Stem Cells in Lung Cancer

**Reporting Period:** Year 1

We identified a putative tumor-initiating stem/progenitor cell that goes rise to smoking-associated non small cell lung cancer (NSCLC). We examined 399 NSCLC samples for this tumor-initiating stem/progenitor cell and found that the presence of this cell in the tumor gave rise to a significantly worse prognosis and was associated with metastatic disease. This stem/progenitor cell is known to be important for repair of the airway and is present in precancerous lesions. We believe that this cell undergoes aberrant repair after smoking injury, which leads to lung cancer. We are currently trying to identify the genetic and epigenetic mechanisms involved in this aberrant repair as a means to identify a novel therapy to prevent the development of lung cancer. The presence of these stem/progenitor cells may also be used as a biomarker of poor prognostic NSCLC even in early stage disease. We have identified markers on these stem/progenitor tumor-initiating cells and identified sub-populations of these cells. We are now determining the stem cell capabilities of each of these sub-populations. We are using a model of the development of lung cancer to determine if giving a stem/progenitor cell sub-population for repair can prevent NSCLC from developing. We examined the blood of patients diagnosed with a lung nodule for circulating epithelial stem/progenitor cells. We found that the presence of these cells in the blood of patients predicted the presence of a subtype of NSCLC as compared to a benign lung nodule. We are currently obtaining many more blood samples from patients to further determine whether circulating epithelial stem/progenitor cells could be used as a biomarker of early NSCLC.

**Reporting Period:** Year 2

We have found a stem cell that is important for lung repair after injury that is located in a protected niche in the airway. After repeated injury, for example in smokers, these stem cells persist in an abnormal location on the surface of the airway and replicate and form precancerous areas in the lung. The presence of these stem cells in lung cancer tumors was associated with a poor prognosis with an increased chance of relapse and metastasis. This was especially true in current and former smokers. We therefore believe we have found a putative stem cell that is a tumor initiating cell for lung cancer. We developed a method to isolate these lung stem cells and to profile these cells and developed in vitro and in vivo models to assess their stem cell properties. Finally, we examined human blood samples to assess levels of surrogate markers of these stem cells to assess whether we could use this as a biomarker to predict the presence or absence of lung cancer in patients with a lung nodule.

**Reporting Period:** Year 3

We found a stem cell that is important for lung repair after injury that we believe may form precancerous areas in the lung. We are characterizing these stem cells and identifying pathways involved in normal repair and aberrant repair that leads to lung cancer. We are also isolating this stem cell population and other cell populations from the airway and inducing genetic changes to determine the tumor initiating cell/s for lung cancer. We are also examining the effect the environment may have on the regulation of genes in these stem cells, in precancerous areas and in lung cancers. Finally, we are examining human blood samples to assess levels of surrogate markers of these stem cells to assess whether we could use this as a biomarker to predict the presence or absence of lung cancer in patients with a lung nodule.

**Reporting Period:** Year 4

During this period of funding we discovered a method to reproducibly recover stem cells from human airways and grow them in a dish into mature airway cells. We also discovered the role that certain metabolic cell processes play in regulating the repair after airway injury. We believe that an inability to shut off these processes leads to abnormal repair and lung cancer and are actively investigating this. We are also determining whether the stem cells we isolate from the airways are the stem cells for lung cancer.
In the last year of funding we identified a novel mechanism that tightly controls airway stem cell proliferation for repair after injury. We found that perturbing this pathway results in precancerous lesions that can ultimately lead to lung cancer. Correcting the abnormalities in this pathway that are seen in smokers could allow the development of targeted chemoprevention strategies to prevent the development of precancerous lesions and therefore lung cancer in at risk populations. We also continued our work on trying to identify a cell of origin for squamous lung cancer and identifying the critical drive mutations that are required for squamous lung cancer to develop.

During this reporting period we discovered and published on how reactive oxygen species drive proliferation of airway basal stem cells. We found that this pathway is critical for homeostasis of the airway epithelium and perturbing this pathway results in precancerous lesions. Interestingly, these precancerous lesions are able to resolve over time, which is similar to the situation in smokers who develop precancerous lesions that almost always resolve. We now have a model to study the driver mutations that take precancerous lesions to invasive squamous lung cancer and with this model we can start to identify novel therapies to prevent the development of precancerous lesions and/or progression of precancerous lesions. We also developed a model of precancerous lesions in a dish which allows us to screen for compounds that promote or resolve these premalignant lesions. Our overall goal is to use these models to develop a targeted chemoprevention strategy for squamous lung cancer.

