Abstracts for IWSSRR-2

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Opening Session

WHAT IS THE PLAN?

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After four decades of human exploration in space, many consider the medical consequences from radiation exposures in space to be the major biological risk associated with long-term missions. This international workshop, the number of participants, and the quality and extent of the research attest to both the importance of this problem and the difficulty in resolving it. At the first international workshop in Arona, Italy, our colleagues eloquently set the pace for us in the opening presentations. Dr. Juergen Kiefer[1] in his opening address questioned whether the systems for radiation protection on Earth are necessarily the best to be applied in space. Dr. Eric Hall[2] noted that cancer risks are not detectable at low doses through epidemiological investigations and proposed that mechanistic studies can lead us to means to extrapolate appropriate data to that low-dose region. Dr. Francis Cucinotta[3] suggested that experimental models could lead to testable theories that ultimately could allow accurate risk projections. Dr. Gerhard Kraft[4] then presented an example of such a theoretical model currently being used successfully in radiotherapy.

These views represent the latest thoughts on a theme that has been evolving during the preceding thirty years. Despite the diversity in both opinions and approaches that necessarily arise in research endeavors such as this, a commonality has emerged from our community. We need epidemiological data for humans, animal data in areas where no human data exist, and data on mechanisms to get from animal to humans. We need a programmatic infrastructure that addresses specific goals as well as basic research. These concepts might be deemed overly simplistic and even tautologous were it not for the fact that they are frequently underutilized and even ignored.

This presentation will review the goals, premises, and infrastructures that have been proposed by various groups and agencies to address radiation risks in space. It will review recent data and calculations that might modify our present directions. Finally, we will propose that the required level of effort demands a unified, focused international effort that is, at the same time, subjected to rigorous peer review, if we are to be successful. There is a plan; let us be certain that it is being implemented to maximum advantage.

1. J.Kiefer, "Space radiation research in the new millenium – from Where We Come and Where We Go." Physica Medica, 17, 1-4 (2000).
2. E. J. Hall, "Genomic Instability, Bystander Effect, Cytoplasmic Irradiation and other phenomena that may achieve fame without fortune." Physica Medica, 17, 21-25 (2000).
3. F. A. Cucinotta, "Once we know all the radiobiology we need to know, how can we use it to predict space radiation risks and achieve fame and fortune?" Physica Medica, 17, 5-12 (2000).
4. G. Kraft, "What we can learn from heavy ion therapy for radioprotection in space." Physica Medica, 17, 13-20 (2000).

COSMIC RADIATION AND HUMAN MISSIONS TO MARS

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In view of the increasing interest in human exploratory missions, above all to the neighbor planet Mars, ESA has initiated a study HUMEX (Humans in exploratory missions) of the human responses, limits and needs with regard to the stress environments of interplanetary and planetary missions. Emphasis was laid on human health and performance care (radiation effects, microgravity and reduced gravity, psychology and health maintenance) and advanced life support developments including bioregenerative life support systems and environmental monitoring. The study was lead by DLR with cooperation of MEDES (France), DERA (UK), Astrium (Germany) and the University of Clermont (France).
Concerning radiation risk issues a matrix has been constructed for the determinants of radiation hazards, from the primary space radiation sources and radiation transport processes through shielding, to the secondary radiation field, internal radiation field parameters, space flight environment, countermeasures, and biological responses, respectively. Each determinant was characterized with due consideration of the critical issues, the research needed and countermeasures proposed. The radiation risk assessment resulted in a roadmap of the following steps to be taken before sending humans to Mars:

- R&D activities on the ISS for space radiation protection purposes: (i) determine the depth dose distribution inside habitats and human body; (ii) determine interactions of space radiation and other space factors, e.g., microgravity; (iii) develop concepts for determining the personal biological significant radiation dose through personal dosimeters (passive and active), biodosimetry (e.g., chromosome aberrations), and biodiagnostic systems (e.g., cellular bioassays); (iv) develop dietary concepts for minimising oxidative stress.
- R&D activities on robotic precursor missions to Mars: determine the space radiation scenario for a whole exploratory mission and its biomedical implications by active radiation dosimetry installed on orbiters and landers.

R&D activities using terrestrial testbeds and simulation facilities, e.g., heavy ion accelerators: (i) improve and validate transport codes; (ii) use microbeams from heavy ion accelerators to assess the biological effectiveness of single heavy ions; (iii) install a fast rotation clinostate at a heavy ion accelerator to determine interactions of radiation with microgravity; (iv) use differential gene analysis to determine the interindividual variability of radiation responses.

STUDIES ABOUT SPACE SCIENCE PROMOTE NEW FIELDS IN RADIATION BIOLOGY

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Astronauts are constantly exposed to space radiation of various types of energy with a low-dose rate during long-term stays in space. Therefore, it is important to determine correctly the biological effects of space radiation on human health. Studies about biological effects at low dose and low-dose rate should include aspects of microbeams, bystander effects, radioadaptive responses and hormesis, as well as the relative biological effectiveness (RBE) of space radiation containing high LET radiations. Especially, neutrons might bring reverse phenomenon in low dose rate effects. We also are interested in *p53*-centrated signal transduction pathways involved in the cell cycle, DNA repair and apoptosis induced by space radiations. In addition, RBE has been reported to be affected by microgravity environment. To confirm this, we must prepare centrifuge systems in an International Space Station (ISS). Of course, we have to prepare many specific types of equipment for space experiments in ISS, because we cannot bring conventional equipment. The research for space radiation might give us useful information about birth and evolution of life on the earth. In addition, we can realize the importance of preventing the ozone layer from depletion by use of exposure equipment to sunlight at ISS. Therefore, we desire to educate space researchers of the next generation base on consideration of preservation of the earth from research about space radiation.

1. The space radiation environment and protection dosimetry

FIRST JOINT AUSTRIAN – RUSSIAN DOSE MEASUREMENTS AT SIX DIFFERENT POSITIONS ONBOARD THE INTERNATIONAL SPACE STATION

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In the framework of the joint Austrian – Russian project RBO-2 (Biological Radiation Dosimetry for space flight) dosemeter sets were exposed for 254 days, starting in February 2001 at six different locations onboard the International Space Station ISS. The project RBO – 2 deals with the further development of dosimetric methods for the determination of the biologically relevant radiation exposure in complex mixed radiation environments such as the ISS. The Austrian dosemeter sets for this first exposure on the ISS contained different kinds of passive thermoluminescent dosemeters: the commonly used TLD 600 (^{6}LiF:Mg, Ti), TLD 700 (^{7}LiF:Mg, Ti) as well as the more sensitive TLD 700H (^{7}LiF: Cu, P) and TLD 300 (CaF_2:Tm). The LiF thermoluminescent dosemeters will be read out and analyzed according to the high temperature ratio method (HTR – method) developed at the Atominstitute of the Austrian Universities and which allows besides the measurement of the absorbed dose also the determination of an "averaged" LET of this radiation field and therefore a mean quality factor and dose equivalent according to the definitions in ICRP 26. A similar method for the determination of dose equivalent based on the different LET efficiencies of the two main peaks of TLD 300 is currently investigated. Irradiations for a better understanding of the LET efficiency of all the above mentioned dosemter types are currently undertaken. First results of the data gathered from the first space exposure on the ISS will be presented and discussed.

