company as well as from the Department of Defense (administrative denial of funding) and CTEP/NIH. Other fundraising opportunities may allow this critical project to go forward.

Basic Science Program

The EZ Mesothelioma Clinical Program initially would establish a research laboratory for projects focused on malignant pleural mesothelioma possibly within joint space with the Departments of Surgery and Pulmonary and Critical Care Medicine (Building 114). This space would be occupied by a basic science research team. The team would be responsible for a close collaboration with the clinical team with weekly research meetings to discuss ongoing projects, results, as well as proposals for future work. The research director would report to the overall Center director. Program faculty and staff include the following personnel.

Senior Researcher/Research Director. This position would be filled by a senior researcher with experience in cell biology, immunology, molecular biology and preferably with a focus in thoracic oncology either in lung cancer or prior experience with mesothelioma research. A record of established research funding would be recommended. The Director would be responsible for project planning, grant submission, grant administration. Performance and result reporting for each project. The Director would also work with the other scientists and collaborators to maximize research output and patient biospecimen use. The senior researcher and director will responsible for laboratory safety and all personnel within the laboratory itself.

Research Scientists. This position would require one or two experienced scientists who would oversee and be responsible for a subproject under the entire overall project. Each scientist would coordinate and oversee experimental design, trouble shooting, result analysis, and reporting including presentation of projects and their results at the weekly Center meetings but also at the ***Annual Mesothelioma Clinical and Basic Science Research Symposium.*** Each scientists is output and patient biospecimen use.

Research Assistants. This position would require one or two experienced intermediate research assistants who will be responsible for the day to day basic activities of the laboratory. These assistants will help in the performance of the actual research projects themselves as well as act as a resource for the research scientists in terms of preparation of materials, laboratory cleaning and assay assessment, etc.

Basic Science Research Projects

The EZ Mesothelioma Clinical Program would initiate several basic science projects. These will be based on existing knowledge of the field of mesothelioma research but also based on discussions with clinicians and other scientists involved in cancer research. Advice will be actively sought from the advisory boards. It is anticipated that several projects will be the initial focus of the basic research projects.

Project 1. This project would investigate the use of stromal (mesenchymal) cell manipulation in the adjuvant intra-postoperative therapy of mesothelioma. There is ample evidence in lung cancer that using bone marrow derived mesenchymal stem cells themselves has an antitumor effect and when additional manipulations are performed, such as transduction of these mesenchymal cells with interferon and a myriad of antiangiogenic agents there is a dramatic increase in therapeutic antitumor activity. Although this has been a focus of Dr. Sharma's research in the last 1-2 years, we are now ready to translate this into mesothelioma where the model of stromal cell manipulation is much more relevant due to the known profound angiogenic phenotype of nearly all mesothelioma tumors as well as the intraoperative opportunity to introduce cell therapy into the tumor "bed" so that the high rate

of regrowth of the tumor can be affected. This is an extremely exciting area of research unique to the West Los Angeles VA Medical Center.

Project 2. This project would .investigate the biologic events occurring over time during the period of tumoragenesis after exposure to asbestos and theoretically a result of chronic inflammation. This information would be used to attempt interventions that might alter the inflammatory cascade and mileau in order to prevent the induction of mesothelioma. This approach would then be used to guide clinical trial planning for a translational trial of anti-inflammatory agents, such as aspirin and celebrex.

Project 3. This project would investigate the combination of cryotherapy and immunotherapy. Cryotherapy has been found to be very successful in terms of controlling localized tumor recurrences. This low morbidity and high efficacy therapy is useful when the areas of recurrence are limited. However, with effective tumor killing, the opportunity arises to use the same necrotic tissue as an immunostimulant which can be augmented by adding immune adjuvants through the same needle that is used for the cryoablation. This would essentially be a method of autologous tumor cell vaccine. If there is more diffuse disease (or even with surgically unresectable disease) this would be a potential way to induce a strong immune reaction from an already existing treatment. This would require an animal model which would be preferably a mouse flank model but may require also a rat pleural model of multifocal disease and cryotherapy of a sentinel nodule with injection of the immunostimulants and cytokines. We will explore this type of model and approach to generate early supportive data that would then be used for further grant applications.

Collaborators

The EZ Mesothelioma Clinical Program would seek to establish cooperative research arrangements with research groups around the world. The initial focus will be on local groups with resources to offer the program. Two candidate groups include the UCLA Comprehensive Mesothelioma Program and the Pacific Meso Center. Within the context of these three institutions (including the VA), some economies of scale will be realized by avoiding duplication of effort in instrumentation as well as other research resources. The collaboration will also provide further interaction for evaluation of research ideas. Further contact are expected to lead to more collaborators including the cooperative groups (SWOG) and other public and private academic institutions.

Collaborator 1. This collaborator is the UCLA Comprehensive Mesothelioma Program which includes the “Punch” Worthington Research Laboratory at UCLA which has been involved in mesothelioma research, primarily in the area of immunotoxins and hyperthermia/hyperthermic chemotherapy perfusion for nearly eight years. Dongmei Hou, PhD. is active in that laboratory at the current and is currently working on models of in vitro cryotherapy as well as other orthotopic murine models for testing of future therapeutic approaches.

Project 2. This collaborator is the Pacific Meso Center of the Pacific Heart, Lung, & Blood Institute which was established in 2003 and has been active in supporting mesothelioma patients, their families, and research through donations as well as an active intramural research program.

