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Distinguished Scholars in Toxicology Lecture Series

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Dr. Joel Pounds
Pacific Northwest National Laboratory

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101 Biochemistry

Systems toxicology of engineered nanomaterials

Research in the Pounds Laboratory

One grand challenge in nanotoxicology is to satisfy the urgent need for rapid hazard assessment of emerging nanomaterials through development of suitable high-throughput in vitro assays, in vivo testing strategies and computational tools. The benefits of nanomaterials to the energy, medical and electronics industries and the consumers they serve will not be realized without adequate health and safety data for these novel materials. The open question now is whether advances in the biological, computational and risk sciences will be applied as testing approaches are developed for these novel submicron materials. Our research team is developing and applying novel tools and approaches for addressing fundamental questions regarding the safety of nanomaterials. Two computational dosimetry tools are in development that supports simulation of cellular dosimetry in vitro as well as regional respiratory tract dosimetry following inhalation of nanomaterials. The advancement of nanotechnology and new nanoscale materials has outpaced our understanding of the potential human health risks of these materials. Secondly, unbiased approaches are needed to identify new suites of biomarkers that are predictive of nanoparticle toxicity to guide development and regulation of safe nanomaterials. Our research strategy is to distinguish the cell processes and signaling networks activated by non-cytotoxic inflammatory stimuli from those that are indicative of nanoparticle toxicity for the identification of new pathway-based biomarkers for high-throughput screening. Global microarray and proteomic technologies were used to evaluate the early response pathways and downstream extracellular protein biomarkers of nanoparticle exposure, using a macrophage cell line model system. Dose response studies were conducted with nano-sized amorphous silica, crystalline silica, single-walled carbon nanotubes and lipopolysaccharide (LPS) to provide parallel samples for gene expression profiling at 2hr post-exposure, global proteomic analysis of secreted proteins after 24hrs, and cytotoxicity assessment at 24hrs. We identified >500 genes that are significantly regulated following particle exposure but unaffected by LPS. These genes represent many cell processes, including cell cycle regulation, response to stress, nucleotide metabolism and apoptosis. Global proteomic analyses of secreted proteins confirmed many of the inflammatory markers identified in the microarray data, including divergent response pathways characterized by markers unique to particle exposure (HSPA8, NDRG1) and unique to LPS exposure (CSF3). Other identified protein effectors were associated with macrophage survival (MIF), proteolysis (ITIH2), cell adhesion/migration (LGALS3), complement activation (C3, C4B) and regulation of immune response (FKBP4) only after particle exposure. We are using these data to infer signaling networks that capture the critical biological pathways involved in the cell response from nanoparticle exposure.

References

Waters KM, Pounds JG, and Thrall BD. (2006) "Data Merging for Integrated Microarray and Proteomic Analysis." *Briefings in Functional Genomics and Proteomics* (in press).

Adkins JN, Monroe ME, Auberry KJ, Shen Y, Jacobs JM, Camp DG III, Vitzthum F, Rodland K, Smith RD, and Pounds JG. (2005). "A Proteomic Study of HUPO's Plasma Proteome Project Pilot Samples using an Accurate Mass and Time Tag Strategy." *Proteomics*. 5:3454-3466.

Omenn GS, States DJ, Adamski M, Blackwell TW, Menon R, Hermjakob H, Apweiler R, Haab BB, Simpson RJ, Eddes JS, Kapp EA, Moritz RL, Chan DW, Rai AJ, Admon A, Aebersold R, Eng J, Hancock WS, Hefta SA, Meyer H, Paik Y-K, Yoo J-S, Ping P, Pounds JG, Adkins J, Qian X, Wang R, Wu CY, Zhao X, Zeng R, Archakov A, Tsugita A, Beer I, Pandey A, Pisano M, Andrews P, Tammen H, Speicher DW, and Hanash SM. (2005). "Overview of the HUPO Plasma Proteome Project: Results from the pilot phase with 35 collaborating laboratories and multiple analytical groups, generating a core dataset of 3020 proteins and a publicly-available database." *Proteomics*. 5:3226-3245.