**#118 Non-random chromosomal changes in high- and low-invasive tumor cells derived from early passage mouse lung adenocarcinoma cell strains.** Ing X. Ensell, Steven H. Reynolds, Michael L. Kashon, Amy M. Jefferson, Lowry David, Anne-Carine Ostvold, Jamie R. Senft, Frederick L. Tyson, Robert C. son, Linda M. Sargent. *St Jude Children's Research Hospital, Memphis, TN, ter for Disease Control/ National Institute for Safety and Health, Morgantown, University of Oslo, Oslo, Norway, National Institute for Environmental Health ces, Research Triangle Park, NC, Spectral Genomics, Houtson, TX.*

he incidence of adenocarcinoma is increasing in the United States, however, the ficulty in obtaining lung cancer families and representative samples of early to stages of the disease have lead to the study of mouse models. We used a battery sts to detect molecular changes associated with tumor invasion. Spectral karyo- ng, mapping with fluorescently labeled genomic clones, comparative genomic ridization arrays, expression arrays, Western blot and real time polymerase n reaction (PCR) were used to analyze nine pairs of high invasive and low sive tumor cell strains derived from early passage lung adenocarcinoma cell ins. The duplication of chromosome 1 and 15 and deletion of chromosome 8 significant in high invasive cultures compared to low invasive cultures. The lication of chromosome 1 between bands E2 and H1 was the most significant omosomal change in the invasive cell strains. Mapping with fluorescent in situ ridization and comparative genomic hybridization (CGH) array further nar- ed the minimum region of duplication of chromosome 1 to 71 to 82 centimor- (cM) as well as three deleted regions from 67-69 cM, 84-84 cM and 100-110 Analysis of an expression array and confirmation by real time PCR identified eased expression of genes that were associated with the invasive phenotype. The plified copy number and expression of vacuolar protein sorting 4B (SKD1), ulin, and DYRK3 were significantly elevated in the invasive cell strains at 0.00001. The copy number of NUCKS and tubulin α-4 showed a trend for eased expression in the cell strains that were able to invade a gel matrix. The eased copy number and expression of genes involved in cell movement, prolif- ion, and inhibition of apoptosis were associated with the invasive phenotype. homologous linkage groups on human chromosomes 1q32-41, 2q, 8q24 and are altered in invasive human lung cancer. Increased copy number and expres- of the genes on mouse chromosome 1 may play a functional role in lung cancer elopment and may aid in the identification of mouse and human lung cancer eptibility genes. *"The findings and conclusions in this report (abstract/presenta- ) have not been formally disseminated by the National Institute for Occupational ty and Health and should not be constructed to represent any agency determination olicy."*

**#119 Epistasis governs the nature of *Kras* mutations and neoplastic wth of urethane-induced mouse lung tumors in chromosome substitution ins (CSS).** Lori D. Dwyer-Nield, Jay McQuillan, Ming You, Joseph H. deau, Eric Lander, Alvin M. Malkinson. *University Colorado Health Sci. Center, ver, CO, Washington University, St. Louis, MO, Case Western Reserve University, eland, OH, Massachusetts Institute of Technology, Boston, MA.*

CSS or consomic mice provide a novel opportunity to examine gene interactions affect neoplastic development. The B6.A series of 20 CSS strains have a 7BL/6 (B6) background bearing a single A/J chromosome pair (*e.g.* B6.A6 mice B6 mice with A/J chromosome 6). The parental B6 strain is resistant to carcin- n-induced lung tumor formation while A/J mice are vulnerable. Lung tumors e induced in 11 B6.A strains as well as A/J and B6 mice. Sixteen wks later these nors were counted, sized, and their *Kras* codon 61 mutational status determined. A6, B6.A11, and B6.A17 mice developed significantly more lung tumors than B6 mice. Susceptibility loci on chromosomes 6 and 17 had previously been ected by QTL mapping of B6 and A/J mice, but the locus on chromosome 11 is el. B6.A6 mice contain the susceptible A/J *Pas1* locus previously shown to ount for >60% of the difference in urethane-induced lung tumor susceptibility ween A/J and B6 mice. However, this CSS strain developed only 1.8 tumors/ use compared to 30 tumors/mouse in similarly treated A/J mice. In addition, A6 lung tumors grew more slowly and were more highly differentiated than A/J nors. This indicates that B6 alleles on other chromosomes partially inhibited full notypic expression of the A/J *Pas1* allele. The *Pas1* locus contains the proton- ene *Kras*, whose activating mutation is thought to be the initiating event for use lung tumors. Urethane treatment induces codon 61 mutations in *Kras*. In B6 B6.A mice, predominantly Gln to Arg mutations occurred in *Kras* codon 61, ile A/J mice exhibited Gln to Leu mutations at this site. Thus, sites distant from *Kras* structural gene modulate the *Kras* mutational status of mouse lung tumors. contains at least 3 genes that contribute to lung tumor susceptibility and wth, in addition to *Kras*. B6 alleles on chromosomes other than chromosome 6 eract with *Pas1* to regulate lung tumor multiplicity and progression, and this dulation may be mediated in part by the particular *Kras* mutation contained in clonally expanded cells. (Supported by CA33497 and CA96133.)

