

Kentucky Lung Cancer Research Program

Cycle 8 Grant Abstracts

<u>Principal Investigator</u>		<u>Grant Research Title</u>
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Haribabu Bodduluri, Ph.D.	UL	Decoy Receptors as Probes for the Function of Inflammatory Chemokines in Lung Cancer Development
J. Scott Bryson, Ph.D.	UK	Allogeneic Immunotherapy of Lung Cancer
Geoffrey J. Clark	UL	The Role of Nore1 Inactivation in the Development of Lung Cancer
Rolf Craven, Ph.D.	UK	A novel approach for targeting the epidermal growth factor receptor (EGFR) in lung cancer
Yong Li	UL	MicroRNAs Target P53 in Lung Cancer
Joseph P. McGillis, Ph.D.	UK	Genetic Regulatory Network Control of Tumoricidal and Tumor Promoting Macrophage Phenotypes
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Carolina Salvador, Jun Yan, M.D., Ph.D.	UL	Lung Cancer Bio-immunotherapy using Particulate β -glucan in Combination with the Anti-VEGF Monoclonal Antibody Bevacizumab
Thomas Tucker, Ph.D.	UK	Youth Smoking Prevention and Cessation Pilot
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Principal Investigator: **Michael Andrykowski, Ph. D., University of Kentucky**

Research Title: Disparities in Mental Health Outcomes Between Rural and Nonrural Lung Cancer Survivors

Healthy People 2010 establishes an agenda for improving the nation's physical and mental health. One of the goals of Healthy People 2010 is the elimination of disparities in physical and mental health due to certain population characteristics such as race/ethnicity, gender, socioeconomic status or geographic area of residence. It is well known that cancer diagnosis and treatment can significantly affect an individual's mental health. However, very little research has examined whether disparities might exist in these mental health outcomes across certain groups of cancer patients and survivors. In particular, disparities in mental health outcomes due to whether a cancer patient or survivor resides in a rural area has received little attention - this question has never been examined in lung cancer survivors. Lung cancer survivors bear a considerable physical and mental health burden. Lung cancer survivors residing in rural areas are likely to have fewer resources available to them to cope with this burden relative to lung cancer survivors residing in nonrural areas. Thus, the likelihood that significant disparities exist in mental health outcomes as a function of whether a lung cancer survivor resides in a rural or nonrural area is high. Consequently, examination of the possibility that rural survivors might shoulder a disproportionate share of the mental health burden posed by lung cancer (Study Aim 1) represents a significant area of study. Furthermore, identification of factors (intrapersonal, interpersonal, informational, tangible) potentially associated with disparities in mental health outcomes among lung cancer survivors (Study Aims 2 and 3) can provide a blueprint for the design of interventions to reduce these disparities. Rural (n=150) and nonrural (n=150) non-small-cell lung cancer (NSCLC) survivors will be recruited from the population-based statewide SEER Kentucky Cancer Registry (KCR). 2003 USDA Rural-Urban Continuum codes will classify survivors as rural (codes 7-9) or nonrural (codes 1-6) based on county of residence. Survivors will complete a telephone interview and questionnaire packet about 10-15 months post-diagnosis. Information regarding a variety of negative (i.e., distress) and positive (i.e., growth) mental health outcomes will be obtained as will information regarding factors (intrapersonal, interpersonal, informational, tangible) potentially linked to disparities in mental health outcomes. Analyses will focus upon identification of: (a) the nature and magnitude of disparities in mental health outcomes in NSCLC survivors linked to rural residence (Aim 1); and (b) differences between rural and nonrural NSCLC survivors in resources (intrapersonal, interpersonal, informational, tangible) potentially linked to observed disparities in mental health outcomes (Aims 2 and 3).

