mulations propelled the development of new strategies in therapy of several human lung diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease, lung cancer, tuberculosis, etc. Safety and lack of adverse health effects remain the major pre-requisites for broader applications of these novel technologies. Toxicological assessments of nano-particles typically are performed on normal animals. Thus possible effects of CNP on tumor growth have not yet been considered. The immune system safeguards the host from infections and malignancies. Recognition and undesirable interactions of CNP with cells of the immune system may lead to immunomodulation, hence increasing the host's susceptibility to infections and cancer. Here, we show that single wall carbon nanotubes (SWCNT) promote metastatic establishment and growth of Lewis lung carcinoma in C57BL6/J mice. The effect was mediated by increased local and systemic accumulation of myeloid-derived suppressor cells (MDSC), as their depletion abrogated pro-tumor activity in vivo. These data are important for the design of novel theranostics platforms with modules capable of depleting or functionally suppressing MDSC to ensure effective immunosurveillance in the tumor microenvironment.

PS 462 IL-33 Modulates Chronic Airway Resistance Changes Induced by Multiwalled Carbon Nanotubes.

X. Wang, J. Shannahan and J. M. Brown. *Pharmacology & Toxicology, East Carolina University, Greenville, NC.*

As the field of nanotechnology rapidly grows, the potential health hazards for human exposure rise. We have previously demonstrated that oropharyngeal instillation of multi-walled carbon nanotubes (MWCNTs) in C57BL/6 mice leads to increases in total respiratory system resistance (R) and Newtonian resistance (Rn), which is a measure of central airway resistance. In this study, we hypothesized that IL-33, a critical immune system alarmin, modulates mechanisms of pulmonary toxicity following exposure to MWCNTs. We assessed lung histology and pulmonary function in C57BL/6 and IL-33$^{-/-}$ mice 30 days following oropharyngeal aspiration of MWCNTs. The total number of bronchoalveolar lavage cells and the recruitment of neutrophils was increased in C57BL/6 mice following MWCNT exposure. In contrast, IL-33$^{-/-}$ mice exposed to MWCNTs did not demonstrate alterations in bronchoalveolar lavage cell content. Furthermore, C57BL/6 mice displayed increased inflammation around the airways demonstrated by histopathology which was unseen in IL-33$^{-/-}$ mice. To determine if these histopathological changes impact airway resistance, MWCNT exposed C57BL/6 were challenged with cumulative doses of methacholine (Mch) between 1.5 mg/ml and 24 mg/ml. Aerosolized Mch increased R and Rn in a dose-dependent manner in all groups with MWCNT instilled C57BL/6 mice responding with significantly higher R and Rn compared to control C57BL/6 mice. Importantly, increases in R and Rn induced by MWCNT were dependent on IL-33, as there was no significant difference between MWCNT treated and control IL-33$^{-/-}$ mice. In conclusion, these results indicate IL-33 plays an important role in pulmonary toxicity induced by MWCNT by influencing airway resistance via an inducible inflammatory response. This work supported by NIH RO1 ES019311.

PS 463 Pulmonary Toxicity Assessment of Multiwalled Carbon Nanotubes after Single Intratracheal Instillation in a One-Year Bioassay of Rats.

M. Naya, N. Kobayashi, K. Honda, M. Ema and J. Nakanishi. *National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Japan.*

Well-dispersed multi-wall carbon nanotubes (MWCNTs) were instilled intratracheally at dosage of 1.0 or 2.6 mg/kg body weight to male Wistar rats. A negative (vehicle) control, 0.5 mg/mL Triton X-100 was administered in a similar manner. After instillation, the bronchoalveolar lavage fluid (BALF) was assessed for the inflammatory biomarkers, and the lung, liver, kidney, spleen, and cerebrum were examined histopathologically at 1-day, 3-day, 1-week, 4-week, 3-month, 6-month, and 12-month post-exposure. Transient pulmonary inflammatory responses were observed up to 3-month post-exposure. In the histopathological examination, 1.0 and 2.6 mg/kg of MWCNTs deposited in the lungs were phagocytosed by the alveolar macrophages and these macrophages were accumulated in the alveoli up to 12-month post-exposure. There was no evidence of chronic inflammation, such as angiogenesis or fibrosis which induced by MWCNT instillation. These results suggest that MWCNTs were being processed and cleared by alveolar macrophages.

PS 464 Thirteen-Week Inhalation Toxicity Study with a Multiwall Carbon Nanotube Test Material in Wistar Rats.

