209
TOXICITY OF 5-FLUORO-2-DEOXYCYTIDINE IN HMLH1 SILENCED COLON CANCER CELLS OCCURS COINCIDENT WITH INDUCED EXPRESSION OF HMLH1. Veigl ML[1], Boothman DA[1], Strickfaden S[1], Polinkovsky A[1], Sedwick WD[1]. [1]Case Western Reserve University and University Hospitals of Cleveland, Cleveland, OH 44106.

Fluorodeoxycytine (FdC) can directly incorporate into DNA or be catabolized to fluorodeoxyuridine (FUdR), a form in which it exerts direct toxicity at the DNA level. When FdC is modulated to directly incorporate into DNA, it causes reversal of methylation dependent inhibition of gene expression. Further, mismatch repair deficient cells are resistant to the cytotoxicity of FUdR versus their mismatch repair proficient counterparts. Using a combination of gene expression and cytotoxicity studies we demonstrate that FdC presents an interesting model for selective killing of *hMLH1* gene silenced tumor cells. FdC is resistant to degradation by nucleotide phosphorylase and susceptible to modulation between cytoxicity and reversal of methylation-dependent gene silencing by the addition of cytidine deaminase inhibitors. In RKO cells, where mismatch repair is silenced by methylation of the *hMLH1* promoter, FdC treatment alone appears to specifically exert cytotoxicity in cells that are induced to express hMLH1. Further data shows that the degree of FdC-dependent cytotoxicity observed in hMLH1-expressing colon cancer cells is augmented by addition of tetrahydrouridine, which blocks cytidine deaminase but allows catabolism of FdCMP to FdUMP thus directing FUdR cytotoxicity more effectively. In contrast, deoxytetrahydrouridine, which inhibits both FdCMP and FdC deamination facilitates direct FdC incorporation into DNA leading to effective induction of hMLH1 expression with reduced cytotoxicity. Further, exogenous thymidine, which reverses FUdR-dependent cytotoxicity, blocks the cytotoxic effects of FdC. Possible therapeutic implications of modulation strategies during exposure of tumor cells to FdC will be discussed. [Supported by NIH Grant RO1C70788 and CA67409].

210
STRUCTURAL AND NUMERICAL CHROMOSOMAL ABNORMALITIES IN SPERM FOLLOWING ACCIDENTAL OCCUPATIONAL EXPOSURE TO ^{192}IRIDIUM. Velazquez-Wong AC[1,2], Sloter E[2,3], Tomascik-Cheeseman LM[2,3], Araujo-Solis MA[1], Wyrobek AJ[2], Salamanca-Gomez F[1]. [1]Unit of Investigation in Human Genetics, Mexican Institute of Social Security, Mexico City, Mexico. [2]Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, Livermore, CA. [3]Genetics and Developmental Biology Program, West Virginia University, Morgantown, WV.

Exposure to ionizing radiation produces chromosomal abnormalities *in vivo* and *in vitro*. Structural aberrations are known to persist in human somatic cells following occupational, medical or environmental exposure to ionizing radiation, yet little is known about the reproductive consequences of these exposures on germ cells. The frequencies of structural and numerical chromosomal abnormalities were studied in sperm from a worker accidentally exposed to ^{192}Ir, a source of ionizing radiation used in industrial radiography. The multicolor ACM FISH assay (Sloter et al. 2000) was used to detect sperm with breaks, duplications, deletions and aneuploidy involving chromosome 1. There were no significant differences in chromosomal abnormality frequencies between two semen samples collected at 12 and 14 months following exposure. Compared to healthy age-matched controls, the frequencies of sperm with segmental duplications of 1p36.3 were ~6-fold higher in the ^{192}Ir-exposed worker ($P<0.01$). There was no effect on chromosomal breaks within the 1cen-1q12 region ($P>0.05$). Frequencies of sperm carrying whole-chromosome numerical abnormalities were 4-fold higher in the exposed worker than in control donors ($P<0.01$). These findings suggest that certain types of structural and numerical chromosomal abnormalities in sperm remain elevated one year following exposure to ionizing radiation and provide suggestive evidence for an increased risk of transmitting chromosomal damage to offspring following exposure. [Work was conducted under the auspices of the US DOE by the University of California, LLNL contract W-7405-ENG-48 with support from the Mexican Institute of Social Security]

