in hemolysis was produced in response to SiO2 and TiO2. FLIM results indicated increases in lipid packing around the fluorescence probe Di-4ANNEPDHQ, as a result of, SiO2 and TiO2 exposure. These results suggest SiO2 and TiO2 generate LMP by inhibiting natural lipid mobility that can potentially induce membrane permeability.

2663 Cell Cycle Alterations after *In Vitro* Exposure to Pegylated Gold Particles in Cancerous vs. Non-Cancerous Lung Cells

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In the past few years engineered metal and polymer based nanoparticles have seen an increase in use in the pharmaceutical industry as drug delivery carriers (DDC) used for cancer therapy. The increased vasculature, altered morphology, and metabolism of cancer cells allow nanoparticles to be specifically engineered to preferentially penetrate these tissues over non-cancerous cells. PEGylated gold nanoparticles are highly utilized as an excipient (i.e. DDC; the non-active ingredient) due to their increased stability over polymer based DDCs while remaining bio-inert (i.e. does not react within the body). However, as the rate of administration of therapeutics containing gold nanoparticles increases, there is a need to characterize the interactions of the excipient with different biological test systems. To identify how the gold nanoparticles interact within the lungs, a pair of cancerous and non-cancerous cell lines from the bronchus (A549 & BEAS-2B) and pleural space (Calu-3 & MeT-5A) were examined for uptake of 20nm PEGylated gold nanoparticles and nanoparticle-induced cell cycle changes. Baseline gene and protein expression of Cyclin dependent kinases (CDKs) and CDK inhibitor p21, along with normal cell morphology were examined prior to exposure. Dose-response changes to the cell cycle were shown regarding changes in cell viability, proliferation, morphology, DNA integrity, and perturbed expression of CDKs and CDK inhibitors. While all cell lines exhibited changes in gene/protein expression, the two cancerous cell lines and pleural space cells were more susceptible to alterations in their normal cell cycle.

2664 Screening *In Vitro* Toxicity Endpoints of Carbon Nanotubes and Nanofibers from United States Facilities

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Significant investment has been made in recent years to harness the economic potential of utilizing the unique characteristics of carbon nanotubes and nanofibers (CNT/F) to advance material science applications. Unfortunately, those same characteristics that provide signif-icant potential for application may also confer adverse health effects. CNT/F represent a broad class of materials and we hypothesized that not all CNT/F produced or utilized in US facilities confer similar toxici-ties. Extensive characterization was done for seven different multiwalled CNT and two CNF that were selected based on primary particle diameter ranging from 10 to 150 nm. The specific surface areas ranged from 18 to 238 m2/g and decreased with increasing primary particle diameter. Key molecular-initiating events (MIE) and functional responses were screened over a wide dose range (0-60 µg/ml) in a human monocytic cell line (THP-1), both wild-type and NLRP3 inflammasome deficient cells, and in primary human lung fibroblast cells (PHF). Membrane damage and cell proliferation in THP-1 challenged with CNT/F for 24 h segregated by diameter with materials greater than or equal to 50 nm in diameter inducing greater toxicity. There was ~150 fold change in IL-1β secreted in THP-1 WT vs NLRP3 deficient cells and for all the CNT/F tested, apart from having a dose-dependent increase, the level of secretions was enhanced with increasing primary particle diameter. Similarly, CNT/F exposure (0-2 µg/cm2) to PHFs elicited increased cell proliferation and collagen I production that was greater with increased primary particle diameter. Structure activity correlations to date indicate that CNT/F could be broadly classified into two groups, materials below 50 nm in primary particle diameter were less bioactive/toxic than tubes greater than 50 nm. Ongoing research and modeling will further elucidate relationships between physicochemical characteristics and toxicity profile of various CNT/F.