Principal Investigator: **Paula J. Bates, Ph.D., University of Louisville**

Research Title: Evaluation of XB05 as a Novel Agent for the Treatment of Lung Cancer

Principal Investigator: **Haribabu Bodduluri, Ph.D., University of Louisville**

Research Title: Decoy Receptors as Probes for the Function of Inflammatory Chemokines in Lung Cancer Development

Principal Investigator: **J. Scott Bryson, Ph.D., University of Kentucky**

Research Title: Allogeneic Immunotherapy of Lung Cancer

Therapeutic strategies for non-small cell lung carcinoma (NSCLC) include the use of surgery, chemotherapy and radiation. Many NSCLC patients present with advanced disease that is not treatable by surgery and does not respond to chemotherapy or radiation treatment. An alternative option would be the use of allogeneic stem cell therapy (ACT). Allogeneic stem cell therapy involves the transfer of donor BM cells and immune cells into an immunosuppressed patient. Patients are immunosuppressed with chemotherapy and/or radiation to prevent rejection of the donor cell graft. Immune cells from the donor have the potential to respond against transplantation antigens on the surface the patient's tumor cells. Major complications of this procedure are graft-versus-host disease (GVHD) and idiopathic pneumonia syndrome of the lung. In these diseases, donor immune cells attack the recipient body resulting in inflammation in the liver, intestinal tract, skin, and lungs. Conversely, it has been shown that a beneficial anti-tumor response is associated with the development of GVHD. Allogeneic stem cell therapy has been successfully utilized to treat a number of malignancies, including solid tumors. This procedure has been shown to mediate the regression of renal cell carcinoma lung metastases. Even more interesting is a recent anecdotal report demonstrating the elimination of NSCLC following ACT. With this in mind, we will utilize an animal bone marrow transplantation model to test the central hypothesis that the allogeneic immune response that develops following ACT will be effective in controlling the growth of lung cancer in the absence of GVHD and other regimen related toxicities. Experiments will utilize reduced intensity conditioning regimens followed by delayed ACT to minimize GVHD and lung inflammation in the recipient animals. Studies will monitor migration of donor cells to the lungs of recipient animals. We will determine the effectiveness of the GVT response that develops after ACT against murine lung tumors. Finally, studies will be conducted that will identify the immune cells that mediate tumor killing in the murine ACT model. These studies will provide the basis for future development of this procedure to enhance the GVT response and reduce regimen-related toxicities to the lungs of treated recipients.

Principal Investigator: **Geoffrey J. Clark, University of Louisville**

Research Title: The Role of Nore1 Inactivation in the Development of Lung Cancer

Lung cancer is caused by the progressive inactivation of tumor suppressor genes and the activation of oncogenes. We have identified a novel protein called Nore1a that may be one of the key tumor suppressors inactivated during the development of many lung tumors. Nore1a appears to serve as part of a “failsafe” mechanism to protect the organism against cancer. Normal cells that acquire activations in certain common oncogenes may be diverted from progression into a tumor and instead progress into growth arrest and death by Nore1a. Loss of function of Nore1a subverts this system and allows the activated oncogenes to function with impunity, driving the cell towards cancer. This project seeks to first confirm and define the role of Nore1a in lung tumor formation experimentally. These experiments include the use of novel human organ culture systems to maximize physiological relevance. Then, in collaboration with a laboratory at the University of Kentucky, we will determine the role of a novel oncogenic binding partner of Nore1a in the development of lung cancer. Thirdly, we seek to explore the possibility of “epigenetic” therapy directed towards Nore1a in a lung cancer model. The inactivation of Nore1a is typically by a so-called epigenetic mechanism. This causes the elements controlling the production of the Nore1a protein to become inactivated by aberrant DNA methylation. Thus, the tumor suppressor gene remains intact, but silent. We hope to identify novel small molecules that can reverse the aberrant DNA methylation and hence restore the normal production and function of the Nore1a tumor suppressor protein to block cancer.

Principal Investigator: **Rolf Craven, Ph.D., University of Kentucky**

Research Title: A novel approach for targeting the epidermal growth factor receptor (EGFR) in lung cancer