211
GENOTOXICITY OF INSOLUBLE NICKEL COMPOUNDS: PREDICTIONS OF CARCINOGENIC POTENTIALS. Verma R[1], Clemens F[1], Kaspin L[1], Landolph JR[1]. [1]Cancer Research Labs, USC/Norris Cancer Center, Depts of Mol. Micro/Immun., USC, Los Angeles CA.

Inhalation of very high concentrations of certain insoluble nickel (Ni) compounds has been associated with increased respiratory cancer risk. A genotoxicity ranking of Ni-containing substances would be useful for predicting their potential carcinogenicity to humans. In vitro studies can evaluate genotoxicities of Ni-containing samples relative to Ni compounds well-characterized in animal inhalation studies (e.g., Ni subsulfide). Two Ni subsulfide samples (< 10 μm diameter) induced dose-dependent morphological transformation in 10T1/2 cells. Our previous studies indicated that spherical particles of elemental Ni (average diameters: 2.3 and 11 μm) did not. To look at the effect of particle size, we studied one sample of Ni subsulfide of smaller particle size (1.35 μm diameter), and one sample of ultrafine (UF) elemental Ni (0.5 - 1.0 μm diameter), water insoluble Ni(III) hydroxide and Ni carbonate. We used these data to rank all present and previously studied samples for their predicted carcinogenic potentials. The approximate order of phagocytic uptake and cell transformation of the new set of samples was: ultrafine elemental Ni > > Ni subsulfide > Ni(III) hydroxide ≥ Ni carbonate. The order of cytotoxic potency (LC50 values in μg/ml, in parentheses) was: Ni3S2, 1.35 μm (0.35 ± 0.2) > Ni0, UF (0.45 ± 0.3) > Ni(OH)3, powdered form (2.96 ± 2.4) > NiCO3 (4.08 ± 3.8). Ultrafine elemental Ni and Ni subsulfide also induced chromosome breakage. These results indicate that particle size could play a significant role in uptake and subsequent chromosome damage and morphological transformation in Ni carcinogenesis.

212
INDUCTION OF MICRONUCLEI IN THE BLOOD AND BONE MARROW CELLS OF MICE EXPOSED TO JET FUEL JP-8. Vijayalaxmi[1], Hyde J[2], Rowland S[2], Cameron IL[3], Witten ML[2]. [1]Department of Radiation Oncology, The University of Texas Health Science Center, San Antonio, TX 78229, USA. [2]Department of Pediatrics, University of Arizona, Tucson, AZ, USA. [3]Department of Cellular and Structural Biology, The University of Texas Health Science Center, San Antonio, TX 78229, USA.

During the past few years, the jet propulsion fuel JP-8, a kerosene-based middle distillate fuel, has become a preferred fuel for the U.S. and NATO military operations, due to its high flash point, low vapor pressure, and reduced potential for crash-related explosions and fires. In vitro exposure of cultured mammalian cells to JP-8 was reported to be cytotoxic and induced DNA strand breaks (Grant et al., 1999, 2000). In this investigation, adult mice were exposed to JP-8 (inhalation route, 50 mg/cubic meter), 1 hour/day, for 7 consecutive days. Unexposed mice were used as controls. Mice which were injected with mitomycin C were also included as positive controls. Twenty-four hours following the last exposure, all mice were sacrificed, blood and bone marrow smears were prepared, and stained with acridine orange. Coded slides were evaluated for the incidence of micronuclei in both tissues. For each animal, 2000 consecutive PCEs were examined to determine the incidence of micronuclei. Preliminary results indicated a significant increase in the incidence of micronuclei, in both tissues of mice exposed to JP-8.