laboratory has demonstrated that NRTI treatment in vivo induces direct endothelial dysfunction, a hallmark of atherogenesis, while results from in vitro studies have suggested that compromised mitochondria may play a role in NRTI-induced endothelial dysfunction. In the present study, human umbilical vein endothelial cells (HUVEC) treated with micromolar concentrations of the NRTIs zidovudine, lamivudine, and tenofovir disoproxil fumarate were found to have increased levels of reactive oxygen species (ROS), decreased activity of mitochondrial complexes I, II+III, and IV, decreased ATP production, and a decreased NAD+/NADH ratio as early as 4-6 hrs after treatment. Moreover, levels of two markers for endothelial dysfunction and activation, vascular cell adhesion molecule-1 and the vasoconstricting peptide endothelin-1, were increased after NRTI treatment. Interestingly, ROS levels and ATP production return to levels comparable to those in untreated cells after 18-24 hrs of treatment, suggesting the existence of a compensatory mechanism for the clearance of damaged mitochondria. Using confocal microscopy, we have shown specific colocalization of mitochondria with lysosomes and early autophagosomes in treated cells, which is indicative of mitochondrial autophagy (mitophagy), a phenomenon which may be involved in the removal of NRTI-damaged mitochondria. Thus, short-term endothelial NRTI toxicity may manifest in a compensated state, whereas more chronic exposure may result in pathogenic maladaptation. These data taken together with our prior studies may suggest a potentially causal relationship between NRTI-induced disruption of mitochondrial function and endothelial dysfunction, as well as a distinction between short-term and long-term effects of NRTI treatment.

## PS 184 DRUG-INDUCED CARDIAC LEFT VENTRICULAR DYSFUNCTION AND ARRHYTHMIA ASSOCIATED WITH MITOCHONDRIAL IMPAIRMENT.

P. J. Acton, K. Derakhchan, R. W. Chui, Y. Qu, M. Fang, B. Gao, I. Senal, R. Hernandez, D. Robert, H. M. Vargas and J. W. Lawrence. *Comparative Biology and Safety Sciences, Amgen, Thousand Oaks, CA.*

Early stage safety assessment assays are used to profile agents for their potential to cause cardiac electrical and mechanical (contractility) dysfunction. During development of a drug candidate series, left ventricular contractility deficits were identified as a common finding in the chloralose-anesthetized dog model. In one case, a candidate molecule also evoked polymorphic ventricular tachycardia. Investigations of off-target mechanisms demonstrated that cardiac β1-adrenoceptor and sodium/calcium channel blockade could not account for the contractility deficit. A custom built mitochondrial function profiling platform was used to assess potential mitochondrial mechanisms associated with reduced left ventricular contractility. Profiling mitochondrial mechanism demonstrated that the left ventricular contractility deficits were associated with potent mitochondrial complex V (ATP synthase) inhibition and did not involve electron transport chain inhibition, TCA or fatty acid substrate oxidation inhibition, mitochondrial membrane potential, mitochondrial permeability transition, or calcium loading potential deficiencies. The concentrations that inhibited complex V were also shown to inhibit contractility in the isolated rabbit heart preparation. Assessment of several structurally similar compounds clearly demonstrated that the contractility decreases were associated with complex V inhibition and unrelated to sodium and calcium channel mechanisms. We conclude that these agents reduced left ventricular contractility through inhibition of mitochondrial ATP synthase. In addition, ATP synthase inhibition in concert with hERG blockade may be pro-arrhythmic.

## PS 185 INTERFERON SIGNALING, SYSTEMIC INFLAMMATION, AND ATHEROSCLEROSIS FOLLOWING WELDING FUME INHALATION EXPOSURE: FROM THE LUNG TO THE BLOOD TO THE VASCULATURE.

A. Erdely, T. Hulderman, A. L. Liston, R. Salmen-Muniz, S. Stone, B. T. Chen, D. G. Frazer, S. Li, M. L. Kashon, J. M. Antonini, P. P. Simeonova and P. C. Zeidler-Erdely. *NIOSH, Morgantown, WV.*

Inhalation of particulates can result in measurable systemic markers related to adverse cardiovascular outcomes. Our aim was the determination of a systemic signature and atherosclerosis progression following gas metal arc-stainless steel (GMA-SS) welding fume exposure. C57BL/6 mice were exposed for 10d to GMA-SS by inhalation (40mg/m3 for 3hr/day) and harvested 4hr, 14d and 28d post-exposure. Systemic responses were measured by serum protein profiling and microarray (Ingenuity pathway analysis and real-time RT-PCR confirmation) for whole blood cells, aorta and lung. Atherosclerotic susceptible apolipoprotein E knockout (apoE-/-) mice were exposed (40mg/m3 for 3hr/day) during week 6 and 7 of two months of Western (high fat) diet feeding. Exposed C57BL/6 mice exhibited a specific network of type I interferon signaling in blood cells and aorta from 4hr to 28d post-exposure. The central component of the network was the transcription factor interferon regulatory factor 7 (Irf7), the master regulator of the type I interferon response. Increases in related genes (Oasl2 and Ifitm3) were also validated. Type I interferon signaling was also a top network in the lung supporting the concept of a systemic signature reflecting the ongoing pulmonary response. Serum levels of primary inflammatory mediators were not elevated although oncostatin M, an IL-6 family cytokine and type I interferon enhancer, was increased. In apoE-/- mice, pulmonary inflammation, serum levels of IL-1β and MAC-3 and blood cell expression of Irf7 were increased post-GMA-SS exposure. Atherosclerosis severity, determined by plaque area and intensity in the aorta (en face), was increased. The data suggest an immunomodulatory and mild systemic inflammatory effect with increased progression of atherosclerosis due to GMA-SS exposure. Most notably, a pulmonary and corresponding systemic signature of type I interferon signaling was consistently evident across tissue and time.