Lung cancer is responsible for 28 percent of all cancer deaths and is a particular concern in Kentucky due to the high rate of smoking. For decades, lung cancer has been treated with drugs that are essentially poisons that kill all growing cells. As a result, chemotherapy has harsh side effects and kills healthy cells in the immune system, gastrointestinal tract and skin. One of the most important advances in cancer research is the discovery of proteins that are specific to cancer cells, and when these proteins are blocked, cancer cells die. In contrast, noncancerous cells do not express the proteins and are unaffected by the drugs that block them. One of the main cancer-specific proteins in lung cancer is an oncogene (cancer-causing gene) called the EGFR (the epidermal growth factor receptor), and EGFR is inhibited by the drugs erlotinib, gefitinib/Iressa and erbitux/cetuximab. The advantage of these new drugs is that they have relatively few side effects because they block a protein that is only made by tumors. However, the disadvantage is that the drugs have a relatively small effect on patient outcomes because some people's tumors do not respond to them and other people's tumors develop resistance. There are two ways to improve this. First, we can screen patients with tests that will identify those who will respond to the new anti-EGFR drugs. Second, we can find new drugs that will block EGFR in a different way. We have developed a novel drug that blocks a protein called PGRMC1 (progesterone receptor membrane component 1) that stabilizes EGFR in lung cancer cells. After treatment with the anti-PGRMC1 drug, EGFR disappears and the lung cancer cells die. In this proposal, we will screen samples from lung cancer patients and determine whether people with high levels of PGRMC1 in their tumors also have high levels of EGFR. This will allow us to identify people who might respond to combinations of anti-EGFR and anti-PGRMC1 drugs. We will then test new ways of using the anti-PGRMC1 drug that we developed, such as combining our new drug with chemotherapeutic drugs or drugs that deprive tumor cells of oxygen. By analogy, EGFR is like a foot on the gas peddle, accelerating a car, and the anti-EGFR drugs are like a brake. When the car figures out a way to bypass the brake, we will provide a second brake. We want to find the cars that are easiest to stop and test whether we should use both brakes at once, or one brake after the other. The findings will be significant because they will provide a new therapeutic option for lung cancer patients that have developed resistance to EGFR inhibitors, and they will characterize a subset of patients that will likely respond to the therapy.

Principal Investigator: **Yong Li, University of Louisville**

Research Title: MicroRNAs Target P53 in Lung Cancer

Principal Investigator: **Joseph P. McGillis, Ph.D., University of Kentucky**

Research Title: Genetic Regulatory Network Control of Tumoricidal and Tumor Promoting Macrophage Phenotypes

Lung cancer is a leading cause of death from cancer in the United States. Close to 200,000 people will die of lung cancer in the United States in 2008. Notably, lung cancer rates in Kentucky are the highest in the nation. Over 80% of lung tumors belong to the non-small cell lung carcinoma subgroup (squamous cell, adeno and large cell carcinoma). Current treatments are not very effective and the 5 year survival rate is less than 15%. Recently, there has been interest in the role of a particular immune cell, the macrophage, in cancer. Different types of macrophages have a number of functions, including positive and negative regulation of immune responses and inflammation and tissue repair and regeneration. In solid tumors like lung cancer, macrophages are the most common non-cancer cell in the tumor stroma. There is a strong correlation between the abundance of tumor associated macrophages and poor prognosis for lung, prostate, ovarian and cervical cancers. Tumor associated macrophages are predominantly of the M2 subtype. Macrophages can differentiate into subtypes with distinct functions. One type, classically activated or M1 macrophages, stimulate immune responses and have tumor killing abilities (tumoricidal). Another type, alternatively activated or M2 macrophages, suppress immune responses and inflammation and are not tumoricidal. Their primary function is to promote tissue repair. This includes influencing new cell growth and formation of new blood vessels (vascularization), processes that can potentially be subverted by the tumor to promote its own growth and survival. While some of the factors that influence polarization to M1 and M2 macrophages are known, little is known about the genetic regulatory networks involved in macrophage polarization. The studies described here will use state of the art analysis of the genes expressed in M1 and M2 macrophages to identify genes direct naïve macrophages to differentiate to M1 or M2 macrophages. The studies will include functional studies with a cell culture system to confirm the function of M1 and M2 specific genetic regulatory proteins and will then confirm that M2 specific regulatory genes are upregulated in macrophages taken from lung tumors in mice. Collectively, this data will fill a gap in our current understanding of the genetic regulatory networks regulating the M1 and M2 macrophage subtypes with an emphasis on their role in tumor associated macrophages.