Stem Cells in Lung Cancer

**Grant Type:** New Faculty II

**Grant Number:** RN2-00904

**Project Objective:** The overall goal of this grant is to characterize proximal airway epithelial cell stem cells in injury or diseased states, and to identify the cell of origin in lung squamous cell carcinoma.

**Investigator:**

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<tr>
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<th>Brigitte Gomperts</th>
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<tr>
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**Disease Focus:** Cancer, Lung Cancer, Respiratory Disorders, Solid Tumors

**Human Stem Cell Use:** Adult Stem Cell, Cancer Stem Cell

**Award Value:** $2,381,572

**Status:** Closed

**Application Title:** Stem Cells in Lung Cancer
Lung cancer is the most deadly cancer worldwide and accounts for more deaths than prostate cancer, breast cancer and colon cancer combined. Non small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers. The current 5-year survival rate for all stages of NSCLC is only 15%. Although early stage lung cancer has a much better survival rate. Current therapeutic strategies of chemotherapy, radiation therapy and trials with new targeted therapies have only demonstrated, at best, extension in survival by a few months. Clearly, a novel approach is required to develop new therapies for this devastating disease and to detect the disease at an early stage. Cancer stem cells have been identified as the initial cell in the formation of carcinomas. Chemotherapy, radiation and even targeted therapies are all designed to eliminate dividing cells. However, cancer stem cells “hide out” in the quiescent phase of growth. This provides an explanation as to why our cancer therapies may produce an initial response but are often unsuccessful in curing patients. Lung cancer develops through a series of step wise changes that result in the progression of pre-malignant lesions to invasive lung cancer. The mechanisms of how lung cancer develops are not known and if we can prevent the formation of pre-malignant lesions, we will likely be able to prevent lung cancer. We have discovered a subpopulation of stem cells that circulates in the blood and is essential for normal lung repair. Blocking these cells from entering the lung results in a pre-malignant condition in the lungs. We have also identified a subpopulation of stem cells in the lung that is responsible for generating pre-malignant lung cancer lesions. We hypothesize that the interaction between the stem cells in the blood and the stem cells in the lung are critical to prevent lung cancer. We plan to use cutting edge technologies to characterize these different stem cell populations in the lung, and determine how they form pre-malignant lung cancer lesions. We also plan to use preclinical models to try to prevent lung cancer by giving additional stem cells derived from the blood as a therapy. Lastly, we plan to determine whether levels of stem cells in the blood in patients may be used as a blood test to measure the chance of recurrence of lung cancer after therapy. The long term goals of our work are to develop a screening test for lung cancer stem cells that can predict which patients are at high risk for developing lung cancer in order to diagnose lung cancer at an early stage, and to potentially develop a new stem cell based therapy for preventing and treating lung cancer.

According to the Center for Health Statistics, California Department of Health Services, 13,427 people died of lung cancer in the state of California in 2005. This is more than the deaths attributed to breast, prostate and colon cancers combined. The devastating effects of this disease on the citizens of California and the health care costs involved are enormous. Most cases of lung cancer occur in smokers, but non smokers, people exposed to second hand smoke and ex-smokers are also at risk. In addition, of special concern to California residents, is that exposure to air pollution is associated with an increased risk of lung cancer. Current therapeutic strategies for lung cancer are in general only able to prolong survival by a few months, especially for late stage disease. One reason for this may be that the cancer initiating stem cell is resistant to these therapies. Understanding the stem cell populations involved in repair of the lung and how these cells may give rise to lung cancer is important for potentially generating new therapeutic targets for lung cancer. We propose to study the stem cell populations of the lung that are crucial for normal airway repair and characterize the putative cancer initiating stem cell in the lung. We have also found stem cells in the blood that are critical for normal airway repair and we plan to test their role in the prevention of premalignant lung cancer lesions. We also plan to test whether levels of these stem cells in the blood may be used as a biomarker of lung cancer. Ultimately, the ability to perform a screening test to detect lung cancer at an early stage, and the development of new therapies for lung cancer will be of major benefit to the citizens of California.