## PS 186 A COMMON LINK FOR PULMONARY INFLAMMATION TO VASCULAR EFFECTS OF ENVIRONMENTAL TOBACCO SMOKE AND BENZO-A-PYRENE IN BOTH PIGS AND RATS.

L. P. Weber, A. N. Al-Dissi and N. J. Gentner. *Toxicology Graduate Program, University of Saskatchewan, Saskatoon, SK, Canada.*

Despite extensive research, the mechanisms behind cardiovascular effects of prolonged environmental tobacco smoke (ETS) remain unclear, but may be related to ETS-induced inflammation, oxidative stress and endothelial dysfunction. We hypothesized that polycyclic aromatic hydrocarbons (PAHs) in ETS are responsible. Parallel studies were carried out in rats and juvenile pigs to examine the cross-species consistency of the role of cytochrome P450 1A1 (CYP1A1), inflammation and oxidative stress in causing adverse cardiovascular effects. Male juvenile pigs were exposed to ETS or ambient air for 28 days (1 hr/day) and effects compared to 7 days of intravenous injection of the PAH, benzo-a-pyrene (BaP; 5 mg/kg). The pig experiments were compared to a similar 28-day ETS exposure or 7-day intranasal BaP (0.01 mg/kg) instillation in male Sprague-Dawley rats. As early as 7 days in both species, ETS caused impaired endothelial function (indicated by impaired flow-mediated dilation or FMD) in pigs, while causing increased arterial stiffness (indicated by increased arterial pulsewave dP/dt) in rats. Intranasal BaP mimicked the ETS effects to cause increased arterial stiffness in rats, but intravenous BaP in pigs did not affect FMD. Both ETS and BaP caused a significant increase in serum nitrotyrosine (both species) and C-reactive peptide (pigs), but had inconsistent effects on indicators of total NO production. ETS exposure resulted in increased CYP1A1 activity in the lung but not the liver in both species, while BaP treatment had no effect (rats) or the opposite effect in both organs (pigs). However, there was a consistent increase in pulmonary white blood cells (WBCs) after ETS exposure (both species) and after intranasal BaP (rats), but not after intravenous BaP (pigs). In conclusion, increased pulmonary WBCs after ETS or intranasal BaP exposure may be the common link to increased oxidative stress and endothelial dysfunction in multiple animal models, suggesting these findings may be broadly applicable to all species.