THERMOLUMINESCENT DETECTORS FROM THE INP KRAKÓW FOR DOSIMETRY OF COSMIC RADIATION

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At the Institute of Nuclear Physics (INP) in Kraków a variety of lithium fluoride thermoluminescent detectors has been developed and is produced. Changing composition of activators and isotope concentration enables adjusting their properties, including dependence of efficiency on ionization density. Available detectors range from specially developed LiF:Mg,Ti with increased concentration of dopants, which posses high relative efficiency to densely ionizing radiation, to LiF:Mg,Cu,P showing very low response to high-LET particles when compared to gamma radiation. Combining different detector types it is possible to separate between components of a radiation field and to estimate ionization density.
LiF detectors may be also prepared with different dimensions. Particularly the unique thin detectors (thickness even < 0.1 mm) have been prepared and they were found very useful for measurements of weakly penetrating radiation in open space.
The characteristics of different detectors will be presented, together with the results of exposures at ground high-energy fields (CERN), in airplanes and in space (ISS and Biopan experiment).

USING TISSUE EQUIVALENT PROPORTIONAL COUNTERS TO DETERMINE QUALITY FACTORS FOR HZE PARTICLES

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Real-time dosimetry of energetic charged particles during manned space flight is important for assessment of dose and dose equivalent to astronauts, particularly for extended missions. NASA is currently using Tissue Equivalent Proportional Counters (TEPC) for this purpose. A TEPC gives details of the dose rate as well as integrated dose. There is still considerable uncertainty in the response of these detectors to the types and intensities of particles encountered during manned space missions. The objectives of this research are to understand the response a spherical TEPC to cosmic rays including the evaluation energy loss due to the escape of high-energy delta rays and increased energy deposition due to enhanced delta ray production in the wall of the detector. Experiments have been performed at ground-based accelerators that can generate the types and energies of particles found in trapped radiation belts as well as galactic cosmic rays. Data from experiments with ^{56}Fe particles from 200-1000 MeV/nucleon demonstrate that although the TEPC does not measure the true LET distribution of the incident particles, it does make an accurate measurement of absorbed dose. Also, the dose averaged values of lineal energy, y, can be used to obtain quality factors. Additional data for particles with Z between 6 and 26 will be presented.
This work has been supported in part through the NASA Specialized Center for Research and Training awarded to Colorado State University and Lawrence Berkeley Laboratory.

NUCLEAR ABUNDANCES INSIDE MIR MEASURED WITH SILEYE-2 EXPERIMENT

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In this work we present measurements of cosmic ray nuclear abundances above ≅150 MeV/n performed inside Mir space station between 1998 and 2000. Data have been obtained with SilEye-2 detector, a 6 plane silicon strip detector telescope designed to measure environmental radiation and investigate on the Light Flash phenomenon. In standalone mode, SilEye-2 is capable to measure LET distribution spectra and identify nuclear species with energy above 100 MeV/n: a total of 100 sessions comprising more than 1000 hours of observation were perfomed in the years 1998-2000, recording also several Solar Energetic Particle (SEP) events. Cosmic ray abundances inside a spacecraft can differ from the primary component due to interaction with the interposed material of the hull and the instruments. We report on LET measurements and relative abundances from Boron to Iron measured in different regions and at different geomagnetic cutoffs, in solar quiet conditions and during SEP events, showing how the composition varies in these different situations.

LIGHT FLASH AND RADIATION ENVIRONMENT MEASUREMENTS ON THE INTERNATIONAL SPACE STATION WITH A NEW DEVICE

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In this work we present the characteristics of the Sileye-3 detector. The device is devoted to the study of Light Flash and cosmic ray environment on board the International Space Station. Sileye-3 represents the next step after the previous two devices which worked on borad Mir between 1995 and 2000. It is composed of a telescope of 8 silicon strip detector planes triggered by two scintillators (AST: Advanced Silicon Telescope). Light Flash (LF) measurements come through a joystick which is pressed by the astronaut. In addition, LF perceptions will be correlated in real time for the first time with an electroencephalograph worn by the astronaut. All devices can work together or independently in order to maximize observation time and scientific goals. The device is scheduled for launch by next year and will provide information for the construction of the following Sileye-4/Altea facility.

ANALYSIS OF THE NEUTRON RADIATION ENVIRONMENT INSIDE THE INTERNATIONAL SPACE STATION AS OBTAINED BY A BONNER BALL NEUTRON DETECTOR

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A Bonner Ball Neutron Detector (BBND) experiment was conducted on the International Space Station (ISS) US Laboratory Module in order to evaluate the neutron radiation environment inside the ISS. The experiment was performed over eight months during solar maximum, and included the influence of solar proton events. BBND consists of six proportional counters covered with polyethylene moderators of various thicknesses and measures the neutron energy spectrum from thermal energy to 15 MeV. The measured energy spectrum is similar to the results of simulations carried out using the HERMES code.
The neutron dose equivalent was also obtained from the experimental results. The neutron dose equivalent at high latitude during solar proton events was observed to be higher than that in the South Atlantic Anomaly.

FLUENCE-BASED AND MICRODOSIMETRIC EVENT-BASED METHODS FOR RADIATION PROTECTION IN SPACE

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The National Council on Radiation Protection and Measurements (NCRP) has recently published a report

that discusses various aspects of the concepts used in radiation protection and the difficulties in measuring the radiation environment in spacecraft for the estimation of radiation risk to space travellers. Two novel dosimetric methodologies, fluence-based and microdosimetric event-based methods, are discussed and evaluated, along with the more conventional quality factor/LET method of estimating radiation risk. It was concluded that for the present, any reason to switch to a new methodology is not compelling. It is suggested that because of certain drawbacks in the presently-used conventional method, these alternative methodologies be kept in mind and that as new data become available and dosimetric techniques become more refined, the question should be revisited and that in the future, significant improvement might be realized. In addition, such concepts as equivalent dose and organ dose equivalent are discussed and various problems regarding the measurement/estimation of these quantities are presented.