Currently, there is interest in manipulating tumor promoting M2 macrophages to become more like tumoricidal M1 macrophages. Unfortunately, no one has yet considered manipulating the genetic regulatory networks that determine the M1 and M2 status and functions of macrophages due to a lack of information about these networks. The information gained from this proposal will be useful for designing gene-therapy based approaches targeting genetic regulatory elements that specify the M1 vs. M2 status of tumor associated macrophages, with the ultimate goal of converting replacing M2 tumor associated M2 macrophages with tumoricidal M1 macrophages.

Principal Investigator: Kelly M. McMasters, Sam H. Zhou, Ph.D., University of Louisville

Research Title: Selectively Inducing Apoptosis in Cancer Cells with Truncated E2F-1 Lacking Transcriptional Activity

E2F-1¹ is capable of promoting both cell cycle progression and apoptosis. Oncogenic properties of E2F-1 are associated with its transcription activity and cell cycle progression. Multiple studies have demonstrated that overexpression of E2F1 effectively induces apoptotic cell death in a variety of cancer cells. Studies on the molecular basis of E2F-1-induced apoptosis demonstrated that a carboxy-terminal deletion mutant of E2F-1, lacking transactivation, can also induce apoptosis. As oncogenic properties of E2F-1 are associated with its transcription activity, a truncated E2F-1 (E2Ftr) may improve its potential clinical utility. We have created a truncated E2F-1 and shown that the truncated form of E2F-1 has advantages over the full-length form, in that it is a more potent inducer of apoptosis in cancer cells and has less oncogenic potential. We propose to create novel cancer expression system, in which we will combine a tumor-specific promoter with a Tet-off expression activator, so that the E2Ftr expression can be specifically induced in cancer cells and express at high levels. The adenovirus-mediated E2Ftr apoptosis can be used in lung cancer therapy, because adenoviruses naturally target human airway cells. We will also test the hypotheses that such Ad vector is effective as an anti-tumor agent in cell culture and in animal models of cancer. As the mechanism of E2Ftr-induced apoptosis is largely unknown, the novel Ad E2Ftr vector will enhance further mechanistic studies by comparing apoptotic effects induced by wild-type and truncated E2F-1. Once we have the tumor-specific Tet-off-inducible promoter, this expression system should also benefit broad applications by controlling other therapeutic genes. Our long-term goal is to develop adenoviral gene therapy that will be used in human clinical trials. We believe that the proposed studies will further our long-term goal of developing E2F-1 adenoviruses that can be used in human clinical trials for treatment of lung cancers.

Principal Investigator: **Isabel Mellon, Ph.D., University of Kentucky**

Research Title: Inhibition of nucleotide excision repair by cigarette smoke

Exposure to tobacco smoke is a well established risk factor for lung cancer. Even secondhand exposure to cigarette smoke has been linked to an increased risk of lung cancer. Although significant progress has been made in treating many types of cancer, lung cancer remains among the most difficult to treat and accounts for about one third of cancer deaths among developed nations. The chemical composition of cigarette smoke is complex and there is some debate about which chemicals in smoke play roles in the development of lung cancer. However, it is well established that several of the chemicals found in smoke introduce damage to the DNA in our cells. Damage to DNA can lead to the formation of mutations and it is widely thought that the formation of mutations plays a significant role in cancer development. Our cells possess a number of different ways to "fix" damaged DNA and prevent mutations from being produced. These are called DNA repair pathways. One of these DNA repair pathways is called the nucleotide excision repair pathway (NER) and it "fixes" a large number of different types of damage that can be formed in the DNA of our cells when we are exposed to many agents in the environment including cigarette smoke and ultraviolet light present in sunlight. We have recently found that exposing human lung cells to cigarette smoke significantly inhibits the NER pathway. This is a novel and potentially significant finding. If cigarette smoke inhibits the NER pathway then the act of smoking in itself would inhibit the repair of DNA damage that is introduced by smoking. This would likely increase mutations in cells of the lung formed by exposure to the DNA damaging agents present in smoke and could play a significant role in causing lung cancer. In addition we have also found that treating human lung cells with arsenic inhibits the NER pathway. Exposure to arsenic that is present in cigarette smoke or that is present in the environment (such as ground water) has also been linked to lung cancer. Our finding that cigarette smoke and arsenic inhibit the NER pathway may be important in understanding why lung cancer is significantly elevated beyond what is generally associated with smoking in certain geographical regions including regions in the state of Kentucky. The arsenic present in the environment may amplify the effects of agents in cigarette smoke that inhibit NER and this may play a significant role in causing lung cancer. The goals of this proposal are to better characterize the effects of cigarette smoke and arsenic on the NER pathway.