**#5120 Creation of mouse models of human lung cancer by activation of PI3K/AKT-dependent signaling.** Kentaro Iwanaga, Amy E. Hanna, Hong Wu, Francesco J. Demayo, Jonathan M. Kurie. *MD Anderson Cancer Center, Houston, TX, University of California at Los Angeles, Los Angeles, CA, Baylor College of Medicine, Houston, TX.*

Activation of phosphatidylinositol 3'-kinase and its downstream mediator, Akt, promotes cellular survival and induces malignant transformation. Previous studies have reported loss of the PTEN lipid phosphatase, a negative regulator of AKT, and increased Ser473-phosphorylation of AKT in non-small cell lung cancer (NSCLC) biopsy samples and cell lines. Further, AKT phosphorylation is increased in biopsy samples of bronchial premalignancy, raising the possibility that AKT activation contributes to early stages of lung tumorigenesis. We investigated the role of this pathway in lung tumorigenesis by two creating mouse models: one with conditional *PTEN* loss and the other with over-expression of an activated form of AKT (gag-AKT). For the conditional *PTEN* model, *PTEN* was deleted by Cre-mediated recombination. Cre was expressed under the control of a bronchial epithelial-specific gene promoter (*clara cell secretory protein* or *CCSP*). By 3 months of age, *PTEN* deletion resulted in bronchial epithelial hyperplasia. Immunohistochemical analysis revealed increased Ser473 phosphorylation of Akt in hyperplastic regions. For the gag-AKT model, expression of the gag-AKT transgene was induced by the mifepristone regulator GLp65, which was under the control of a type II alveolar cell-specific gene promoter (*surfactant protein C* or *SP-C*). Preliminary studies have shown that mefipristone treatment induced gag-AKT expression in the alveolar epithelium. Studies are ongoing in both models to examine the tumorigenicity of these oncogenic signals in the lung.

**#5121 Hyperproliferation, apoptosis & tumorigenesis in response to MYC activation in the mouse lung.** Thaddeus D. Allen and J. Michael Bishop. *University of California, San Francisco, San Francisco, CA.*

Lung cancer remains the largest cause of cancer-related death. MYC is activated in a large percentage of both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) and activation of MYC-family genes via amplification is associated with poor prognosis. However, the role of MYC in the multistage progression of lung epithelial cells through preneoplastic stages to invasive cancer is not presently clear. Mouse models have show that MYC activation can cause rapid onset of malignancy in the liver and hematopoietic system but it is not known whether MYC activation has a similar effect in the lung. To address this issue a doxycycline (DOX)-inducible model of MYC activation has been built. Mice carrying a tetracycline-inducible promoter-driven MYC transgene (TRE-MYC) were crossed to a surfactant protein C (SPC) promoter-driven reverse-tetracycline transactivator transgenic line (SPC-rtTA) with the goal of inducing MYC expression in the SPC+ cell compartment. In double transgenic mice MYC was induced rapidly in response to DOX, resulting in the rapid proliferation of type II pneumocytes in the lung periphery. This hyperproliferative response was short lived, however, as apoptosis prevailed as the dominant response to MYC activation. Within 7-10 days of DOX treatment the hyperproliferative cells had regressed and normal tissue homeostasis appeared to be restored. The regression was associated with the induction of the BH3-only proteins Bim and Puma and the proapoptotic Bcl-2 family members Bax and Bok via a non-transcriptional mechanism. The tumor suppressor protein p53 was activated during this process. However, crossing SPC-rtTA/TRE-MYC mice onto a p53 null genetic background does not result in rapid onset of lung tumorigenesis. The data suggest that a MYC-induced program of apoptosis is responsible for the restoration of tissue homeostasis in this model. Despite this program, long-term administration of DOX to SPC-rtTA/TRE-MYC double transgenic mice does predispose to the formation of papillary lung adenocarcinomas that can metastasize to the liver. In conclusion, MYC activation induces a rapid apoptotic response that protects the SPC+ cell compartment of the lung from tumorigenesis. Additional genetic changes that accumulate over time appear to be required to abrogate this response and predispose MYC-overexpressing cells to malignancy.

