a first step to investigate the use of LPNPs as novel drug delivery devices, their interaction with a part of the human immune system, complement has been explored. The complement system is the most important biochemical cascade in the blood for the recognition, opsonization and killing of foreign materials. This presentation covers from general knowledge on complement system to the state of the art on complement activation by other nanomaterials. The last part of the talk is focused on presenting the first systematic study of the blood biocompatibility properties of lipid-polymer nanoparticles functionalized with methoxyl (OCH3), amine (NH2), and carboxyl (COOH) functional groups. Our results show that LPNPs –OCH3 generate negligible levels of complement activation, while LPNP-NH2 induced the highest complement activation among carboxylic and methoxyl groups. None of these nanoparticles activated the coagulation cascade. In general, lipid-polymer nanoparticles functionalized with these three functional groups present good biocompatibility profiles in comparison to Zymosan, a well known activator of the complement system. The main contribution of this work is the creation of an effective and practical method to modulate the levels of activation of the complement system via the interaction of different functional groups on nanoparticle's surface.

S 821 RECOGNITION OF NANOPARTICLES BY MACROPHAGES—FROM PRINCIPLES TO CONSEQUENCES AND TOXICITY.

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Engineered nanomaterials (EN) have unique physico-chemical properties that make them promising for many biomedical applications. However, with the burgeoning capabilities to manipulate structures at the nano-scale, employing this machinery for safe and efficient drug delivery is not fully explored. To this end recognition of EN by the immune system, our primary defense outpost against foreign invasion is a critical point. Recognition versus non-recognition of EN by the immune system not only determines the distribution of nanomaterials in the body but may also dictate their toxic potential. Recent studies showed that autophagy may have emerged as the initial and primordial defense of eukaryotic cells against microbes. It is therefore not surprising that immune-competent cells may respond to EN in a similar manner as to viruses/bacteria. Consequently, there are complex relationships between the infection process and inflammatory responses to EN resulting in potent effects of nanoparticles on pulmonary clearance of bacteria. Elucidation of how EN impact the conserved mechanism of autophagy, recognition and/or phagocytosis promise to be an interesting and fruitful area for better understanding of interactions of EN with the cells of innate immune system, particularly macrophages. It becomes clear that the presence of specific recognition patterns primarily defined by the EN' size and charges are essential for their recognition and uptake by macrophages. Further, the presence of specific signals on the surface of EN, such as adsorbed lipids or proteins, confers additional features to the effectiveness of the recognition of nanoparticles by professions phagocytes. Finally, oxidative stress - known to act as an underlying mechanism that drives the toxicities of EN *in vitro* as well as *in vivo* – may be triggered as a macrophage response to recognized nanoparticles. Overall, the mechanisms of recognition, cellular internalization of EN by immune competent cells, particularly macrophages, represent an important new field of molecular nanotoxicology.

S 822 DEVELOPMENT OF CYT-6091 (AURIMUNE®): A MODEL CANCER NANOMEDICINE.

L. Tamarkin and G. F. Paciotti. *CytImmune, Rockville, MD.* Sponsor: S. Casinghino.

The use of nano-sized drug delivery systems to target potent, but toxic anticancer therapeutics to solid tumors is best accomplished by avoiding the drug's uptake by the immune system and by limiting its biodistribution. Binding recombinant human tumor necrosis factor alpha (TNF) to the surface of 27 nm PEGylated colloidal gold particles (CYT-6091) meets these objectives. Each component serves a specific function. The gold nanoparticles limit biodistribution, while PEGylation prevents immune detection. TNF serves to localize the nanoparticle to the tumor and causes vascular disruption of the tumor blood supply. Clinically, an IV injection of 0.4 mg native TNF (the MTD) has no anticancer action. But, 1 mg TNF perfused regionally and combined with chemotherapy [Isolated Limb Perfusion (ILP)] is very effective, resulting in an 85% complete local response rate. Our goal is to systemically administer 1 mg TNF formulated as CYT-6091 to cancer patients. The completed CYT-6091 Phase I clinical trial demonstrated that CYT-6091: induced a fever that was eliminated by pre-treatment with acetaminophen/indomethacin, induced acute lymphopenia that resolved within 24 hours, did not induce an anti-TNF antibody response, showed no DLT at the highest dose of 0.6 mg/m2 (>1 mg TNF per dose), and targeted the tumor as determined by the presence of gold nanoparticles in patient biopsies. A Phase II combination trial with docetaxel, mimicking the ILP protocol design, but administered systemically, will assess efficacy. The Phase I trial highlights three fundamental characteristics for cancer nanomedicines: development of a controlled manufacturing process that creates a nanomedicine that may be well-characterized, which when injected IV does not traffic to the mononuclear phagocyte system (the liver and spleen), and does traffic to tumors, limiting the drug's biodistribution, reducing systemic toxicity and potentially bringing more drug to the site of disease. Further, since an intact tumor vasculature is critical for nanomedicines' targeting tumors, the treatment of solid tumors should begin with a nanomedicine prior to surgery, even for resectable tumors.

