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Paul Felder

Washington University in St. Louis

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PATERNAL CIGARETTE SMOKE EXPOSURE INDUCES FETAL DEMISE AND TESTICULAR GERM CELL DEATH: UTILIZATION OF *IN VIVO* AND *EX VIVO* TOXICOLOGY MODELS

Paul Felder

Mentors: Kelle Moley and Prabakaran Esakky

Cigarette smoking and secondhand smoke exposure cause 480,000 deaths in the U.S. per year, more than HIV, illicit drug use, alcohol use, motor vehicle injuries, murder, and suicide combined. In human males, exposure to nicotine is known to reduce sperm count and motility, and increase abnormal sperm morphology. However, effects of paternal smoking on fetal outcomes and the threshold levels at which cigarette smoke disrupts spermatogenesis have not been determined. In this study, we utilized a mouse testicular explant model and a mouse mating model to test the hypothesis that exposure to cigarette smoke condensate (CSC) above a certain threshold induces DNA damage and apoptosis in the testes and spermatogenic lineage cells, which proves to be detrimental to fetal development. Our testicular explant data demonstrate CSC has a spermatogenic germ-cell toxicity threshold in mice of 160 μg (7.06 mg of nicotine/kg body weight) which is below the lower bound of the nicotine exposure range of light smokers ($< 7.5\text{--}24$ mg nicotine/kg), defined as adults who smoke fewer than 15 cigarettes per day. In male mice, we found that this level of CSC exposure in a single cycle of spermatogenesis (35 days in mice, 76 in humans) is sufficient to produce DNA damage leading to germ cell and spermatocyte death through activation of both intrinsic and extrinsic apoptotic pathways. In murine mating studies with CSC-treated males and unexposed females, we found a higher rate of fetal resorptions, which in humans correlates to fetal demise. We believe that CSC exposure has the potential to produce heritable genetic defects that increase the risk of developmental abnormalities in offspring.