2665 Cytotoxicity of Applied Nanoclusters for Cellular Imaging

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Nanoclusters (NCs) are recognized for their unique optical and biodispersion properties. NCs possess possible applications in tissue imaging and treatment strategies. However, the toxicity and optical properties of these compounds have yet to be evaluated in human cells. Recently a human microglial cell line was employed to investigate if noncancerous human neuronal cells can synthesize NCs of imaging capacity, and if pre-synthesized gold (Au) and iron (Fe) NCs result in cell stress and death. Cells were either treated with chloroauric acid ($HAuCl_4$) or Au and Fe NCs for up to 72 hrs. Exposure to $HAuCl_4$ or Fe NCs resulted in a dose-dependent loss of cell viability within the first 8hrs of exposure, with a continuing loss through 72 hrs. High $HAuCl_4$ exposure lead to significant increased reactive oxygen species (ROS) within 12 hrs following exposure, which continued through the exposure study. Similarly, Fe NCs resulted in ROS within two hours after exposure, signal was found to rise through the exposure time. Interestingly, Au NCs did not produce a notable increase in ROS during the first 24 hrs, however; once induced, ROS signal plateaued after another 24hrs. Fluorescent imaging revealed increased cell fluorescence following exposure to all compounds, with fluorescence seen in the cytoplasm during $HAuCl_4$ and Au NC exposures; and dispersed throughout the cell during Fe NC exposure. Transmission electron microscopy confirmed cellular uptake of all compounds and suggest localization within cellular vesicles. Inductively coupled plasma-mass spectrometry also indicated increased uptake of materials in a temporal and concentration-dependent manner. Taken together these results highlight i) the capacity for human neuronal cells to self-synthesize NCs following $HAuCl_4$ treatment, ii) the bioavailability and cytotoxicity of pre-synthesized nanocluster, iii) the ability for human cells to uptake pre-synthesized NCs, and iv) the resulting increased intracellular fluorescence from all these material treatments.

2666 Differentiation State of Airway Epithelium Organotypic Culture Models Is a Potential Mediator of Silver Nanoparticle-Induced Toxicity

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Engineered nanomaterials, including silver nanoparticles (AgNP), are one of the largest groups of emerging toxicants. They are used in hundreds of consumer products due to their antimicrobial properties, and have a potential to aerosolize through the manufacturing and usage of these products. AgNP are respiratory toxicants with potential to cause allergic airway inflammation; however, the genetic, environmental, and temporal factors that may mediate their toxicity have yet to be fully elucidated. This study has developed airway epithelium organotypic culture models (AE-OCM) as a platform to identify these potential mediators and use them to inform Adverse Outcome Pathways (AOP) for allergic airway diseases, such as asthma. We are quantifying gene × environment × time interactions (G×E×T) using AE-OCM derived from two inbred founder strains of Collaborative Cross mice (AJ and C57BL/6J), differentiated under two conditions (- IL-13 and + IL-13; 25 ng/mL), and treated with AgNP (12.5, 25, and 50 µg/mL) at two time points—a four-hour repeated exposure over five days (5×4 hours), and 24 hours. Endpoints of interest include: changes in epithelial barrier function, cytotoxicity, and enrichment of gene ontologies for pathways associated with allergic airway inflammation. In AE-OCM + IL-13, we found significant reductions in epithelial barrier function, as measured by transepithelial electrical resistance (TEER; ohm×cm^2), after AgNP treatment (25 and 50 µg/mL) at 5×4 and 24 hours compared to untreated control at day *in vitro* 25. We also found significant increases in cytotoxicity, as measured by LDH Release (%), after AgNP treatment (12.5, 25, and 50 µg/mL) at 5×4 and 24 hours compared to untreated control. We found few significant differences in cytotoxicity across strains, with A/J showing increased susceptibility compared to C57BL/6J. Compared to preliminary data for AE-OCM, AE-OCM + IL-13 shows reduced epithelial barrier function at baseline, and increased cytotoxicity after AgNP treatment, suggesting that differentiation state may mediate AgNP-induced toxicity.