MODEL PREDICTIONS AND VISUALIZATION OF THE PARTICLE FLUX ON THE SURFACE OF MARS

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Model calculations of the particle flux on the surface of Mars due to the Galactic Cosmic Rays (GCR) can provide guidance to several on-going and future biological research initiatives as well as current Mars exploration science objectives. Particle flux calculations for six different particle species: neutrons, protons, alpha, light, medium, and heavy ions have been accomplished for several GCR environment scenarios over the full range of the predicted phi values of the solar cycle. These particle flux calculations are then used to estimate the average particle hits per cell in various organs in a conceptual shelter vehicle. The estimated particle hits by the protons for an average location on the skin depth on the Martian mean surface level (alt = 0 km) are about 10 to 100 particle-hits/cell/year and the particle hits by heavy ions are estimated to be 0.001 to 0.01 particle-hits/cell/year. These flux calculations included variations in the Martian surface altitude based on the data from the Mars Global Surveyor (MGS) mission with its Mars Orbiter Laser Altimeter (MOLA). Particle hits per cell are estimated for 12 different organ depths of a human body behind a given conceptual vehicle with known water equivalent shielding. Visualization of the particle flux distribution on the Martian surface showing variations of particle flux, dose, and particle-hits per cell are presented. These variations include the changes due to Martian topography from the MOLA data. Quantifying the radiation risk uncertainty and mitigating the radiation risk on the Martian surface has been a priority for future manned missions to the Mars and for radiobiological investigations of the current era.

LUNAR LAVA TUBES RADIATION SAFETY ANALYSIS

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An analysis of radiation safety issues on lunar lava tubes as potential manned habitats has been performed. Lava tubes are formed when an active low-viscosity lava flow develops a continuous and hard crust, which thickens and forms a roof above the still flowing lava stream. At the end of the extrusion period, an empty flow channel free from molten magma is left. Lava tubes are commonly observed on the Earth, on basaltic volcanic terrains, with typical sizes of the order of 1-2 km of length, and few meters for cross-sectional parameters (i.e. height and width). Under lunar conditions (i.e. lower gravity field, absence of atmosphere), lava channels and tubes are at least an order of magnitude larger in each size dimension, i.e. hundreds of meters wide by hundred of meters or more deep, and tenths of kilometers long. For many years it has been suggested that these natural cavities on the Moon could provide an ideal location for a manned lunar base, by providing shelter from various natural hazards, such as cosmic rays radiation, meteorites, micrometeoroids, and impact crater ejecta, and also providing a natural environmental control, with a nearly constant temperature, unlike that of the lunar surface showing extreme variation in its diurnal cycle.
The analysis has been performed considering radiation from galactic cosmic rays (GCR) and Solar Particle Events (SPE) interacting with the lunar surface, modeled as a regolith layer and rock. The chemical composition has been chosen as typical of the lunar regions where the largest number of lava tube candidates are found. Particles have been transported all through the regolith and the rock, and received particles flux and doses have been calculated. The radiation safety of lunar lava tubes environments has been demonstrated.

A RADIATION ANALYSIS OF LUNAR SURFACE HABITATS

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An analysis is performed on the radiation environment found on the surface of the Moon, and applied to different possible lunar base mission scenarios. An optimization technique has been used to minimize the astronaut radiation exposure and at the same time control the effect of shielding, in terms of mass addition and material choice, as a mission cost driver. The optimization process performs minimization of mass along all phases of a mission scenario, considered in terms of time frame, equipment, location, crew characteristics and performance required, radiation exposure annual and career limit constraints (those proposed in NCRP 132), and implementation of the ALARA principle. On the lunar surface the most important contribution to radiation exposure is given by background Galactic Cosmic Rays (GCR) particles, and by locally induced particles, mostly neutrons, generated by interaction between GCRs and surface material. In this environment manned habitats are to host future crews involved in the construction and/or in the utilization of moon based infrastructure. Three different kinds of lunar missions are considered in the analysis, Moon Base Construction Phase, during which astronauts are on the surface just to build an outpost for future resident crews, Moon Base Outpost Phase, during which astronaut crews are resident but continuing exploration and installation activities, and Moon Base Routine Phase, with shifting resident crews. In each scenario various kinds of habitats, from very simple shelters to more complex bases, are considered in detail (e.g. shape, thickness, materials, etc) with considerations of various shielding strategies. The results for all scenarios clearly showed that the direct exposure to the space environment like in transfers and EVAs phases gives the most of the dose, with the proposed shielded habitats and shelters giving quite a good protection from radiation. Material choice and distribution in the habitable sections of spacecraft and habitats showed to be crucial in reducing radiation

dose to crewmembers. Operational constraints on hardware and scenarios have all been considered by the optimization techniques. Within the limits of this preliminary analysis, the three Moon Base related mission scenarios are perfectly feasible from the astronaut radiation safety point of view with the currently adopted and proposed exposure limits.

MOON EVA RADIATION SPACESUIT DOSE EVALUATION

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The environment on the surface of the Moon is imbedded in ionizing radiation, composed of both background Galactic Cosmic Rays (GCR) particles, mostly protons, alpha particles, and some heavy ions, and by locally induced particles, mostly neutrons, created by interaction between GCR and surface material, and emerging from below the surface due to backscattering processes. This is the environment in which astronauts will perform a huge amount of EVA activities when involved in the construction or in the utilization of Moon-based infrastructure. They will wear particularly suited spacesuits for active work during extravehicular activities. The radiation risk is to be evaluated for these crewmembers when exposed to the Moon radiation environment. A detailed spacesuit computational model is being developed at the NASA Langley Research Center for radiation exposure studies. The details of the construction of the spacesuit are critical to estimation of exposures and assessing the risk to the astronaut on EVA. Fine detail of the basic fabric structure, helmet, and backpack are given to assure a valid modeling. Experiments have been performed with the proton beam and a set of high-resolution detectors at DOE Lawrence Berkeley National Laboratory to estimate the non-uniform response of the liquid cooling and ventilation garment (LCVG) due to the association between water-filled tubes and fabric, and the different cord lengths of beam paths through the tube. Exposures in different EVA scenario on the Moon surface are evaluated, both in normal conditions and during Solar Particle Events.

LET DISTRIBUTIONS MEASURED IN THE CERF-FACILITY WITH THE RRMD-III

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The LET distributions on the 80 concrete side shield at the CERF-facility have been measured by the Si-detector telescope(RRMD-III) covered with acrylic plates of 1 cm thick and without them. In these measurements, a slight difference between both LET distributions was seen as a result of recoil protons and/or carbon ions. Also, the LET distributions are compared with the microdosimetric spectrum, (that is, lineal energy distribution) measured under the same condition with TEPC.

