macological effect in cancer patients occurs at full target engagement, the therapeutic anti-cancer effect theoretically cannot be separated from potential deleterious effects to the fetus. Therefore, pregnancy risk based on the mechanism of action of anti-PD-1 mAbs should be assumed and considered similar for all effective PD-1 inhibitory therapeutics. This is in contrast to typical drug candidates, where potential effects on reproduction would not be related to their pharmacological action and developmental and reproductive toxicity (DART) studies in animals are conducted to identify potential risk in humans and to determine exposure-margin risk assessment. However, when the reproduction risk can be predicted by a mechanism-based evaluation, and published data generated from murine models confirm such a risk, the conduct of DART studies with the clinical drug candidate is deemed not warranted. Such an approach has been used in the evaluation of pregnancy risk of anti-PD-1 agent, pembrolizumab, and has been demonstrated as a valid and highly desired alternative to performing DART studies in nonhuman primates.

W 2358 Case-by-Case Approach for Assessing DART Risk of Oligonucleotide-Based Therapies

J. Cavagnaro. *Access BIO, Boyce, VA.*

Oligonucleotide drugs (ONs) have attributes of small molecule pharmaceutical and large molecule biopharmaceuticals. As such, both sets of guidelines are considered. The approach to DART testing takes into account both the potential effects of chemical structure as well as the intended pharmacology of the ON. Standard reproductive toxicity species can often be used because most ON toxicity is related to chemical structure. Animal-active surrogates can also be useful to assess potential reproductive effects related to pharmacology in addition to effects related to the chemical back- bone. The choice of the relevant animal model, the dosing regimen, and whether to use the clinical candidate or an animal surrogate, all need to be considered carefully based on the specific product attributes of the ON. Information from general toxicity studies and previous experience with similar ONs can also help to inform these decisions. Dosing regimens are tailored to ensure adequate exposure throughout the period of organogenesis without compromising the ability to assess PD- and PK-related effects. This talk will discuss how the above points are considered and applied to ONs.

W 2359 Thinking Beyond DART Studies for Risk Assessment of Biotherapeutics

P. Del Valle. *US FDA/CDER, Silver Spring, MD.*

This presentation will discuss ICH regulatory guidances S9, S6(R1) and M3(R2) relevant to nonclinical reproductive and developmental toxicity studies needed for safety assessments of biotherapeutics. Weight of evidence accumulated during repeat-dose toxicology studies, comparative PK assessments in animals and humans, mode of action, and species specificity among other considerations should be incorporated when proposing alternative designs for DART studies with biotherapeutics, or in the generation of product-specific assessment based on the use of appropriate literature of reproductive and developmental toxicity potential. The ultimate goal of DART studies should be the generation of useful data for labeling purposes to communicate human risk. Case studies describing innovative designs proposed in regulatory submissions will illustrate the regulatory challenges for safety testing, including the use of alternate species and dosing schedules, as well as legal limitations with the use of a literature approach alone.

W 2360 Circulatory Mechanisms Underlying the Systemic Effects of Inhaled Nanoparticles and Complex Combustion Mixtures: Common Pathways for Diverse Toxicants

M. Campen. *University of New Mexico, Albuquerque, NM.*

Numerous studies highlight that inhaled agents may cause systemic health effects, including cardiovascular, neural, and renal diseases, yet the mechanisms underlying this relationship remain uncertain and highly contentious. Most inhaled xenobiotics are confined to the lung. Inhaled gases are metabolized and particulates are largely removed to the gut by mucociliary action, with only trace concentrations attaining extrapulmonary compartments; however, systemic pathophysiological outcomes of inhaled pollutants are routinely reported. Recent findings show that pulmonary toxicity can cause production and release of novel biomolecules into the blood, with downstream implications for vascular cell activation and extrapulmonary inflammation. Progress in this area provides not only knowledge with which to protect public health from environmental and occupational hazards, but also informs the basis of comorbidities in complex inflammatory clinical conditions, such as metabolic syndrome and cardiorenal disease. This workshop will highlight the latest evidence for lipid, protein, and metabolite modification in response to a diverse array of inhaled agents and the transduced effect, such modifications on the vasculature, brain, and other major organ systems.