Highlighted text above was omitted from the published copy. A. Erdely provided the first two lines of text.

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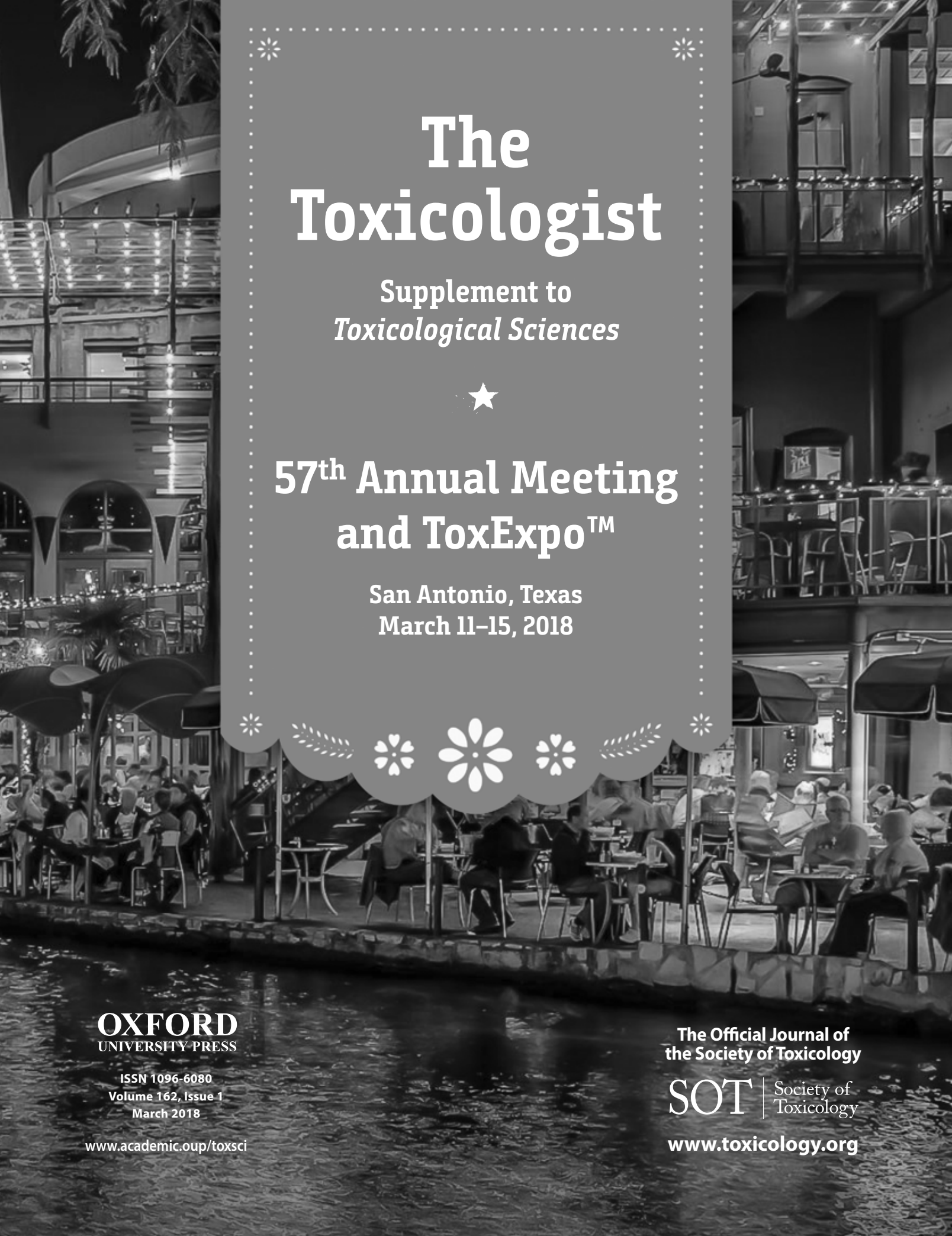

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