NASA/NCI PROGRAM ON GENOMIC INSTABILITY

Joel Bedford (Colorado State Univ.) HZE Radiation-Induced Chromosome Instability. Measure development or maintenance of numerical chromosome instability and compare a normal human cell line with a classical aneuploid/hyperdiploid tumor cell line, and the development of instability during low oxygen tension growth

Antone L. Brooks, Univ. Washington In Vivo Induction and Repair of Genomic Instability. Use frequency of micronuclei in Wistar rat tissues: tracheal epithelium (resistant to radiation-induced cancer), deep lung epithelium (sensitive to radiation-induced cancer), and deep lung fibroblasts, a well as chromosome aberrations in bone marrow as endpoints for the induction of genomic instability.

David Chen (formerly LASL, now LBNL) Roles of Human Recombination in Genome Instability. Determine whether human homologs of the yeast RAD51 and RAD52 genes have a role in maintaining genome integrity, such that loss of expression or defficiency of these genes will exacerbate radiation-induced heritable genome instability, based on the observation that the yeast genes are involved in maintaining the global integrity of the genome.

Helen Evans, Case Western Induction of Genomic Instability in Human Lymphoblasts. Establish the extent to which tansient or permanent inactivation of any one of a large number of genes in a population of human lymphoblasts contributes to the mechanisms responsible for genomic instability

Eric Hall, Columbia Univ. High Energy Ions and Genomic Instability. Measure genomic instability in human bronchial cell cultures exposed to iron beams at AGS, by growing them for 30 generations and injecting the cultured cells into immune suppressed mice to titrate the incidence of tumors as a function of radiation exposure.

Amy Kronenberg, LBNL High-LET Radiation and Genomic Instability in Human Cells. Characterize individual clones of human TK6 lymphoblasts that survive exposure to passage of single proton or iron particles, using karyotypic analysis and a measurement of the mutation rate at the autosomal, heterozygous thymidine kinase locus, approximately 25-30 generations post-exposure

Thea Tlsty (UCSF) Mechanisms of Radiation-Induced Genomic Instability. Measure homologous and non-homologous DNA recombination using a plasmid to target specific genes in a variety of human cell populations. Data are providing strong evidence that both types of mitotic recombination are up-regulated in transformed human cells and suggest different roles for this type of recombination in a genomic instability seen in cancer

William F. Morgan, Univ. MD. Mechanisms of High-LET Induced Genomic Instability. In a hamster/human cell hybrid conaining a single copy of human chromosome 4, measure delayed chromosomal instability as a function of radiation type and ascertain relative

contribution of nuclear and extranuclear cellular compartments and the hypothesized existence of a "mutator" phenotype

Robert Ullrich, UTMB Genomic Instability in High-LET Carcinogenesis. Determine the influence of cellular environment on the induction, persistence, and propagation of genomic instability as a function of radiation quality; determine the impact of alterations in the function of critical genes involved in cell cycle checkpoint control and programmed cell death on the persistence and propagation of radiation-induced instability; characterize cellular processes involved

NASA SPECIALIZED CENTER OF RESEARCH AND TRAINING (NSCORT)

Aloke Chatterjee- LBNL (PI): Theoretical Modeling of DNA Damage and Cellular Responses. Develop theoretical model of mutation induction, valid down to the lowest doses and single-particle effects. Currently: quantitative analysis of local clusters of double-strand breaks in DNA, faithfulness of repair and correlation with gene specific mutational spectra characterized by point mutations, small and large deletions and translocations.

Amy Kronenberg-LBNL: Mutagenesis and Chromosomal Alterations. Developed and synchronize a cell line with strongly attenuated programmed cell death that can be held in late G1 phase for up to 15 hours, without loss of viability or DNA degaradation, allowing the study of DSB rejoining and repair fidelity for up to 12 hours post-irradiation. Extensive studies of mutations in the X-chromosome show Fe ions are significantly more toxic than x-rays. Results on cellular clustering and mutation will be integrated with signal transduction studies in NSCORT.

Mary Helen Barcellos -Hoff -LBNL: The Role of the Microenvironment in the Radiation Response of Epithelial Cells. Measure the proliferation and apoptosis indices of two cytokines, TGF-ß1 and FGF-2, to determine the degree to which radiation-induced alterations of the microenvironment affect multicellular tissue responses relating to tumor progression in a three-dimentsional cell culture model of human mammary gland.

Priscilla Cooper LBNL: DNA Repair and Early Development of Chromosomal Changes. Molecular and cytogenetic measurements of induction and repair of DNA damage in normal and repair-deficient mutant cells, as well as in a hamster-human hybrid cell line developed by other NSCORT investigators. Developed a novel methodology for measurements of DSB misrejoining and clustering of DNA damage.

