previously demonstrated that CADM1, a member of the immunoglobulin superfamily cell adhesion molecules, is highly expressed in around 75% of SCLC. In addition, SCLC expresses a splicing variant, CADM1v8/9, which is observed specifically in normal testis. Here, we report that the extracellular fragment of CADM1v8/9 is digested by ADM17 and released into cell medium or human serum. Then, we generated specific monoclonal antibody against CADM1v8/9 using Cadm1-deficient mice and developed a serum diagnostic marker for SCLC. Preliminary study shows that CADM1v8/9 detects 47% of SCLC, which is independent of and partly overlaps with the cases detected by ProGRP. CADM1v8/9 can also detect a significant portion of patients with limited disease of SCLC. Furthermore, the amount of CADM1v8/9 fragments correlates well with the disease activity of SCLC before and after the chemotherapy. These findings indicate that detection of CADM1v8/9 in serum from patients is a novel and promising approach to detect and follow up SCLC patients. CADM1 would also provide a promising target for the treatment of SCLC.

**B23 Unraveling the Mechanisms of Small-Cell Lung Cancer Brain Metastasis**

**F. Qu,1 A. Pasca,1 C. Kong,2 M. Winslow,3 J. Sage4**
1Department of Pediatrics, Stanford University School of Medicine, Stanford, CA/US, 2Department of Pathology, Stanford University School of Medicine, Stanford, CA/US, 3Department of Genetics, Department of Pathology, Stanford University School of Medicine, Stanford, CA/US, 4Department of Pediatrics, Department of Genetics, Stanford University School of Medicine, Stanford, CA/US

Brain metastases are the most common type of intracranial tumors and are associated with high morbidity and mortality rates in cancer patients worldwide. Therapeutic options to treat brain metastases remain extremely limited, in part because of a lack of preclinical models and a limited understanding of the mechanisms allowing tumor cells from various primary sites to grow in the brain microenvironment. Small-cell lung cancer (SCLC) is a highly lethal type of lung cancer that frequently metastasizes to the brain. We have recently developed two preclinical models to investigate the interactions of SCLC cells with cells in the brain microenvironment and to identify mechanisms of SCLC brain metastasis. First, we have developed a direct intracranial transplant approach in which fluorescently labeled SCLC cells form tumors in the brain of recipient mice, including immunocompetent mice. Second, we have developed a coculture system in which SCLC cells invade brain organoids engineered from human iPS cells. Using these two models, we have found that GFAP-positive reactive astrocytes interact with SCLC cells in the brain and potentially affect the growth of SCLC brain metastases. GFAP-positive astrocytes actively infiltrate SCLC brain metastases in our preclinical models and in patients. We also show that astrocytes can promote the growth of SCLC cells in culture. Previous studies have shown that Nfib, an oncogenic transcription factor that drives the metastatic progression of SCLC, can induce expression of neuronal gene programs in metastatic SCLC cells. Neuron-astrocyte interactions play a critical role in neuronal growth and migration during development. Therefore, in an effort to determine the mechanisms underlying the interactions between SCLC cells and astrocytes, we have knocked down Nfib in SCLC cells and transplanted them into mouse brains. We found that Nfib is critical for the growth of SCLC brain metastases and that SCLC tumors with reduced Nfib expression show elevated rates of apoptosis, impaired invasion, and decreased astrocyte infiltration. Ongoing work is focusing on characterizing Nfib-downstream factors that are critical for SCLC growth and migration in the brain microenvironment, especially those with functions in neuron-astrocyte interactions.

These studies will provide better mechanistic insight into how cancer cells adapt and grow in the brain microenvironment, which may eventually help identify new therapeutic targets to treat brain metastases.

**B24 The Role of Cigarette Smoke and miR520a in Pulmonary Frizzled 9 Expression**

**A. Smith, P. Do, M. Tennis**
University of Colorado Anschutz Medical Campus, Aurora, CO/US

Lung cancer is the deadliest cancer, and for this reason treatment is highly researched. Alternatively, chemoprevention can be used to combat lung cancer in individuals who are at high risk of diagnosis, such as cigarette smokers. Frizzled 9 (Fzd9) is required in vitro for chemopreventive effects of iloprost, a prostacyclin analogue, in the lung. In non-small cell lung cancer (NSCLC) cell lines, Fzd9 activates PPARγ, leading to inhibition of transformed growth. Cigarette smoke exposure decreases Fzd9 expression. The goal of this study is to elucidate the relationship between cigarette smoke and miRNA regulation of Fzd9 expression. NSCLC cells exposed to cigarette smoke condensate (CSC) showed decreased Fzd9 3′ UTR activity, suggesting CSC regulates Fzd9 expression through miRNA. miRNA database analysis suggested miR-95, miR-106b, and miR-520a as potential regulators of Fzd9. Immortalized human bronchial epithelial cells (HBEC) and an Fzd9-positive NSCLC cell line (A549) transfected with miR-520a oligonucleotide mimic showed decreased Fzd9 3′UTR lucerase activity, miR-520a expression increased in HBEC and NSCLC cells after CSC exposure. We have tested a miR-520a inhibitor to use for future rescue experiments in an Fzd9-negative cell line (H322). Transient overexpression of miR-520a in HBEC and A549 did not affect cell viability or proliferation, so we made a stable miR-520a expressing HBEC line that we will use for longer-duration cell assays. miR-520a may play an important role in the regulation of Fzd9 by cigarette smoke, and future experiments will characterize this relationship and potentially impact the application of iloprost chemoprevention.

**B25 Mapping the SOX2 Functional Network in Small-Cell Lung Cancer**

**M.J. Vande Kamp,1 D.G. May,1 E. Thompson,2 H. Wollenzien,2 K.J. Roux,1 M.S. Kareta1**
1Sanford Research, Sioux Falls, SD/US, 2University of South Dakota, Vermillion, SD/US

Small-cell lung cancer (SCLC) is a devastating and often recurring disease for which there has been little change in standard-of-care treatment over the last decade. Despite the advancement of cancer therapeutics, SCLC still has a five-year survival rate of less than 7%. By elucidating the genes and protein networks that drive SCLC tumor formation and growth, new avenues for treatment can be discovered. The transcription factor, SOX2, maintains stem cell pluripotency and is required for embryonic development. We have shown that SOX2 is a driver of SCLC. The SOX2 interactome has been studied in stem cells; however, in SCLC, the network of genes and proteins that SOX2 interacts with is still unknown. Here we present SOX2 chromatin targets as determined by chromatin immunoprecipitation (ChiP-seq) and CUT&RUN and compared binding to various epigenetic marks. The identification of SOX2 post-translational modifications suggests that they may impact its function in SCLC. Furthermore, the detection of SOX2 proximal proteins through BioID shows that SOX2 interacts with known regulators of lung cancer. As transcription factors are notoriously difficult to target therapeutically, our description of the SOX2 network presents novel targets for therapeutic development in SCLC.