USING MONTE CARLO MODELS TO ESTIMATE SOLAR PARTICLE FLUENCE IN AN INTERPLANETARY TRAVEL

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By assuming solar particle events (SPE) as random events, we have developed a Monte Carlo model to estimate the particle fluence in an interplanetary travel.
Our Monte Carlo code, assume a source (with an arbitrary location) to be characterized by a flux function, which gives the average number of particles generated per unit time, energy, and solid angle.
At present, a first version of the Monte Carlo code, estimates the particle fluence in three different scenarios. The spaceship in a circular orbit with an external source, in an elliptical orbit with a constant angular velocity, in a circular orbit and the source as a simple Gaussian flare.
A second version of the code will be applied to two classes of Mars missions, conjunction class, and opposition class.

THERMOLUMINESCENCE IN SINTERD CaF_2:Tb

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Thermally luminescence (TL) in sintered CaF_2 doped with Tb_4O_7 and Sm_2O_3 induced by ultraviolet (UV) radiation was studied. A several kind of lanthanides elements are doped in pure CaF_2 powder crystals and properties of the TL to UV were observed. The TL intensity from CaF_2:Tb was the highest among the samples doped with the other lanthanides elements. The TL emission may be due to the recombination reaction; Tb^{2+} + hole→Tb^{3+*}→Tb^{3+}+hν. The TL peaks are observed at about 353K, 378K and 458K. It was found that the 378K TL peak intensity of CaF_2:Tb became strong by addition of Sm_2O_3. The378K TL peak may also be suitable for use as a dosimeter.

SOMATIC MUTATION IN EPIDERMAL CELLS OF THE LARVAE FROM DIAPAUSING EGGS OF THE SILKWORM, BOMBYX MORI, IRRADIATED WITH HEAVY ION BEAM

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Mutagenesis in P^S gene responsible for the integument color of the silkworm, *Bombyx mori*, was induced in the larvae which were hatched from carbon ion (400 MeV/u)- orr neon ion (290 MeV/u)-irradiated eggs. When carbon ions were irradiated to the 15-day old after oviposition which have been kept at 25℃ or 15℃, the occurrence of the mutagenesis was higher in 15℃ than in 25℃. This result will be caused by the lower amount of the accumulated substances such as sorbitol in 15℃-eggs than that in 25℃-eggs. The neon beam irradiation to the diapusing eggs show the dose- and LET-dependent effects and the relationship between RBE and LET for the induction of somatic mutation in the epidermal cells of the

Bombyx larvae. Irradiation at LET=150keV/μm caused highest rate of mutation.

SECONDARY PARTICLE PRODUCTION IN TISSUE-LIKE AND SHIELDING MATERIALS FOR LIGHT AND HEAVY IONS CALCULATED BY MONTE-CARLO SIMULATION (SHIELDHI).

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The production of secondary particles of different LET when high-energy ions interact with human organs and shielding materials is of importance for the evaluation of biologically equivalent doses delivered to patients undergoing radiation therapy with light ions and astronauts in long-term manned interplanetary missions. The accuracy of dose determination must be high, especially in the case of radiotherapy, which poses strong demands on the accuracy of the determination of secondary particle spectra.
The Monte Carlo code SHIELDHI, a spin-off of SHIELD (available as RSIC CCC-667), has been used for evaluating the secondary particle production by light and heavy ions interacting with different materials. SHIELDHI extends the transport of hadron cascades in shielding materials to that of ions in tissue- like materials, including ion energy-loss straggling (Gaussian or Vavilov) and multiple scattering (Gaussian) effects. The consistency with experimental data and other existing Monte Carlo codes for ion transport, including protons, has been verified first comparing depth energy deposition profiles of protons and ^{12}C impinging on water up to depths well beyond the Bragg peak. As opposed to some of the codes available, SHIELDHI yields profiles consistent with a proper treatment of nuclear inelastic collisions, and energy deposition beyond the peak due to nuclear fragmentation is also well predicted.
An accurate track-length algorithm for the evaluation of the fluence differential in energy of primary ions and their secondaries and higher-order generations of all particles has been implemented, keeping the default particle-number-counter fluence estimator for comparison. Detailed fluence calculations differential in energy, in regions close to the Bragg peak, have been made for ^{1}H, ^{12}C and ^{26}Fe ions with energies up to 1000 MeV/u transported through water, soft tissue, A-150 tissue-equivalent plastic and aluminium. They are compared with experimental data of GSI for ^{12}C ions of around 300 MeV/u. The integrated fluences of various particles types at different depths are also compared with results for ^{12}C ions measured at GSI. The calculated fluence spectra are used for the determination of quantities relevant to the dosimetry of light and heavy ions, like spectral mean stopping-power ratios, and mean values of the energy necessary to produce ion pairs in detectors.

DEVELOPMENT OF SPACE RADIATION EFFECTS ANALYSIS SOFTWARE PACKAGE

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Applying the research achievement on space radiation environment models and radiation effects analysis methods, as well as developing some effects analysis methods ourselves, integrating all necessary modules into one package, the Space Radiation Effects Analysis (SREA) software was produced. The package consists of AP8 and AE8 earth trapped radiation models and CREME model, and the latter depicts galactic and solar cosmic ray. Shielding of geomagnetic field and solid earth on cosmic ray is taken into account. Transport of energetic particles in materials is analyzed, in which several codes such as NFRG, HZETRN and BRYNTRN were applied, so that secondary radiation environment inside

spacecraft can be assessed, which has great significance for heavy manned spacecraft. Shielding analysis for simple and real 3-D geometry distribution of materials can be implemented, and the latter is essential in the spacecraft system design. The accumulated radiation effects as Total Ionizing Dose and Displacement Damage are evaluated with SHIELDOSE and EQFRUX codes respectively. Using I-RPP methods Single event effects (SEE) rate induced by heavy ions is predicted with the necessary input data experimentally available at home. Although there are many existing methods to predict SEE rate induced by protons, it is difficult for us to perform ground-based tests with suitable proton beams. As a solution to the difficulty we developed a practicable method to predict proton SEE rate with input data obtained from heavy ions testing. Comparison between results analyzed by SREA and some internationally known packages, such as SPENVIS and CREME96, shows that our package can give proper assessment on space radiation effects as accurate as others, and the package has played important role in some space missions.