S 823 CASE STUDY: INTERACTION OF DEXTRAN NANOMATERIALS WITH THE IMMUNE SYSTEM—*IN VIVO* AND *IN VITRO* STUDIES.

S. Casinghino, G. B. Freeman, M. L. Mirsky and T. T. Kawabata. *Pfizer Inc., Groton, CT.*

While nanomaterials made of biocompatible polymers hold great promise as drug delivery platforms, biological consequences resulting from interaction of nanomaterials with the immune system have not been fully elucidated. Dextran is well established as a biocompatible polymer with extensive use as a plasma expander. Hydrophobic derivatives of dextrans that were developed to enable manufacture of drug-polymer nanoparticles, elicited severe toxicities in rat in vivo studies. Results of these studies suggested that the dextran derivatives were being recognized by the immune system and were capable of activating macrophages and the complement cascade. In vitro assays were used to screen for immune system activation and after further modifications to the polymers, dextran derivatives were identified that showed improved safety profiles in subsequent in vivo studies. These screening assays have the potential to facilitate selection of materials to minimize unwanted interaction with the immune system and to aid in the rational design of nanoparticle drug delivery systems.

S 824 TOXIC CELL-DEATH: SIGNALING PATHWAYS, CROSS-TALK, AND HIGH-THROUGHPUT ANALYSIS.

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Cell death is the ultimate result of toxicity caused by damage to critical cell functions and/or activation of death signaling pathways. Toxicants can trigger multiple modes of cell death (apoptosis, necrosis, necroptosis, and autophagic cell death) with distinct morphological and biochemical characteristics. In fact, several cell death modalities may coexist within the same lesion with cross-talk between them. To address this important topic, we will begin by discussing the role that cell death plays in toxic insult and disease, and how improved knowledge of cell death signaling pathways and mechanisms will help us understand how toxicants might interfere with cell viability and function. After the description of various cell death modalities, and the possible cross-talk between them, mechanisms of apoptotic cell death caused by anesthetics in the developing brain and of lead-induced apoptosis in retinal photoreceptors will be presented as examples of cell death caused by toxic insult. These studies illustrate the critical roles of the calcium ion and of reactive oxygen species as mediators of neurotoxicity, as well as the difference in sensitivity of the mitochondrial populations in rods and cones to apoptotic stimuli. Thereafter, the mechanisms of action of certain chemotherapeutic agents and fungal toxins will be discussed to illustrate the role of sphingolipid signaling molecules in cell death and disease. Finally, a molecular epidemiology approach using novel technologies to assess cell death and environmental impact in individual cells and in human populations in a high-throughput manner will be presented. The program will cover important toxicity mechanisms in multiple target organs and will hopefully contribute to a better understanding of the role of cell death mechanisms in toxic insult and disease.

S 825 MODES AND PATHWAYS OF TOXICANT-INDUCED CELL DEATH.

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Cell death is the ultimate result of toxicity. It is now apparent that during toxicity multiple cell death programs, i.e. apoptosis, necrosis, necroptosis and autophagy, can be activated. Some of them are shared by different tissues; others are tissue-specific and are linked to particular functions. Elucidating the signaling pathways regulating various modes of cell death, is highly relevant for our understanding of the

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