D. Schuler[1], K. L. Reed[2], M. P. DeLorme[2], Y. Okazaki[1], Y. Muro[4], H. J. Chevalier[3] and D. B. Warheit[2]. *[1]Harlan Laboratories Ltd., Fuellinsdorf, Switzerland; [2]DuPont Haskell Lab, Wilmington, DE; [3]Anapath GmbH., Oberbuchsiten, Switzerland; [4]Showa Denko K.K., Tokyo, Japan.*

A subchronic inhalation toxicity study of an inhaled vapor-grown multiwall carbon nanotube (MWCNT) test substance was conducted in male and female Wistar rats. The test sample was composed of > 99.5% carbon, containing limited (Fe) catalyst metals; BET surface area measurements of ~25 m2/g; and average lengths/diameters of 9 μm and 100 nm, respectively. Four groups of rats per sex were exposed nose-only, 6 h/day, for 5 days/week to aerosol concs. of 0, 0.013 (low), 0.055 (mid) or 0.53 (high) mg/m3 MWCNT (MMAD ranging from 0.85 – 1.64 μm) over a 91-day period and evaluated 1 day later. Toxicity evaluations included clinical and histopathology methods, and bronchoalveolar lavage fluid (BALF) analyses. Additional control and high exposure groups were evaluated at 3 months PE.
Results demonstrated that MWCNT exposures produced no significant adverse extrapulmonary effects. Absolute and relative lung weights were increased in high exposure conc. vs. controls and to a lesser extent after the recovery period. The results of BALF studies demonstrated increased GGT, LDH and ALK PHOS levels vs. controls in mid/high exposure groups. In addition, increased numbers of BALF cells were recovered at 0.53 mg/m3 MWCNT. Principal histopathological findings consisted of granulomatous lesions in centriacinar regions of male/female rats exposed to 0.53 mg/m3, and in some females at 0.055 mg/m3. The lesion was characterized by aggregation of pulmonary macrophages and focal pulmonary hypertrophy/hyperplasia of lung epithelial cells. In the nasal cavities, an increase of eosinophilic inclusions in the respiratory/olfactory epithelium was noted at 0.53 mg/m3 which was followed by the olfactory epithelial injury in the recovery animals. Based on the findings in respiratory tract tissues (lungs and nasal cavities), the overall LOAEL was considered to be 0.055 mg/m3, and the corresponding NOAEL was determined to be 0.013 mg/m3 under the conditions of this study.

PS 465 Carbon Nanotube Dosimetry: From Workplace Exposure Assessment to Inhalation Toxicology.

M. Dahm[1], B. T. Chen[2], M. E. Birch[1], D. E. Evans[1], M. K. Schubauer-Berigan[1], T. Hulderman[2], S. A. Bilgesu[2], H. D. Leonard[2], W. McKinney[2], D. Frazer[2], J. M. Antonini[2], D. W. Porter[2], V. Castranova[2], P. C. Zeidler-Erdely[2] and A. Erdely[2]. *[1]NIOSH, Cincinnati, OH; [2]NIOSH, Morgantown, WV.*

Relevant dosimetry for toxicology studies involving multi-walled carbon nanotubes (MWCNT) has not been well described due to a lack of detailed occupational exposure assessments. In response, exposure assessment findings from U.S.-based MWCNT manufacturers and users were extrapolated to results of an inhalation study in mice. Inhalable and respirable personal breathing zone (PBZ) samples from 9 facilities were collected for the mass concentration of elemental carbon. Upon analysis, 95% of the PBZ samples found exposure concentrations to be <10 μg/m^3 with an average inhalable concentration of 8.5 μg/m^3. At facilities where respirable and inhalable PBZ samples were collected, respirable samples were approximately 25% of the inhalable size fraction. Using 10 μg/m^3, standard worker ventilatory parameters, and assuming 11% alveolar deposition, alveolar deposition was calculated to be 10.56 μg/d. Extrapolation to mouse equivalence by surface area equals 5.2 ng/d. In complement, a 19 d inhalation exposure to MWCNT with daily alveolar depositions of 1250 ng (=240 d of human exposure at 10 μg/m^3), 125 ng (=24 d), and 12.5 ng (=2.4 d) was conducted. Mice were sacrificed at day 0, 3, 28, and 84 post-exposure. Pulmonary cytotoxicity (LDH activity) and polymorphonuclear cell (PMN) influx were evident at the high dose through day 84. For the middle dose, no PMN influx was evident and cytotoxicity was significant only at day 0. Lung inflammatory gene expression was increased at the high and middle dose. Alveolar macrophages harvested after exposure and stimulated with LPS showed enhanced cytokine release at the high dose and day 0 for the middle dose. No exposure effects were observed at the lowest dose. These results show a no effect dose lies somewhere in between the middle (=456 d at 10 μg/m^3) and low dose (=45.6 d). The findings stress the importance of exposure assessment when extrapolating results of animal MWCNT exposures to potential human outcomes.

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