NEUTRON PRODUCTION CROSS SECTIONS MEASUREMENTS RELEVANT TO GALACTIC COSMIC RAY TRANSPORT IN NASA SHIELDING MATERIALS

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An important element in determining the risk to astronauts from exposure to the radiation environment in space is an understanding of Galactic Cosmic Ray (GCR) transport through shielding and human tissue. As the primary GCR field is transported through materials, it can undergo nuclear interactions and create a shower of secondary particles. Because of their relative abundance and biological effectiveness, neutrons are an important component of the secondary radiation field. In thickly-shielded environments, such as a lunar or Martian base constructed from regolith and other local materials, calculations estimate that neutrons are responsible for up to 50% of the dose equivalent. Such calculations rely on a data base of experimentally-determined particle production cross sections for verification of input and output from the code. We report on experimental neutron production cross sections from interactions of GCR-like heavy ions on polyethylene, International Space Station wall materials, and a simulated Martian regolith target. The cross sections were measured at the Heavy-Ion Medical Accelerator in Chiba (HIMAC), Japan.

RADIATION ENVIRONMENT AND EFFECT MODELS AND TOOLS IN SPENVIS

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The ESA SPace ENVironment Information System (SPENVIS) provides standardized access to models of the hazardous space environment through a user-friendly WWW interface. The interface includes parameter input with extensive defaulting, definition of user environments, streamlined production of results (both in graphical and textual form), background information, and on-line help. It is available on-line at http://www.spenvis.oma.be/spenvis/. Intranet versions are also available.
SPENVIS is based on internationally recognised standard models and methods in many domains. It uses an ESA-developed orbit generator to produce orbital point files necessary for many different types of

problem. It has various reporting and graphical utilities, and extensive help facilities. SPENVIS includes models of the radiation environment and effects, including NIEL and internal charging. It also contains an active, integrated version of the ECSS Space Environment Standard, and access to in-flight data. Apart from radiation and plasma environments, SPENVIS includes meteoroid and debris models, atmospheric models (including atomic oxygen), and magnetic field models.
The SPENVIS radiation module features models of the proton and electron radiation belts, as well as solar energetic particle and cosmic ray models. The particle spectra serve as input to models of ionising dose (SHIELDOSE), Non-Ionising Energy Loss (NIEL), and Single Event Upsets (CREME). Material shielding is taken into account for all these models, either as a set of user-defined shielding thicknesses, or in combination with a sectoring analysis that produces a shielding distribution from a geometric description of the satellite system. A sequence of models, from orbit generator to folding dose curves with a shielding distribution, can now be run as one process, which minimizes user interaction and facilitates multiple runs with different orbital or shielding configurations.

FITTING SEASONAL VARIATIONS AND SOLAR CYCLE DEPENDENCE ON SAMPEX/PET TRAPPED PROTON DATA

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The low-altitude trapped proton population exhibits strong time variations related to geomagnetic secular variation and neutral atmosphere conditions. The flux measurements of the Proton Electron Telescope (PET) onboard the polar satellite SAMPEX constitute an adequate data set to distinguish different time scales and to characterise the respective variations. Four years of data have been analysed up to now; the data from 1996 up to the present are now being processed. The flux measurements have been binned, for each energy channel, over a coordinate grid in (K,$h$min) space, where Kaufmann's $K=I\sqrt{B}$ replaces the traditional McIlwain L value, and $h$min is the minimum altitude on the particle drift shells. We opted for these coordinates as they take into account the secular variation of the geomagnetic field and the movement of the dipole centre with respect to the Earth's centre of mass.
Running flux averages have been made over one month intervals. In order to separate the seasonal variation in the data from the solar cycle variation, the averages corresponding to the same month in successive years were fitted to the $F10.7$ solar radio flux. The resulting fit parameters for each month of the year were in turn fitted to a sine curve. In this way, the full time resolution of the data is modelled by a limited number of parameters per coordinate bin and energy channels. For the four years of data currently available, we are limited to a linear fit in $F10.7$. When the remaining five years of data are added, a parabolic fit will be used, which is more suitable.

SPACE RADIATION PROTECTION: COMPARISON OF EFFECTIVE DOSE TO BONE MARROW DOSE EQUIVALENT

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In many instances, bone marrow dose equivalents averaged over the entire body have been used as a surrogate for whole-body dose equivalents in space radiation protection studies. However, career radiation limits for missions in space are expressed as effective doses. This study compares calculations

of effective doses to the average bone marrow dose equivalents for several large solar particle events (SPEs) and annual galactic cosmic ray (GCR) spectra, in order to examine the suitability of substituting bone marrow dose equivalent for effective doses. Organ dose equivalents are computed for all radiosensitive organs listed in NCRP Report 116 using the BRYNTRN and HZETRN space radiation transport codes and the Computerized Anatomical Man (CAM) model. These organ dose equivalents are then weighted with the appropriate tissue weighting factors from NCRP Report 116 to obtain effective doses. Various thicknesses of aluminum shielding, which are representative of nominal spacecraft and SPE storm shelter configurations, are used in the analyses. For all SPE comparisons, the average bone marrow dose equivalent is considerably less than the calculated effective dose. For comparisons of the GCR, there is less than a ten percent difference between the two methods. In all cases, the gonads made up the largest percentage of the effective dose.

THERMOLUMINESCENCE RADIATION DOSIMETRY IN SPACE:A CRITIQUE OF CURRENT PRACTISE AND FUTURE PERSPECTIVES

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Radiation dosimetry in space presents one of the few remaining challenges in the field of radiation protection. This arises mainly from the highly complex nature of the radiation fields encountered in space leading to serious problems in the interpretation of data recorded by dosimetric devices, e.g., there are currently large uncertainties in the estimation of the neutron and HZE contribution to the total dose equivalent (1). The current approach uses a number of different types of passive detectors, each capable, in principle, of measuring a different component of the radiation field – the interpretation of such an array is certainly a heroic task. LiF-TLDs are the most commonly used passive detector, however, these are said to provide no LET information (1) (not true with sophisticated analysis) and tend to underestimate the total dose due to a decreasing TL efficiency with increasing ionization density (LET). Attempts have been made to convert heavy charged particle/neutron induced LiF-TL signals to radiation dose equivalent (2) but these are almost surely/inevitably doomed to failure (3,4).
Herein, we demonstrate a new direction using passive LiF-TLD based on nanodosimetric principles (5), i.e., the usage of existing molecular nanostructures in TL solid state materials as Q/RBE equivalent nanodosimeters. The concept is based on mimicking radiobiology (specifically the ionization density dependence of double strand breaks (DSBs) in DNA) by using the similar ionization density dependence of simultaneous electron-hole capture in spatially correlated trapping center/luminescent center pairs (of approximately the same dimensions as the DNA molecule) in the TL of peak 5a in LiF:Mg,Ti(TLD-100). This simultaneous electron-hole capture has been shown to lead to geminate/localized recombination and to an ionization density dependence in the relative intensity of peak 5a to peak 5 of [5a/5]H/L = 3.4 +- 0.6 (1 SD), similar to the ratio of DSBs to single strand breaks (SSBs) for low energy He ions. Hence the peak 5a Q-DSB nanodosimeter. Such a nanodosimeter, when properly characterized/calibrated could yield an estimate of the total dose equivalent combining all the components of the radiation field in a single measurement without the necessity of any concurrent knowledge of the specific components of the space radiation field to be measured. Much work, however, remains to be done and success is not guaranteed.