Principal Investigator: **Mark P. Pfeifer, University of Louisville**

Research Title: Aggressive Symptom Management in Lung Cancer Patients using a Telehealth Device

Principal Investigator: **Andrew Pierce, Ph.D., University of Kentucky**

Research Title: The Gene Cluster Instability Assay as Clinical Lung Cancer Biomarker

We have developed the “gene cluster instability” (GCI) assay, a molecular test for a previously unassayable form of genomic instability. The GCI assay determines whether human cancer cells have lost biochemical control of homologous recombination. Ordinarily in human cells, the potential for recombination to compromise genomic instability is very highly suppressed, but we have detected loss of recombination control and resulting genomic rearrangements in a subset of the NCI-60 collection of human cancer cell lines, including a significant presence in lung cancer lines. Since tobacco smoke is a significant risk factor in the etiology of lung cancer, and because genotoxic agents found in tobacco smoke are known inducers of recombination, dysregulation of recombination, and the resulting genomic scrambling, may be particularly relevant in the development and clinical evolution of lung cancer.

The GCI assay scores genomic rearrangements on the megabase-scale and requires fresh, unfrozen, unfixed cells. We therefore propose a pilot-scale two-year translational study to directly determine the feasibility and potential utility of using the GCI assay clinically on freshly obtained lung cancer surgical pathology samples. Using this assay, we will determine which lung cancer surgical patients seen at the University of Kentucky have disease cells that exhibit the molecular signature of dysregulated recombination relative to these patients’ non-disease cells. We will then prospectively correlate various clinically relevant endpoints, such as initial response to chemotherapy, progression-free survival and eventual long-term survival to the dysregulated recombination molecular phenotype of the disease cells.

The long-term goal is to be able to use the GCI assay as clinical cancer biomarker with prognostic and / or predictive value for lung cancer treatment outcomes.

Principal Investigator: **Vivek Rangnekar, Ph.D., University of Kentucky**

Research Title: Suppression of Lung Cancer Progression by Extracellular Par-4/SAC Protein

Lung cancer is the leading cause of deaths in the world and there is a critical need for new targeted approaches for primary and metastatic lung cancer. Moreover, 10% of non-small cell lung cancer (NSCLC) patients have brain metastasis at presentation, and another 25-40% (who may not have metastatic disease initially) eventually develop brain metastasis. Approaches that allow suppression of both primary lung tumor growth and brain metastasis are critical for improving patient survival. Lung cancer development and progression results from activation of cell survival pathways and roadblocks in the cell death pathways, contributing to uncontrolled tumor growth and metastasis. Based on this concept, we propose studies with the effector domain SAC of the pro-apoptotic gene Par-4 for suppression of primary lung tumors and brain metastasis in mouse models. As Par-4 or the SAC domain effectively kills cancer cells, but not normal cells, in cell culture studies and mouse models, and our recent studies have shown that Par-4 or SAC is secreted and exerts its effects via cell surface receptor interaction, we hypothesize that extracellular (secreted) Par-4 or SAC will inhibit the growth and metastasis of lung cancer cells. The studies will allow us to determine whether extracellular Par-4/SAC have potential for treatment of lung cancer.

Principal Investigator: Carolina Salvador, Jun Yan, M.D., Ph.D., University of Louisville

Research Title: Lung Cancer Bio-immunotherapy using Particulate β -glucan in Combination with the Anti-VEGF Monoclonal Antibody Bevacizumab