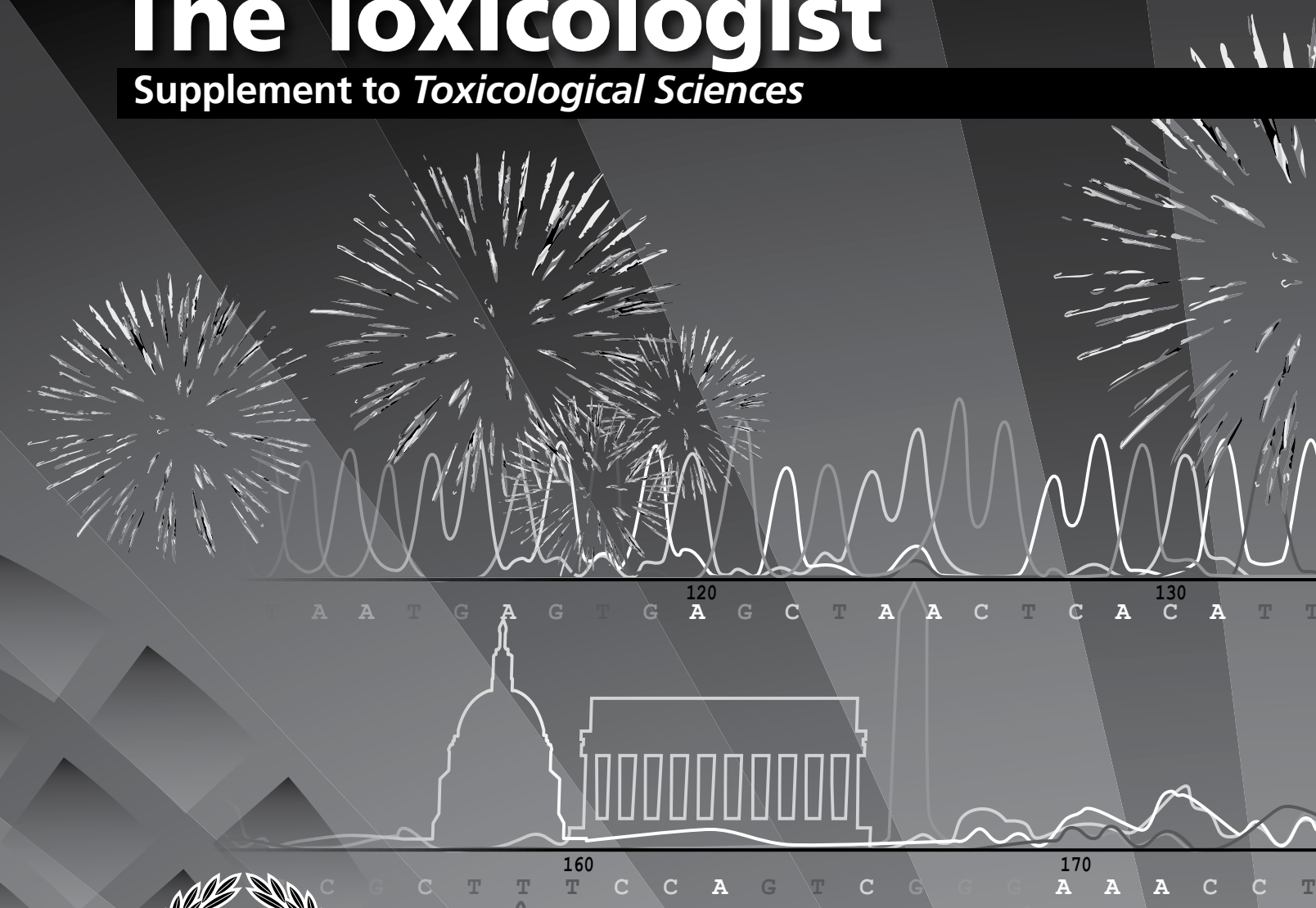
## PS 187 CIGARETTE SMOKE-DEPENDENT CHANGES IN THE RESPIRATORY AND CARDIOVASCULAR SYSTEM OF SPONTANEOUSLY HYPERTENSIVE (SH) RATS AND THE EFFECT OF SMOKING CESSATION.

M. Lietz[1], B. Friedrichs[1], I. Gallitz[1], S. Quadt-Humme[1], Y. Steffen[1], K. Stolle[1], S. Lebrun[2] and A. Berges[3]. *[1]Philip Morris Research Laboratories GmbH, Cologne, Germany, [2]Philip Morris Products S.A., Neuchatel, Switzerland and [3]Philip Morris Research Laboratories Bvba, Leuven, Belgium.* Sponsor: T. Mueller.

Previously, we have shown that cigarette smoke affects cardiac function, hypertrophy status, and serum proteins in SH rats (Abstract 912; 48th Annual Meeting & ToxExpoTM [2009]). Here, we investigate the reversibility of these effects after smoking cessation (SC). SH rats were exposed to diluted cigarette mainstream smoke (MS) from the Reference Cigarette 3R4F (MS-only; 900 µg total particulate matter/day; 5 days/week) or to fresh air (sham) for 90 days. SC experiments covered exposure for 30 days MS + 60 days sham (SC-1) and 60 days MS + 30 days sham (SC-2). Endpoints tested were body weight, heart hypertrophy status, neutrophils in bronchioalveolar lavage fluid, expression levels of matrix metalloproteinase-1 (MMP-1) and metallopeptidase inhibitor-1 (TIMP-1). At 90 days, parameters were decreased (body weight) or increased (all other endpoints) in the MS-only group compared to both cessations groups, which, importantly, display a sham-like phenotype: Body weight [g]: 275.9+16.8 (MS-only), 316.0±18.5 (SC-1), 311.8+19.6 (SC-2), 301.7±28.7 (Sham); Hypertrophy status [left ventricle weight (g)/tibia length (mm)]: 0.023±0.002 (MS-only), 0.020±0.001 (SC-1),

# The Toxicologist

Supplement to *Toxicological Sciences*




SOCIETY OF TOXICOLOGY
50th Anniversary
1961–2011

*Celebrating 50 Years of Service in Science*

# 50th Anniversary Annual Meeting and ToxExpo™ Washington, D.C.

**An Official Journal of the Society of Toxicology**

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 120, Supplement 2
March 2011

www.toxsci.oxfordjournals.org

SOT | Society of Toxicology

**Creating a Safer and Healthier World by Advancing the Science of Toxicology**

**www.toxicology.org**

# Preface

**This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.**

**An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.**

**The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.**

**The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence.**

**Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:**

**Society of Toxicology**
**1821 Michael Faraday Drive, Suite 300**
**Reston, VA 20190**

**www.toxicology.org**