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RESEARCH AND DEVELOPMENT OF RADIATION MONITOR USING SCINTILATOR FIBER STACKS

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We report the characterization of a scintillating fiber dosimeter which developing for an aria monitor for developing space use. In this system, the detector is a scintillating fiber stack which measures the track and the energy of not only charged particles but also neutrons by means of measuring scattered protons. The detector consists of 200 fiber layers stacked in XZ and YZ directions by turns. Two images of the tracks of charged particles for both directions are read by an image intensifier tube and a CCD camera coupled to fibers to get tracks in three dimensions. The uniformity and the linearity of the detector were measured in calibration with alpha particle beams. The Brag curve of alpha particles was recognized in the images, therefore the arrival direction was determined.

POSSIBLE PERSONAL DOSIMETRY IN SPACE USING AL_2O_3: C

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A simple, user-friendly and reliable personal radiation monitor is needed for personal dosimetry for astronauts, as stay in space is becoming longer and the mission tasks have become complicated. The recently commercialized Al_2O_3: C (ALOC) dosemeter has attractive characteristics of a robust structure with very low fading of approximately zero under room temperature for 120 days and excellent physical and chemical stability. To apply this material for space radiation dosimetry, we have taken some data on responses to selected heavy ions like ^{4}He, ^{12}C, ^{40}Ar and ^{56}Fe. The dose responses to He and C showed fairly good values with about less than +-20% to the delivered dose, while heavier ions like Ar and Fe gave lower responses of about 40% of the delivered dose. To compensate these low responses, we are modifying filter compositions and testing them for ^{40}Ar irradiation.

CALCULATION OF RIGIDITY CUT UNDER DISTURBED GEOMAGNETIC FIELD.

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Solar Energetic Particles (SEPs) produced by flares and/or coronal mass ejections are one of major obstacles to human activity in Space. They give higher dose to astronauts than usual and it might hazard their health. If astronauts work in the space craft flown on the low-earth-orbit, the most effective shield to SEPs is the geomagnetic field. It prevents invasion of low energy particles and the threshold energy of the particles that are not able to enter the vicinity of the earth is called cut off rigidity. The value of cut off rigidity depends on the configuration of the geomagnetic field and it is changed by interplanetary disturbances. Flares and CMEs themselves make such disturbance and also they are often occurred when

the interplanetary field was highly disturbed, so that the usual value of rigidity cut often can not adopt SEPs. There are some geomagnetic field models which take account of the metamorphosis of the geomagnetic field by interplanetary conditions. We have calculated rigidity cut with such models and tried to improve the estimation of the DOSE that astronauts received from SEPs. We also studied dose level that passenger and crew of the high altitude civil air transporter received from SEPs.

RADIATION EXPOSURE MANAGEMENT PLAN OF JAPANESE ISS ASTRONAUTS

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Japanese astronaut will stay onboard the International Space Station (ISS) for 3 to 6 months, a few years later. Space radiation is primary hazard for astronauts. Therefore, National Space Development Agency of Japan (NASDA) established the Committee for Space Radiation Safety (CSRS), which consists of experts from the outside of NASDA and has been discussing a guideline on radiation exposure management for Japanese ISS astronaut. This presentation describes our overall plan of radiation exposure management for Japanese ISS astronaut, based on the guideline which has been studied by the CSRS.

NEUTRON DOSIMETRY AT HIGH ALTITUDE AND SPACE ENVIRONMENT USING AN ACTIVATION TECHNIQUE

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Activation analysis using reactor neutrons of the order of $10^{10\sim13}$ cm^{-2} s^{-1} has widely been used to determine trace amount of materials of the order of $10^{-6\sim-9}$ g g^{-1}. Inversely, if sufficient amount of material (1~100 g) is used as target material, low level neutrons of the order of $10^{-2\sim3}$ cm^{-2} s^{-1} can be measured though low background counting system is required to detect extremely low level radionuclides induced by environmental neutrons.
We have succeeded to detect a number of “natural” radionuclides in various metals and chemical reagents exposed to environmental neutrons at ground level and at 0.5~12km of altitude. Table 1 shows candidates of target-product pairs applicable to assess neutron dose at space environment.
In this paper, I will discuss focusing mainly on the applicability of the activation method to neutron dosimetry in space environment.

Table 1. Candidates oftarget-product pairs for the neutron measurement in space environment

Target nuclide	Isotopic abund. (%)	Cross section[1] (b)	Product nuclide	Half-life[1] (h)	Activity[2] (Bq g^{-1} for 0.1n cm^{-2} s^{-1})	Relative to ^{198}Au
^{23}Na	100	0.53	^{24}Na	15 h	4.74E-03	0.16
^{27}Al	100	0.11	^{24}Na	15 h	8.38E-04	0.03
^{40}Ar	99.6	0.61	^{41}Ar	1.83 h	7.25E-03	0.25
^{45}Sc	100	27	^{46}Sc	83.82 d	1.19E-03	0.04
^{55}Mn	100	13.3	^{56}Mn	2.576 h	1.12E-01	3.84
^{63}Cu	69.1	4.5	^{64}Cu	12.7 h	1.13E-02	0.39
^{71}Ga	39.8	5	^{73}Ga	14.1 h	6.13E-03	0.21
^{75}As	100	4.5	^{76}As	26.4 h	7.82E-03	0.27
^{81}Br	49.48	3	^{82}Br	35.3 h	1.88E-03	0.06
^{108}Pd	26.7	12	^{109}Pd	13.4 h	6.70E-03	0.23
^{115}In	95.7	205	^{116m}In	54 m	8.23E-01	28.2
^{121}Sb	57.25	6	^{122}Sb	2.7 d	1.64E-03	0.06
^{139}La	99.911	8.9	^{140}La	1.68 d	5.76E-03	0.20
^{141}Pr	100	12	^{142}Pr	19.20 h	1.45E-02	0.50