**#5122 Heterozygous inactivation of transforming growth factor-B1 (TGF-B1) and mutational activation of K-ras predisposes early lung tumor progression.** Sonia B. Jakowlew, Tyler Jacks, Jyotsna Pandey. *National Cancer Institute, Rockville, MD and Massachusetts Institute of Technology, Cambridge, MA.*

Growth inhibition of TGF-B1 in lung epithelial cells is associated with direct, rapid stimulation of Ras. K-ras mutations are found in 30% of human lung adenocarcinomas, some of which show altered TGF-B receptor expression, while high levels of TGF-B1 are detected in the circulation of some of these patients. We hypothesized that heterozygous (HT) inactivation of TGF-B1 and mutational activation of K-ras would predispose early lung tumor progression. We generated a mouse model system to examine the molecular effects of disruption of the TGF-B signaling pathway in the presence of a spontaneously mutated activated K-ras mutation. HT TGF-B1 mice, C57BL/6NCr TGF-B1+/-, were mated with mu-

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**Author Block:** *Mang X. Ensell, Steven H. Reynolds, Michael L. Kashon, Amy M. Jefferson, Lowry T. David, Anne-Carine Ostvold, Jamie R. Senft, Frederick L. Tyson, Robert C. Johnson, Linda M. Sargent.* St Jude Children's Research Hospital, Memphis, TN, Center for Disease Control/ National Institute for Safety and Health, Morgantown, WV, University of Oslo, Oslo, Norway, National Institute for Environmental Health Sciences, Research Triangle Park, NC, Spectral Genomics, Houtson, TX

The incidence of adenocarcinoma is increasing in the United States, however, the difficulty in obtaining lung cancer families and representative samples of early to late stages of the disease have lead to the study of mouse models. We used a battery of tests to detect molecular changes associated with tumor invasion. Spectral karyotyping, mapping with fluorescently labeled genomic clones, comparative genomic hybridization arrays, expression arrays, Western blot and real time polymerase chain reaction (PCR) were used to analyze nine pairs of high invasive and low invasive tumor cell strains derived from early passage lung adenocarcinoma cell strains. The duplication of chromosome 1 and 15 and deletion of chromosome 8 were significant in high invasive cultures compared to low invasive cultures. The duplication of chromosome 1 between bands E2 and H1 was the most significant chromosomal change in the invasive cell strains. Mapping with fluorescent in situ hybridization and comparative genomic hybridization (CGH) array further narrowed the minimum region of duplication of chromosome 1 to 71 to 82 centimorgans (cM) as well as three deleted regions from 67-69 cM, 84-84 cM and 100-110 cM. Analysis of an expression array and confirmation by real time PCR identified increased expression of genes that were associated with the invasive phenotype. The amplified copy number and expression of vacuolar protein sorting 4B (SKD1), translin, and DYRK3 were significantly elevated in the invasive cell strains at $p<0.00001$. The copy number of NUCKS and tubulin α-4 showed a trend for increased expression in the cell strains that were able to invade a gel matrix. The increased copy number and expression of genes involved in cell movement, proliferation, and inhibition of apoptosis were associated with the invasive phenotype. The homologous linkage groups on human chromosomes 1q32-41, 2q, 8q24 and 8p are altered in invasive human lung cancer. Increased copy number and expression of the genes on mouse chromosome 1 may play a functional role in lung cancer development and may aid in the identification of mouse and human lung cancer susceptibility genes. *"The findings and conclusions in this report (abstract/presentation) have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be constructed to represent any agency determination or policy."*

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