Required Resources

The EZ Mesothelioma Clinical Program would attempt to use as many existing resources as possible. Uniquely the West Los Angeles VA Medical Center already has many of the resources in place; however, outside of solid organ transplantation, there is little experience in the VHA oncology community with the use of established centers of excellence for relatively uncommon malignancies. Much of the initial effort will have to be in education of the various oncology and pulmonary staff physicians and program coordinators in order to offer the services to all veterans. The initial focus will be within the VISN but certainly a simultaneous national expansion will be planned.

Clinical Program

The EZ Mesothelioma Clinical Program has the following personnel already in place. Positions in need of funding support and personnel recruitment are noted in bold italcs

Surgery Core. This core would be administered and the overall project would be led by Robert B.Cameron, M.D. Dr. Cameron has over 25 years of experience in both research and clinical care of mesothelioma patients and has led both clinical and basic science research. A second thoracic surgeon would be recruited to assist with the surgical care of patients at the West Los Angeles VA Medical Center and possibly to provide clinical leadership in the area of outcomes research in mesothelioma.

Pathology Core. This core would be covered by Dr. and Michael Lewis, M.D. who both have extensive experience in thoracic pathology and the pathology of mesothelioma in particular.

Radiology/Imaging Core. This core would Poonam Batra, M.D. and , M.D. who both have many years of experience in dedicated thoracic radiologic imaging as well as , M.D. who has extensive experience in nuclear medicine cancer imaging including PET-CT scans.

Radiation Oncology Core. This core would be headed by Diana Gage whose training at UCLA exposed her to all the necessary techniques and gave her a unique experience taking care of mesothelioma patients even while training. She will be assisted by ??Guy Guilliard, M.D.

Medical Oncology Core. This core require the recruitment of a second dedicated thoracic medical oncologist. Currently, the West LA campus is covered by a single medical oncologist who is extremely busy with lung cancer. The mesothelioma program cannot be covered by this oncologist alone, particularly with the detailed protocols that require attention for individual cell subtypes, such as epithelioid and sarcomatoid mesothelioma.

Anesthesiology Core. This core will be partially covered by the existing thoracic anesthesiology service from UCLA but expansion of that service will be necessary to handle the increased case volume. This will be monitored and developed under Nir Hoftman, MD. who already partially provides outstanding support for the West LA VA Medical Center thoracic surgery patients.

Pulmonary and Critical Care Medicine Core. This core can be covered by the existing pulmonary service under the direction of Guy SooHoo, M.D. who already provides outstanding support for the lung cancer collaborative project at West LA.

Palliative Care Core. This core would require the assignment or recruitment of a palliative care/pain specialist from either existing staff members or a new faculty member.

Nursing Care Core. This core would include at least two nurse practitioners already has good representation with Graciela Hoal who is an outstanding thoracic NP. However, with long hours and operations that average 7-8 hrs, there will be a definite need for at least one additional person in the immediate future.

Supportive Care Core. This core would recruit representatives from existing resources at the West LA VA Medical Center with the exception of the recruitment of one or two specialized coordinators who will serve to arrange testing for all patients but also travel arrangements and testing coordination with home VA centers for patients who are from distant medical centers.

Data Management Core. This core will require the immediate recruitment of a full time data manager to help review existing data as well as help establish new databases and ensure that all data generated by all activities is captured for research and general purposes.

Statistical Core. This core will require the arrangement of a covering statistician which can be part-time but definitely involved from the start of the project.

Basic Science Program

The EZ Mesothelioma Clinical Program initially would recruit the following research personnel for a research laboratory most likely located in Building 114.

Senior Researcher/Research Director. This position would possibly filled by existing VHA research staff at the West Los Angeles VA Medical Center. A strong candidate is Sherven Sharma, PhD. who has extensive research experience in lung cancer and with stromal cell manipulations in cancer therapy which are the primary areas for initial basic science investigation.

Research Scientists. These position(s) would be recruited from all qualified candidates.

Research Assistants. These position(s) would be recruited from all qualified candidates.

Summary

Function

The ***Admiral Elmo R. Zumwalt, Jr. Mesothelioma Treatment and Research Center ("EZ" Mesothelioma Center)*** for U.S. veterans who have suspected or diagnosed asbestos-related diseases, such as malignant pleural mesothelioma seek to accomplish the following goals:

1. Serve as a center of excellence, educational resource, and referral point for all patients with suspected or diagnosed malignant pleural mesothelioma as well as for patients with undiagnosed pleural effusions suspicious for malignancy. Through remote case review and assistance, telementoring, and standardized referrals to ***The EZ Mesothelioma Center*** for all patients within the VISN as well as from the Western U.S. (VISN's 16-23), the EZ Center would seek to standardize protocols for patient evaluation, treatment, and follow-up. We would educate and vigorously assist physicians in cases of difficult undiagnosed pleural effusions, particularly with a history of asbestos exposure. We also would initially evaluate and make detailed treatment recommendations for all patients with highly suspicious or documented malignant pleural mesothelioma. This would occur primarily at the West Los Angeles VA Medical Center unless it was determined after initial review of medical information that travel was not medically advisable. Other medical centers within the VISN's served would be strongly encouraged to follow the Center's recommendations. ***The EZ Mesothelioma Center*** would be the only site for surgery and radiation therapy but individual oncology units would administer chemotherapy in conjunction with the oncologists at West LA.
2. The current status of treatment for malignant pleural mesothelioma as well as other asbestos-related diseases would be catalogued by ***The EZ Mesothelioma Center*** and uniform treatment standards established, including evaluation testing, imaging, pathology, chemotherapy, radiation, and of course, surgery. Where no medical information exists, randomized prospective trials would be designed to answer such questions. Furthermore, basic science projects would be designed to quickly translate into human trials with potential for therapeutic benefit.
3. A strong basic science and clinical research program with active tissue banking will be integral in the success of ***The EZ Mesothelioma Center.***