Non-small cell lung cancer (NSCLC) in advanced or metastatic stage remains an incurable disease. Recently, humanized anti-vascular endothelial growth factor mAb (anti-VEGF mAb, bevacizumab) has been approved in combination with carboplatin and paclitaxel for patients with advanced or metastatic non-small cell lung cancer, but results are far from satisfactory. There is lack of prognostic factors to response to bevacizumab or its combinations. This proposal is a pre-clinical study in a murine model to investigate a novel combination of the monoclonal antibody bevacizumab with an immunomodulator β -glucan. Yeast-derived β -glucan is a glucose polymer able to prime complement receptor 3 (CR3) on neutrophils (neutrophils are the most prominent cell of the immune system capable of cell killing) that can recognize cancer cells opsonized with complement activation product iC3b as foreign to the body and kill them. β -glucan has been shown to synergize with anti-tumor monoclonal antibodies to engage neutrophils that attack and destroy cancer cells. This synergism is only possible between β -glucan and monoclonal antibodies that capable of activating complement resulting in iC3b coated tumors. Our strong preliminary data have shown that the combination of bevacizumab and β -glucan is efficacious in stopping the growth of human ovarian cancer tumors which express membrane-bound VEGF. The proposed study is to investigate the therapeutic efficacy and mechanism of action of combined β -glucan with bevacizumab in human NSCLC models.

The novelties of this study are triple fold:

- We are proposing a new mechanism of action of bevacizumab.
- We are proposing tumor membrane-bound VEGF as a prognostic marker of response.
- We will study the mechanism of action of the synergistic effect of bevacizumab and β -glucan.

We expect the synergy of β -glucan and bevacizumab to be efficacious in arresting the growth and decreasing the size of lung cancer tumors. These studies will provide a strong rationale for the future clinical trials of lung cancer therapy.

Principal Investigator: **Thomas Tucker, Ph.D., University of Kentucky**

Research Title: Youth Smoking Prevention and Cessation Pilot

In Kentucky, a higher percentage of people get lung cancer, and die from it, than in any other state. We also have a higher percentage of middle-school and high-school students who smoke than any other state. In this study, researchers will test ASPIRE, a new computer-based program designed to help youths quit smoking or not start. The study will involve an estimated 3,000 students in the 7th and 10th grades from rural Appalachian Kentucky counties that have high rates of smoking, lung cancer, and poverty.

Two similar counties will be selected in each of three Area Development Districts in Appalachia Kentucky. Within each county, one 10th-grade class and one 7th-grade class will be selected to be part of the study. One school in each county will be part of the group that offers ASPIRE in regular health classes. The other school will be part of the group that does not offer the program. Researchers will look at whether the students who receive ASPIRE are less likely to start smoking or more likely to quit successfully, compared to the students who did not receive the program.

The researchers also will consider how easy it is to add a computer-based program to regular health classes and whether schools have enough computers and access to the Internet. In addition, students and teachers in the schools that receive ASPIRE will be asked how well the program fit in with the culture of their community.

Principal Investigator: **Vaclav Vetvicka, Ph.D., University of Louisville**

Research Title: Inhibition of Procathepsin D: A Novel Anti-Lung Cancer Agent

The long-term objective is to develop a new treatment for lung cancer based on suppression of the growth factor-like activity of pro cathepsin D. Procathepsin D (PCD) is secreted by lung cancer cells and promotes growth of the primary tumor tissue as well as formation of metastases. The pCD mitogenicity is mediated via interaction with a yet unknown receptor expressed on lung cancer cells. The critical receptor-binding domain in the activation peptide of the pCD has been localized. Proposed aims are based on the central hypothesis that inhibition of interaction of the specific region with receptor and/or inhibition of biosynthesis/secretion of pCD will inhibit lung cancer growth. The proposed aims are focused on the control of pCD mitogenicity via regulation of its production, processing, and interaction with the receptor. This approach represents a novel potential strategy for effective and specific inhibition of lung cancer.

Aim 1 : overproduction of procathepsin D results in an increase in the metastatic potential of lung tumor cells. We plan to suppress the influence of pCD by three approaches covering two therapeutic areas: 1) synthesis of pCD will be inhibited using specifically constructed siRNA; 2) by blocking pCD by anti-pCD ScFv derived from existing anti-APpCD antibodies. In Aim 2, we will evaluate the effects of specific pCD antagonists prepared by combinatorial chemistry and 3D molecular modeling approach.

Principal Investigator: **Wolfgang Zacharias, Ph.D., University of Louisville**

Research Title: The Lysosomal Pathway of Apoptosis as Target for Lung Cancer Therapy