**193** **ASSOCIATIONS BETWEEN CHROMOSOMAL ABNORMALITIES AND SEMEN QUALITY IN HEALTHY MEN.** Sloter E[1,2], Nath J[2], Wyrobek AJ[1]. [1]Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, Livermore, CA 94550. [2]Genetics and Developmental Biology Program, West Virginia University, Morgantown, WV 26505.

Exposure to certain genotoxic agents induces chromosomal defects in sperm and increases the risk for an abnormal reproductive outcome. Many of these agents also adversely affect sperm production, motility, and/or morphology. We surveyed semen from ten healthy non-smoking men to determine whether there are associations between chromosomal abnormalities in sperm and clinical parameters of semen quality (count, motility, and morphology). A multicolor FISH strategy was used to simultaneously detect (a) disomy 1 and diploidy, (b) partial duplications or deletions of 1p which are the result of premeiotic or meiotic rearrangements and (c) chromosomal breaks within the 1cen-1q12 region which are presumably postmeiotic breakage events. Sperm count and motility were assessed both by conventional and computer-assisted semen analysis (CASA) methods. Sperm nuclear morphometry was evaluated by MAP/QUIPS (Morphometry Automation Program/Quantitative Image Processing System) developed at LLNL. The men with higher frequencies of sperm disomy 1 and diploidy (mean = 22 vs. 9 per $10^4$ sperm) and segmental aneuploidy (22 vs. 8 per $10^4$ sperm) exhibited lower sperm counts ($61x10^6$ vs. $318x10^6$ sperm/ml; $p<0.05$) and somewhat larger sperm heads ($p=0.08$). The men with higher frequencies of sperm with chromosomal breaks within the 1cen-1q12 region (mean = 21 vs. 10 per $10^4$ sperm) had reduced sperm motility (34% vs. 53%; $p=0.07$). The generality of these findings is being tested in a larger group of healthy men with no known exposure to environmental mutagens. [This work was performed under the auspices of the US DOE by LLNL, contract W-7405-ENG-48, and funding from NIEHS Superfund P4ZES04705 and WVU.]

**194** **DNA REPAIR GENE-GENE INTERACTION AND BREAST CANCER RISK.** Smith TS[1], Miller MS[1], Lohman K[2], Mohrenweiser HW[3], Hu JJ[1,2]. [1]Dept of Cancer Biology, Wake Forest Univ School of Medicine, Winston-Salem, NC 27157. [2]Dept of Public Health Sciences, Wake Forest Univ School of Medicine, Winston-Salem, NC 27157. [3]Lawrence Livermore National Laboratory, Livermore, CA 94550.

A woman living in the United States currently has a one in eight chance of developing breast cancer in her lifetime. Suboptimal DNA repair is hypothesized to be an important breast cancer susceptibility factor. Polymorphisms of DNA repair genes may lead to amino acid substitutions, altered protein function, deficient DNA repair, and elevated cancer risk. We have completed a pilot case-control study to evaluate the role of DNA repair genetic polymorphisms in breast cancer risk. The study population consisted of 115 cases and 202 controls recruited at Georgetown University Medical Center from 8/95 to 11/96. The genotypes examined include 5 polymorphic sites in 4 DNA repair genes: XRCC1, XRCC3, APE, and XPD. XRCC1 and APE genes are involved in base excision repair, XRCC3 plays a role in recombination repair, and XPD is active in nucleotide excision repair. Genomic DNA isolated from whole blood was used for PCR-RFLP assays. Our data indicate a possible linkage between the XRCC1 (exon 10) variant and the XRCC1 (exon 6) wild-type allele in both cases and controls. The data suggest that XRCC1 (exon 6) variant is associated with breast cancer risk in women with negative family history (age-adjusted odds ratio (OR): 2.5; 95% confidence interval (CI): 1.0,6.8). The most interesting finding of this study is that women with both XRCC1 (exon 6) and XRCC3 (exon 7) variant alleles have a 4.5-fold increased breast cancer risk (95% CI: 1.4,16.0), representing a gene-gene interaction. This study supports the hypothesis that combined genetic polymorphisms of DNA repair genes may serve as potential biomarkers for human breast cancer risk. (Supported by grants from the American Cancer Society and NIH CA73269)