^{148}Nd	5.72	4	^{149}Nd	1.73	h	7.58E-04	0.03
^{151}Eu	47.77	5300	^{152}Eu	13.33	y	5.71E-04	0.02
^{151}Eu	47.77	2800	^{152m}Eu	9.30	h	2.51E+00	86.0
^{152}Sm	26.63	210	^{153}Sm	46.80	h	2.95E-02	1.01
^{154}Sm	22.53	5	^{155}Sm	0.4	h	3.61E-03	0.12
^{158}Gd	24.9	3.4	^{159}Gd	18.5	h	9.40E-04	0.03
^{159}Tb	100	46	^{160}Tb	72.30	d	6.67E-04	0.02
^{165}Ho	100	64	^{166}Ho	26.8	h	4.99E-02	1.71
^{170}Er	27.07	9	^{171}Er	7.52	h	4.70E-03	0.16
^{174}Yb	31.84	46	^{175}Yb	4.20	d	3.23E-03	0.11
^{176}Lu	2.59	2100	^{177}Lu	161	h	7.54E-03	0.26
^{185}Re	37.07	110	^{186}Re	3.72	d	9.39E-03	0.32
^{186}W	28.4	40	^{187}W	23.7	h	8.80E-03	0.30
^{191}Ir	38.5	750	^{192}Ir	73.83	d	3.39E-03	0.12
^{197}Au	100	98.8	^{198}Au	2.695	d	2.92E-02	1.00
^{238}U	99.275	2.73	^{239}NP	2.355	d	7.51E-04	0.03

1 Taken from Karlsruhe Nuclidkarte (1995)

2 Activity just after 12h flight at 12km. (0.1n $cm^{-2}s^{-1}$)

SOME METHODS APPLICABLE TO SPACE RADIOLOGICAL DATA ANALYSIS

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Some methods are presented for analyzing space radiological data, for example, 4π-directional radiation measurement or its dosimetry, and quantities ranging from logarithmic to linear variation.
The classical finite spherical harmonic expansion method in physics or mathematics cannot exactly fit data on finite spherical lattice points with equal interval in azimuth and zenith. For 4π directional assessment of space radiation and its dosimetry, the discrete spherical harmonic expansion method (Kumazawa, 1978) that exactly fits finite spherical lattice point data is given, applying it to the characteristics of directional dependency of effective dose.
Next the logarithmic scale or linear scale uses to illustrate the scatter plots of quantities, but there are not a few data that vary over the range from logarithmic scale to linear scale. For reasonable interpolation or interpretation of space radiological data, the hybrid scale (Kumazawa, 1991) that unifies the logarithmic and linear scales is applied to risk estimates for 1972 solar energetic particles (Badhwar, 1999).
The physical phenomenon in space inherently follows the law of proportionate effect or an increase of snowballing. Adding the constraint against excess increase via feedback, quantities of inherently snowballing become to show the hybrid scale variation. If no constraint, quantities of inherently snowballing are the logarithmic variation. To investigate the feature of variation from the logarithmic to the linear via the hybrid suggests the existence of constraint or not. The magnitude of variation of hazard or risk depends on the constraint. Consequently, the hybrid scale affords an adequate prediction for hazard or risk exposure.
The application of hybrid scale is ample, avoiding the negative interpolation of the finite spherical harmonic expansion, unifying the lognormal and the normal distributions, and modeling dose-response relationships with feedback. This paper presents these methods for space radiological data analysis.

A DEVELOPMENT OF INTEGRATING PASSIVE DOSIMETERS AND THEIR ANALYIS METHOD FOR SPACE RADIATION MEASUREMENTS IN NASDA –A DATABASE CONSTRUCTION FOR THE ANALYSIS-

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We are planning to measure space radiation using passive dosimeters, TLD-MSO (Mg_2SiO_4: Tb) and CR-39 plastic nuclear track detectors. These are very compact and suitable for being installed on a spacecraft. Researchers, who are going to plan space biological experiments, have requested that NASDA deliver dosimetric data for every experiment. Our principal purpose is to evaluate physical quantities such as absorbed doses, dose equivalents, and LET distributions in the LET region over 10 keV/μm-water. We have been establishing methods and technologies for speedy, accurate dosimeter analysis. The sensitivities of TLD-MSO and CR-39 were investigated by exposing them to beams of protons, heavy ions, and gamma rays at temperatures from –80ºC to 60ºC. Samples were stored for six months at maximum at the same temperature and measured in order to study fading properties. Since high-energy protons are the majority elements in space radiation fluxes in the low Earth orbit, we started some preliminary experiments and the development of a computational code to investigate how the protons affect on the radiation doses through target fragmentation. At the outset, we analyzed the energy and LET distributions of target-fragmented particles generated in the CR-39 material. The data from experiments and calculations mentioned above allow us to improve the accuracy in space radiation dosimetry. In this workshop, we report the following results obtained from the experiments: (1) the response of TLD-MSO for protons and heavy ions is proportional to the absorbed dose up to 100 mGy, (2) in the high LET region (exceeding 10 keV/μm-water), the sensitivity of TLD-MSO to heavy ions decreases with increasing LET of an irradiated particle, and (3) the calibration curves of CR-39 are obtained at various incident angles of the heavy ions from 10º to 90º using an automated microscope. We will also announce the temperature dependencies of the CR-39 and TLD sensitivities and the present status of the development of CR-39 analyzing systems. *Research Project with Heavy Ions at NIRS-HIMAC.

DRINKING BEER REDUCES THE RADIATION INDUCED CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES

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Search for chemical agents able to protect human beings from radiation damages is a key issue in radiation biology. In fact, radiation protectors are needed for both acute exposures (e.g. nuclear accidents, radiation therapy, or military applications) and low-dose irradiation (diagnostic radiology, high-altitude and space flights, radon indoors, etc.) It has been known that a number of alcohols, which readily react with the hydroxyl radical, are efficient radioprotectors. We here investigated the radioprotective effects of beer intake on human blood. Whole blood was irradiated with 200 kVp X rays and LET 50 keV/μm carbons from the HIMAC (the synchrotron) at the National Institute of Radiological Sciences (NIRS, Chiba, Japan). Cultures were initiated using 1.0 ml of irradiated whole blood in 9 ml of RPMI 1640 medium supplemented with 20 % (v/v) fetal bovine serum, 0.06 mg/ml kanamycin, 1.25 mg/ml sodium bicarbonate, 10 μl/ml PHA-M, 0.05 μg/ml colcemid. The irradiated blood cells were plated in T-25 flasks and incubated for 52 hr at 37 ℃ in a humidified atmosphere containing 95 % air plus 5 % CO_2. In the present study, we found that radiation induced chromosome aberrations were decreased by intake of beer. The radioprotection was more effective for carbon ions, high-density ionizing radiation, than X rays.

