

Mesothelioma Applied Research Foundation  
2009 Mesothelioma Research Grant Awards

**Lee M. Krug, MD**  
**Memorial Sloan-Kettering Cancer Center**

Title: Randomized Phase II Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma after Completion of Combined Modality Therapy

Dr. Krug and his lab have developed a cancer vaccine that stimulates the immune system to recognize WT-1, a protein strongly expressed in 80% of mesothelioma tumors. With earlier funding from the Foundation, Dr. Krug demonstrated in a phase 1 study that the vaccine was safe and did indeed trigger an immune response in mesothelioma patients. Based on this success, Dr. Krug has been awarded a \$1.5 million grant from the Department of Defense to conduct a phase II mesothelioma clinical trial validating his work. The current Foundation funding will allow him to expand this trial to include more patients and reach accrual more quickly. This exciting trial will allow pleural patients to complete standard multi-modal therapy – extrapleural pneumonectomy or pleurectomy followed by radiation and/or chemotherapy. They will then be enrolled in the trial for vaccine administration with the aim of preventing recurrence or lengthening progression-free survival.

**Prasad Adusumilli, MD – Lance S. Ruble Memorial Grant**  
**Memorial Sloan-Kettering Cancer Center**

Title: WT-1 Targeted Adoptive T-Cell Therapy for Malignant Pleural Mesothelioma

Like Dr. Lee Krug's study, this project also capitalizes on the high expression of WT-1 in mesothelioma tumors. While Dr. Krug is developing a vaccine to stimulate the immune system's T cells, Dr. Adusumilli is directly enhancing human T cells through genetic modification so that they will more effectively recognize and attack WT-1 expressing mesothelioma cells. Testing of these genetically modified human T cells will begin against cell lines derived from patients with mesothelioma and progress into animal models. If successful this study should yield a new therapy which can be administered both systemically and locally, and therefore hold promise even for non-surgical patients.

**Nicholas H. Heintz, PhD – John Sterling Memorial Grant**  
**The University of Vermont and State Agricultural College**

Title: Molecular Targets of Thiostrepton in Malignant Mesothelioma

Many of the current chemotherapeutic agents belong to a class of drugs known as anti-tumor antibiotics. One of these, Thiostrepton, selectively inhibits Fox M1, a regulatory protein that has been shown to stimulate proliferation and survival of malignant mesothelioma cells. This proposal will help to define the molecular targets of Thiostrepton that block expression of Fox M1 in mesothelioma cells in an attempt to enhance the potential of this emerging new therapy.

**Larry H. Matherly, PhD**  
**Wayne State University**

Title: Targeting Malignant Pleural Mesothelioma with PCFT-Targeted Therapeutics

Dr. Matherly aims to establish the proton-coupled folate transporter (PCFT) as a good approach for targeted chemotherapy for malignant mesothelioma. Folate is important in cellular activity including cell division and replication, and is the target of today's most established treatment for mesothelioma, Alimta. The PCFT transporter has been identified as an important pathway in the delivery of Alimta to the malignant mesothelioma cell. Developing novel agents that target PCFT and can be combined with Alimta or related drugs will enhance their transport and therefore their potency while reducing their side effects.

**J. Andrea McCart, MD – Ken Bendix Memorial Grant**  
**University Health Network - Toronto General Research Institute**

Title: Development of a Novel Virotherapy Strategy to Detect and Treat Malignant Peritoneal Mesothelioma

Two major hurdles in treating peritoneal mesothelioma are: 1) it is often diagnosed very late in the course of the disease, making surgery impossible or unsafe, and 2) in those patients that are candidates for surgery, surgery often leaves behind residual disease which recurs at a later date. Dr. McCart is developing oncolytic viruses, viruses that specifically infect and kill cancer cells, for the treatment of peritoneal diseases such as mesothelioma. The goal of this study is to combine a vaccinia virus with a protein that will specifically target mesothelioma cells. This will aid in earlier diagnosis, since the protein is fluorescent and therefore will enhance detection of mesothelioma cells using a fluorescent camera. And after surgical debulking of the main tumor, the virus will be able to kill residual tumor cells. If successful, Dr. McCart's work would yield a treatment that likely could get into patients in a very short time-frame, as vaccinia is already being used safely in other cancers.

**Laura Moro, PhD**  
**University of Piemonte Orientale "A.Avogadro", Italy**

Title: Tumor Repressive Functions of Estrogen Receptor Beta in Malignant Pleural Mesothelioma

Chemotherapy, though effective in cancer, often results in drastic side effects that greatly diminish cancer patients' quality of life. Recently, hormones have been found to play a role in stimulating the proliferation of malignant cells in a number of cancers, and so treatment strategies have been employed to target specific hormones with relatively minor side effects. The fact that in mesothelioma women have a survival advantage has led Dr. Moro to the hypothesis that estrogen might play a role in this advantage. This very novel proposal will study the molecular function of estradiol, the estrogen hormone most highly expressed in women and which to a lesser extent is also expressed in males, focusing on cell cycle regulation and chemo resistance in mesothelioma cells. Analysis of estrogen status and function will provide information to develop novel promising treatments that have the potential to have a strong impact on the disease without compromising quality of life.

**Katherine F. Roby, PhD**  
**University of Kansas Medical Center**

Title: HSP90 Targeted Therapy for Mesothelioma

Heat Shock Protein 90 (HSP 90) is one of the most abundantly expressed proteins responsible for controlling the cellular functions that perpetuate the characteristics of cancer – proliferation, metastasis, and drug resistance. Inhibiting HSP90 ultimately results in death of the cancer cell. Dr. Roby's study will identify the best mesothelioma-specific HSP90 inhibitors that will also function synergistically with the current standard chemotherapies, Alimta and Cisplatin. Studies will be carried out in cell cultures and in preclinical mouse models of mesothelioma to define pharmacokinetics and efficacy. These studies will further the development of a new therapeutic drug that can be combined with current chemotherapy options to cause more significant responses than are achieved today.

**Arti Shukla, PhD**  
**University of Vermont and State Agricultural College**

Title: Bifunctionalized APMS Particles to Target ERK5 in Malignant Mesothelioma Treatment

Doxorubicin is a well-established chemotherapy for other cancers that shows some activity in mesothelioma. With earlier funding from the Foundation, Dr. Shukla's colleagues at University of Vermont have been developing tiny nano-particles known as "bifunctionalized nanoporous beads (APMS)" to more effectively and selectively deliver Doxorubicin to mesothelioma in the pleura. Dr. Shukla and his lab have also discovered that Doxorubicin upregulates and activates a protein that appears to cause chemo-resistance. This protein, which they have identified as extracellular signal regulated kinase 5 (ERK5), promotes cell growth/survival and drug resistance. They hypothesize therefore that by targeting ERK5 and then administering APMS loaded with Doxorubicin, they can overcome drug resistance and achieve greater targeted mesothelioma cell-killing. The study will proceed using human mesothelioma tumors growing in mice. The mice are immunocompromised – they have been genetically modified to shut down their immune systems – in order to verify that the effect on the tumor cells is from a drug response rather than an immune response. Developing this targeted approach may allow drugs already approved in other cancers to quickly become effective agents in mesothelioma.

For more detailed information about these and all of the innovative projects the Meso Foundation has supported to develop more effective mesothelioma treatment, please visit [www.curemeso.org](http://www.curemeso.org).