**195** **THE USE OF CATALYTIC TOPOISOMERASE II INHIBITORS TO PROBE MECHANISMS OF CHEMICAL-INDUCED CLASTOGENICITY IN CHINESE HAMSTER V79 CELLS.** Snyder RD[1]. [1]DuPont Pharmaceuticals, Newark, DE 19714.

Clastogenicity can arise from perturbation of cellular processes in addition to direct DNA/drug interactions. One such alternative process is inhibition of DNA topoisomerase II, during which process the topoisomerase/DNA/drug ternary complex forms stable DNA double strand breaks (cleavable complex) which become templates for recombinational, mutational, and chromosomal fragmentation events. It is generally not possible to distinguish this mechanism-based clastogenicity from that arising via direct drug/DNA interactions. It is demonstrated here that specific catalytic inhibitors of DNA topoisomerase II reduce the clastogenicity of topo II poisons but not that arising via non-topo-dependent mechanisms. In particular, catalytic topo inhibitors such as chloroquine, sodium azide and A-74932 as well as certain intercalating agents such as 9-aminoacridine and ethidium bromide, strongly antagonize the formation of micronuclei induced by the DNA gyrase inhibitor clinafloxacin and the antitumor topo II poison etoposide. These catalytic inhibitors are also shown to antagonize the clastogenicity of experimental compounds and novel pharmaceuticals presumed to be DNA intercalating agents by virtue of their response in a cell-based bleomycin amplification assay. These findings support our earlier hypothesis that the clastogenicity of structurally non-alerting drugs may be due to a hitherto unappreciated propensity for DNA intercalation. It is further proposed that intercalation-dependent inhibition of topoisomerase II may be responsible for this clastogenicity and that this may be detected in intact mammalian cells with the use of catalytic topoisomerase inhibitors.

**196** **MUTAGENICITY AND CARCINOGENICITY OF A FOOD-DERIVED HETEROCYCLIC AMINE IN C-*MYC*/LAMBDA *LACZ* BITRANSGENIC MICE.** Snyderwine EG[1], Thorgeirsson SS[1]. [1]Lab. Experimental Carcinogenesis, Building 37, Room 3C28, NCI, NIH, Bethesda, MD 20892-4255.

Mice harboring the *lacZ* mutation reporter gene (C57Bl/lambda *lacZ*, Muta mouse) and bitransgenic mice over-expressing the c-*myc* oncogene in liver (c-*myc* (albumin promoter)/lambda *lacZ*) were bred to investigate the interaction of the c-*myc* oncogene with an environmental carcinogen during the neoplastic process. The carcinogen examined was 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), a potent rodent hepatocarcinogen and member of a family of mutagenic heterocyclic amines found in cooked meats. When male and female mice were fed 0.06% MeIQx in the diet for up to 40 weeks, a synergism was observed between c-*myc* and MeIQx in the development of hepatocellular carcinoma. To investigate the possible mechanisms for this interaction, MeIQx-DNA adduct levels and mutagenesis in the *lacZ* reporter gene were examined in livers of mice. While MeIQx-DNA adduct levels were not significantly different between C57Bl/*lacZ* and c-*myc*/*lacZ* mice, mutant frequency was significantly elevated in mice harboring the c-*myc* transgene. The results suggest that the mechanism for the synergistic effects of c-*myc* on MeIQx-induced hepatocarcinogenicity involves an enhanced expression of MeIQx-induced mutations. The findings are consistent with the notion that c-*myc* over-expression is associated with a mutator phenotype and an elevated genomic instability. The findings further support the utility of transgenic mouse models to investigate the interaction of environmental chemicals with specific genes during neoplasia.