197 PARAMETERS THAT INCREASE OR DECREASE MUTATION FREQUENCY: AGE, TISSUE TYPE, GENOTYPE, ANTIOXIDANTS AND CARCINOGENESIS. Sommer SS[1], Hill KA[1], Halangoda A[1], Heinmoller PW[1], Buettner VL[1], Kunishige MK[1], Moore SR[1], Farwell KD[1], Chitaphan C[1]. [1]Department of Molecular Genetics, City of Hope National Medical Center/Beckman Research Institute, Duarte CA 91010.

The Big Blue transgenic mouse mutation detection assay offers a well validated approach for analysis of in vivo mutations. Methodological enhancements have increased the efficiency of determining mutation frequency and pattern eight-fold. In the past two years our laboratory has screened 75.1 million plaque forming units and sequenced over 3,188 mutants (3.8 Mb) and has generated a database of over 2,481 independent spontaneous lacI mutations. Effects of the putative DNA repair genotype, antioxidants, ethanol, and carcinogenesis were examined. Mutation frequency was unaltered with the following exceptions. Mutation frequency was increased in old age in some tissues, but not in neurons. Moderate increases in mutation frequency were observed in some T-cell lymphomas from p53 nullizygous or p53 heterozygous mice. Mutation frequency was significantly lower in the male germline compared to somatic tissues. Mutation frequency was significantly reduced in the cerebellum of mice nullizygous for the DNA repair gene ERCC6. Overexpression of the human SOD1 gene significantly reduced mutation frequency in the cerebellum. Vitamin E supplementation produced a significant reduction in mutation frequency in adipose tissue and an overall reduction in the frequency of G to T transversions. Generally mutation patterns were unaltered. Situations in which mutation frequency was decreased are of particular interest since these may suggest chemopreventive approaches to cancer.

198 THE *IN VIVO* INDUCTION OF ADAPTIVE RESPONSE IN RATS USING IONIZING RADIATION. Sorensen KS[1], Tucker JD[1]. [1]Lawrence Livermore National Lab, BBRP, Livermore, Ca 94550.

Small doses of radiation (< 10 cGy) have been frequently shown to modify the effects of subsequent larger doses (1-2 Gy) of radiation. This phenomenon, commonly referred to as the adaptive response, has been demonstrated in different mammalian systems including various human and animal cell lines, mice, and rabbits. Unfortunately, the adaptive response has been shown by many to be a highly variable phenomenon and further investigation is necessary before its impact on the risks due to radiation exposure can be fully assessed. Some investigators have been unable to duplicate the response and others have reported that the small initial "priming" dose has a synergistic effect on the larger "challenge" dose, producing a higher level of aberrations than the challenge dose alone. We have begun testing the adaptive response *in vivo* using Sprague-Dawley rats. Four exposure groups were used consisting of two male rats each. All exposures were done using ^{137}Cs. One group of rats was given 5 cGy followed 8 hours later by 150 cGy. The other groups of rats received only 5 cGy, only 150 cGy or no radiation. Blood was collected, cultured to produce cells in metaphase and analyzed by whole chromosome painting. One hundred cell equivalents were scored from each rat. A definite reduction in the frequency of translocations was seen in the rats that received a priming dose before the challenge dose of 150 cGy, with the priming dose itself not producing any detectable response. Although small, this experiment suggests that rats display the adaptive response *in vivo*. Further experiments are in progress to extend our analyses and determine the reproducibility of the response. Work performed under the auspices of the US DOE by LLNL contract No. W7405-ENG-48.

199 DETECTION OF ONCOGENE PROTEINS IN HUMAN BIOLOGICAL FLUIDS. Spruill MD[1], Wu ZL[2], Whong WZ[1], Ong TM[1]. [1]Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV 26505. [2]Guangzhou Medical College, Guangzhou, China 510182.

Lung cancer is one of the most common and most deadly forms of cancer. Smoking is by far the most important risk factor, however, occupational exposure to hazardous chemicals, dusts or fibers also presents a serious lung cancer risk. Biological markers of exposure and/or cancer-related outcomes need to be identified and integrated into epidemiological studies in order to identify people at risk and/or aid in early diagnosis. It is known that proto-oncogenes and tumor suppressor genes are involved in cell growth and differentiation and that their altered structure and/or expression may be involved in carcinogenesis. The protein products of these genes often reside in body fluids, such as serum and urine. Since urine sampling is least invasive, it is particularly attractive for biological monitoring to ensure worker cooperation. We have analyzed serum and urine samples from 25 lung cancer patients as well as urine samples from age-matched controls to detect differentially expressed genes related to lung cancer risk. Serum (500 µg) or urine (250 µg) samples were separated on 5-17% polyacrylamide gradient gels and electroblotted onto Immobilon-P transfer membranes. The membranes were cut into individual strips that were each probed with an antibody against one of the following proteins: p53, RAS, FOS, JUN, SIS, FES, TGFα, TGFβ, and erbB. Following colorimetric detection, the intensities of the target bands were measured using the Bio Image Whole Band Analyzer. While we have found no correlation between the presence of any of the native proteins in question and lung cancer, preliminary results indicate that the presence of a 42 kDa RAS-related protein in urine samples may correlate with lung cancer and smoking status.