Thomas Borak - Colorado State: Microdosimetry Studies. Investigate the response of Tissue Equivalent Proportional Counters, of the type used for space dosimetry, using ground-based accelerators to generate beams of individual nuclei, including evaluation of energy loss due to escape of high-energy delta rays and increased energy deposition due to enhanced delta rays and nuclear reactions in the walls of such detectors. Also provides sophisticated microdosimetry input for NSCORT radiobiology experiments.

ONGOING NASA RESEARCH SOLICITATIONS

Bruce A. Carnes, ANL: Radiation risk analysis: model issues and interspecies extrapolation. Uses the extensive database on radiation studies involving laboratory animals conducted over four decades at Argonne National Laboratory (ANL) to investigate dose-response models used for the prediction of radiation-induced mortality risks in humans at low doses and dose rates for external exposure to y rays and neutrons. The risk models investigated will include: 1) empirically derived models, 2) biologically motivated models, and 3) Bayesian models. In all cases, the models will be used to test for a dose below which there is no biological response or a threshold dose where a transition in the dose response occurs. In addition, the influence of factors that can modify the risk estimates derived from the models (e.g., age at exposure, exposure pattern, sex, radiation quality) will be examined. Finally, all of the risk models will be evaluated for their ability to predict the radiation-induced risks of mortality for humans (e.g., survivors of Hiroshima and Nagasaki) from data for laboratory animals (principally mice) similarly exposed

Eric J. Hall, Columbia Univ.: Individual susceptibility to radiation effects. The dose limits for astronauts in space flight assume that the human population is uniform in its radiosensitivity.The hypothesis upon which this proposal is based is that the human population is not homogeneous in radiosensitivity, but that radiosensitive sub-groups exist which would suffer an increased incidence of both deterministic and stochastic effects. One possible radiosensitive sub-group consists of AT heterozygotes, i.e. individuals carrying one copy of the mutated gene, ATM, which make up about 1% of the US population. This hypothesis can be tested by the use of AT± knock out mice, which have recently become available

Richard B. Setlow, BNL: Germ-cell mutogenesis in Medaka fish following exposure to heavy, high energy cosmic ray nuclei. Uses a new quantitative specific locus test (SLT) developed in Japan using the Medaka fish (Oryzias latipes) to study germ cell mutations--mutations in progeny--in humans. The fish are oviparous and the embryos may be observed during development over a 6-9 day period, using color markers in the transparent fish. The resulting embryos are scored for color mutations and dominant lethals indicative of mutations in sperm. These data, compared to existing data from gamma irradiation, will give the relative biological effectiveness (RBE) for the HZE nuclei and so give estimates of the hazards to astronauts that may show up in their progeny

Mary H. Barcellos-Hoff, LBNL: "Interactions Between Tissue and Cellular Stress Responses Following Charged Particle Exposure." Mouse embryo fibroblasts (MEF) and mouse mammary epithelial cells primary cultures irradiated with g-rays and heavy ions to look for p53 and TGF-ß signatures and interactions; extended to TGF-ß knockout mice

Eleanor A. Blakely, /LBNL: Lens Epithelium and Proton-Induced Cataractogenesis. In-vitro model of human lens epithelial cells grown on extracellular matrix derived from bovine corneal endothelial cells Proton-induced upregulation of FGF-2 interferes with radiation-induced apoptosis in human lens, alters normal enucleation and protein expression in non-proliferating human lens fiber cells, and interferes with normal cell detachment.

John P. Murnane, UCSF, Telomere Repair and Chromosome Instability After High-LET Particle Radiation: Human primary fibroblast HCA cells irradiated with relativistic particle beams; measure DNA double-strand breaks in telomeric and Alu regions. Repeat with HCA-ltrt cells provided by J. Cami at LBL, which are positive for telomerase activity, do not senesce, and have normal cell cycle characteristics. Telomere destabilization is a hallmark of carcinogenesis; high LET particles generate DNA DSBs in the telomeric regions of the genome and that a fraction of these breaks do not rejoin, leading to loss of functional telomeres, chromosome fusion, and initiation of chromosome instability

NASA SPACE BIOMEDICAL RESEARCH INSTITUTE

John Dicello, Johns Hopkins. Radiation effect and countermeasures. Long-term interplanetary missions will expose astronauts to greater levels and more varied types of radiation than previous missions. Spacecraft on interplanetary missions will pass through the radiation belts encircling the Earth, intergalactic cosmic radiation with many types of energetic particles and will be exposed to solar events. These radiation fields can result in doses equivalent to hundreds of times greater than those experienced on Earth. These high radiation levels may kill cells, damage tissues or cause mutations that lead to cancer, cataracts, central nervous system damage or other diseases. The Radiation Effects Team is studying the risks from these types of radiation for producing tumors or genetic changes and is evaluating if it is possible to reduce cancer risks through pharmaceutical intervention.