W 2361 Evidence for Mechanistic Specificity Driving Pulmonary Particulate Exposure-Induced Cardiovascular Dysfunction

A. Erdely. *NIOSH, Morgantown, WV.*

Adverse cardiovascular effects following a pulmonary particulate exposure are well documented. Exposure to incidental and engineered nanosized materials can alter vascular responsiveness and cause morphologic changes. While particle translocation and neurogenic effects are proposed, recent experimental evidence suggests an alteration in circulating mediators as the predominant mechanism. These studies demonstrate that localized pulmonary responses are often distinct from systemic toxicity. For example, vascular function was unchanged following a nanosilver exposure despite lung injury, increased inflammatory cell influx, and induction of inflammatory genes. Conversely, an incidental nanoparticle exposure to resistance spot welding particles induced marked vascular dysfunction with no alterations in general lung toxicity or inflammation. Following a 10 d ultrafine metal-rich particulate inhalation exposure, molecular signaling induced at the site of exposure was reflected systemically in the circulating leukocytes as well as cardiovascular tissues. The responses predicted cardiac mitochondrial dysfunction and compensation that were confirmed by functional studies. The systemic effects resolved following cessation of exposure despite sustained and, in some cases, increasing lung injury and inflammation one month later. Serum from mice exposed to multi-walled carbon nanotubes (MWCNT) attenuated vascular dilation, decreased nitric oxide production, and induced cellular inflammation. Unlike the pulmonary response, these effects were independent of dose. In contrast to serum of wild-type mice, maximal vascular dilation was achieved with serum collected from MWCNT-exposed MMP9-/- mice. While maximal dilation was restored, lung inflammatory markers were similar to wild-type exposed mice despite predictions that MMP9 would be a primary driver of pulmonary responses to MWCNT. These results indicate that altered circulating factors contributing to vascular dysfunction had mechanistic specificity. In summary, cardiovascular effects following a pulmonary exposure do not necessarily correlate with general measures of pulmonary toxicity and inflammation and were not always dose-dependent. In addition, specific molecular mechanisms induced by an exposure can drive cardiovascular dysfunction via altered circulating mediators.

W 2362 Nanomaterial Inhalation-Induced Serum Biomarkers Associated with Extrapulmonary Microvascular Dysfunction

T. Nurkiewicz. *West Virginia University, Morgantown, WV.*

The mechanism(s) through which engineered nanomaterial (ENM) inhalation disrupts normal extrapulmonary cardiovascular function remains to be fully defined. One of the better studied links that mediates exposure and effect is inflammatory mediator activation. We have reported that ENM inhalation (nano-titanium dioxide, count mode aerodynamic diameter <150 nm, 5-10 mg/m^3, 4-5 hrs) leads to focalized alveolitis, in a dose-dependent manner (pulmonary deposition 10-150 µg), and this initiates a series of plasma-borne mediators that ultimately activate systemic neutrophils and stimulate their adhesion and rolling. One of the revealing characteristics of this interaction is the generation of reactive species in the microvascular wall. We have documented oxidative and nitrosative stress with fluorescent biomarkers, and functionally with various vascular antagonists. The impact of ENM exposure exists in both arterioles and venules, and inter-vessel signaling is typically disrupted. The principal consequence of this disruption is an inability to match capillary inflow and outflow. Physiologically, this alters mechanotransduction and volume blood flow, which in turn compromise the ability to maintain cardiovascular homeostasis. The impact of these microvascular toxicities will be discussed from a cardiovascular health perspective.


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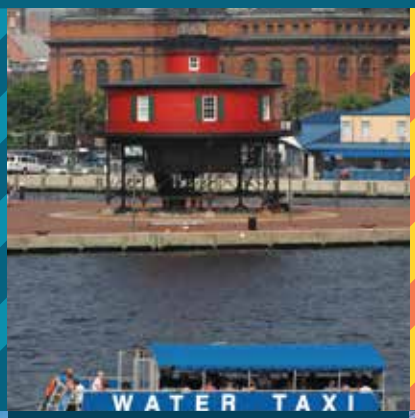

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