200 INDUCTION OF *LACI* MUTATIONS IN BIG BLUE RAT2 CELLS TREATED WITH EITHER N-(2-HYDROXYETHYL)-N-NITROSOUREA OR N-METHYL-N-NITROSOUREA. Sprung CN[1], Wang Y[1], Miller DL[1], Bodell WJ[1]. [1]University of California, San Francisco, CA 94143.

N-alkyl nitrosoureas are well established mutagens which alkylate a variety of sites in DNA including the O^6 and N7 position of guanine. We have observed that in cells the rate of repair of O^6-(2-hydroxyethyl) deoxyguanosine (O^6-HOEtdG) produced by the chemotherapeutic agent N-(2-chloroethyl)-N-nitrosourea (CNU) is significantly slower than that of O^6-methyldeoxyguanosine produced by N-methyl-N-nitrosourea (MNU). To gain a better understanding of this observation, we have compared the induction of mutations by N-(2-hydroxyethyl)-N-nitrosourea (HOENU) which produces significant levels of O^6-HOEtdG with that formed by MNU treatment. Mutational analysis of the *lacI* gene, in the lambda/*lacI* shuttle vector was performed using Big Blue Rat2 cells. The cells were treated for 1 hr with either HOENU (0, 1 and 5 mM) or MNU (0 and 1 mM) and collected 24 hr later. The mutation frequency was 1.0×10^{-4}, 7.3×10^{-4} and 22.0×10^{-4} for the 0, 1 and 5 mM HOENU treatments and 1.7×10^{-4} and 12.3×10^{-4} for the 0 and 1 mM MNU treatments. Comparison of the mutation frequencies demonstrates that 1 and 5 mM HOENU and 1 mM MNU treatments have increased the level of mutation by 7, 22 and 7-fold respectively. Sequence analysis of MNU induced mutations have revealed primarily G to A and C to T transitions. The nature of the *lacI* mutants induced by HOENU treatment is being determined and will be presented. Our studies suggest that the O^6-methyldeoxyguanosine adducts formed by MNU result in the high levels of transition mutations observed. We postulate that O^6-HOEtdG adducts formed by CNU treatment may lead to similar mutations.

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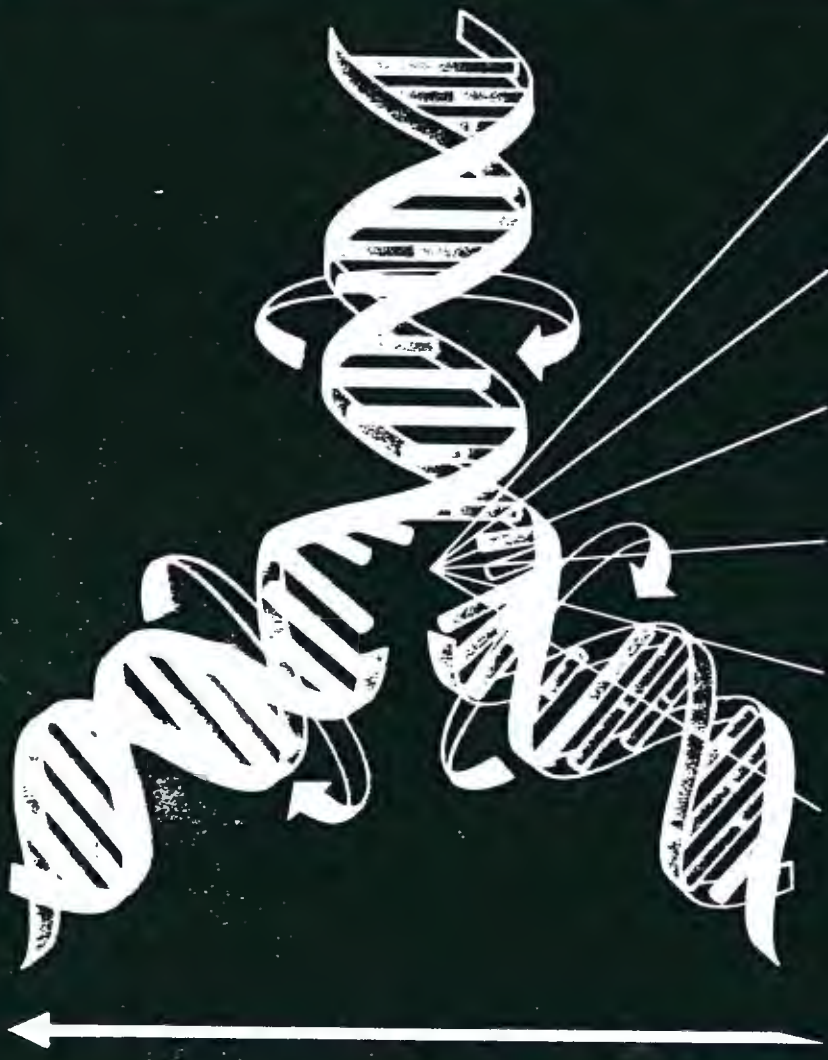

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