Richard R. Sinden, Texas A&M. Quantitation of Radiation-Induced Deletion and Recombination Events Associated with Repeated DNA Sequences. The goal of this research is to develop data on the relationship between gene mutations, including deletions and recombination associated with direct repeats, and the quantity and quality of the radiation that interacts with the biological system so that countermeasures designed to minimize the health risks of radiation exposure in space can be devised. The hypothesis driving this proposal is that DNA damage introduced by high-Z high-energy (HZE) particles induces aberrant DNA repair events involving repeated DNA sequences that lead to recombination, gene conversion, or other mutations, that initiate the sequence of cytogenetic and functional changes which manifest themselves as the long-term health effects of radiation exposure in space, including cancer.

Jerry R. Williams, Johns Hopkins University. Radiation-Induced Cytogenetic Damage as a Predictor of Cancer Risk for Protons and Fe Ions. This project will determine whether

different forms of chromosomal damage are a predictor of cancer induction in a rat model, and if so, to use similar endpoints in human cells as a parameter to set exposure limits to these radiations. The same cytogenetic endpoints wiill be induced in vitro in peripheral lymphocytes and mammary epithelial cell. Parallel radiation studies in normal rat epithelial cells in Sprague-Dawley rats will provide RBE values for similar cell types for both Fe ions and energetic protons for both humans and for the Sprague-Dawley rat. These data will demonstrate whether there is comparable response between cell types, between species (human versus rat) and between in vitro and in vivo irradiation.

FLIGHT EXPERIMENTS

Gautam Badhwar, JSC. Inflight Radiation Measurements. The project was designed to measure radiation dose and dose equivalent rates using both passive (thermoluminscent detector) and active (tissue equivalent proportional counter) at a number of locations on the Mir station during the NASA-Mir program. To date data has been acquired from September 1994 to December 1998. All of the data has been analyzed. These detectors systems are now being used in the Civil Aviation radiation monitoring, and with increasing emphasis in Europe, Canada, and US on radiation exposure to aircraft crew, particularly, high latitude flights, these detectors will be used more and more. Canada and Spain acquired nearly identical systems for their use.

Gautam Badhwar, JSC. Phantom Torso. The project was designed to measure radiation dose and dose equivalent rates using both passive (thermoluminscent detector) at nearly 350 positions inside the Phantom Torso and at five organ locations using active detectors. This data was/is needed to establish the relationship of organ doses that used for crew risk assessment to their skin dose measurements. The data from TEPC and CPDS was used to model the expected doses at organ locations with measurements. All of the data has been analyzed. Models of spacecraft shielding, shielding at organ locations, and some modeling has been. Progress has been slow due to lack of funds for data analysis. Phantom, such as the one flown, are used in radiology departments of teaching hospitals. They are also used to provide calibration of delivered therapy doses. The current work focused on astronauts, but the techniques are applicable for proton therapy.

Richard H. Maurer, Johns Hopkins University. In Situ Spectrometry of Neutrons. We are designing and building a portable, low power and robust neutron spectrometer that will measure the neutron energy spectrum from 10 keV to 500 MeV with at least 10% energy resolution in the various energy intervals. This instrument will monitor the existing neutron environment both inside spacecraft structures and on planetary surfaces to determine the safest living areas, warn of high fluxes associated with solar storms and assist the NSBRI Radiation Effects Team in making an accurate assessment of increased cancer risk and DNA damage to astronauts. A modified version of the neutron spectrometer will be flown on aircraft flights to look at the neutron environment for flight crew exposure and avionics anomalies and to determine the operation of the spectrometer in an environment which simulates those to be experienced in space.

PROGRAMMATIC CONTRIBUTIONS

National Council on Radiation Protection and Measurements (NCRP). Guidance on Radiation Received in Space Activities. Studies on the use of fluence as the basis of a radiation protection system for astronauts (Scientific Committee 88, chaired by Dr. Stanley Curtis); methods of extrapolating radiation risk information from animal studies to humans. (Scientific Committee 1-4, chaired by Dr. David Hoel); research needed to be conducted in order to make radiation protection recommendations for humans involved in deep space missions such as colonizing the moon or a mission to Mars (Scientific Committee 1-7, chaired by Dr. Lawrence Townsend).

Ronald Turner : ANSER. Risk Management Strategies During Solar Events. Development of a comprehensive survey of data, resources and requirements to manage radiation risk associated with Solar Particle Events.