THE ALTEA PROJECT ON THE EFFECTS OF HEAVY IONS AND SPACE ENVIRONMENT ON HUMAN BRAIN FUNCTION ABOARD THE ISS

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ALTEA is an international project designed to investigate the transient and long term effects on human brain function of microgravity, impact of cosmic particles and work/sleep shifts aboard the ISS. The main purpose of ALTEA is to develop a facility to be made available to the international scientific community for human neurophysiological, electrophysiological and psychophysics experiments, studies on particle flux, and dosimetry in the ISS. A number of experiments will define and measure descriptors of electrophysiological brain function, monitor their dynamics over time and across different brain functional states, and identify the effects and potential hazard of space environment. Focus will be on visual function, the abnormal visual perceptions often reported as phosphenes, and the effect on vision of the impact of particle in microgravity conditions. A precursor of ALTEA, the subproject 'Alteino' will help design the facility and prepare the experimental baseline for the ALTEA experiments. The hardware features of both ALTEA and Alteino projects and facility will be outlined. Preliminary evidence of electrophysiological effects of transient heavy ion radiation of the retina/visual cortex, as obtained in *in vivo* studies on mice (experiment ALTEA-MICE) is reported elsewhere. ALTEA is scheduled to fly on the ISS in 2003. Alteino will be transferred to the ISS in April 2002.

DETECTION OF DNA DAMAGE INDUCED BY SPACE RADIATION IN MIR AND SPACE SHUTTLE

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Although physical monitoring of space radiation has been detected, the exact DNA damage caused by space radiation has not been measured yet. We aim to measure DNA damage by using fixed human cervical carcinoma (HeLa) and post-labeling methods in the Russian Mir-space station for 40 days or in an American space shuttle for 9 days. After landing, we labeled space-radiation-induced DNA strand breaks by enzymatic incorporation of [^{3}H]-dATP with terminal deoxyribonucleotidyl transferase (TdT). We detected the DNA damage as many grains on fixed silver emulsion resulting from □-rays emitted from ^{3}H-atoms in the nuclei of the cells placed in the Mir-station (J/Mir mission, STS-89), but hardly any grains in the ground control sample. In the space shuttle samples (S/MM-8), the grains in nuclei were lower than those in the J/Mir mission samples. These results suggest that DNA damages are caused by

space radiation and dependent on the term of the space flight.

APPLICATION OF AN IMAGING PLATE TO RADIATION DOSIMETRY

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Fading correction plays an important role in application of commercially available $BaBrF:Eu^{2+}$ phosphors: imaging plate (IP) to the dosimetry. We successfully determined a fading correction equation which is a function of elapsed time and absolute temperature, as the sum of several exponentially decaying components having different half-lives[1,2]. In this work, a method has been to developed to eliminate the short half-life component by annealing the IP and estimate the radiation dose with the long half-life component. The optimum conditions for quantitative measurement with two types of the IP (BAS-TR and BAS-MS, Fuji Film Co.) were evaluated by using the fading correction equation. Considering the IP as an integral detector for a month, photo-stimulated luminescence (PSL) between with and without annealing the IP at K℃ ; $PSL_{t,K}$ and PSL_t (t:the elapsed time (days) $1 \leqq t \leqq 30$) was compared. When the ratio (r_t), $r_t = PSL_{t,K} / PSL_t$, is closer to 1, the effect of the time elapsed to the dose estimate should be minimized. On the other hand, the annealing causes the loss of sensitivity. It was resulted that r_t was approximately 0.85 and the sensitivity remained over 10% of $PSL_{t=1}$ when BAS-MS was scanned with the image reader ; BAS-5000 after annealing at 80℃ for 24 hours. The results demonstrate new possibilities of radiation dosimetry offered by the IP.

1.H. Ohuchi, A.Yamadera and T. Nakamura, Nucl. Instr. and Meth. A450(2000)343-352.
2.H.Ohuchi and A.Yamadera, Rad. Meas. (in press)

MODELING OF RESPONSE OF THERMOLUMINESCENCE DETECTORS IN LOW AND HIGH-LET RADIATION FIELDS

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Lithium fluoride thermoluminescence detectors in form of chips or pellets, with different isotope composition (Li-6 and Li-7) and activators (LiF:Mg,Ti, LiF:Mg,Cu,P), are broadly used for measurements of radiation doses in space. TL detector signal is frequently normalized to unit exposure of Co-60 gamma-rays which can hardly be associated with equivalent dose. In this paper the approach is presented to calculate the response of MCP-N (LiF:Mg,Cu,P) and MTS-N (LiF:Mg,Ti) detectors for gamma-rays, beta-rays, protons and heavy charged particles. The variation of the relative detection efficiency, □, of thermoluminescent MCP-N detectors for different radiation qualities were assessed using the microdosimetric one - hit detector model. Using two model parameters (target size d=24 nm, saturation parameter □= 0.0091 Gy^{-1}) and microdosimetric distributions calculated using Monte Carlo track structure codes TRION and MOCA-14, it was possible to describe and predict a great variety of experimental data for photons, X-rays, beta-electrons, protons, alpha particles and heavy ions. For low penetrating radiation (X-rays, low energy protons) transport inside the detector and TL light self-absorption in the detector were taken into account in calculation. The calculation method can be useful for determination of the detector response when the radiation spectrum is known . It can also be helpful to calculate the variation of response of LiFMg,Ti and LiFMg,Ti detectors in different radiation fields and to assess equivalent dose after the exposure in space.

NECESSARY ACCURACY OF DOSE ESTIMATION

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The purpose of this study is to estimate the influence of broad dose intervals used ordinarily in the risk assessment on the risk value accuracy obtained for low-dose region and to estimate the necessary dose measurement accuracy or the possible dose averaging interval. As the material for the determination of such accuracy the results concerning to leukemia mortality from "Life Span Study" (LSS, Hiroshima and Nagasaki) are used as the typical data in this field. No attempts to re-estimate of LSS or T65D doses were done. The rectangular statistical distribution of the dose values inside averaging interval and Gaussian statistical distribution of the leukemia mortality events were supposed. By means of Monte-Carlo simulation the threefold worsening of the risk value accuracy after taking into account the dose averaging interval widths was demonstrated. As the necessary relative accuracy of dose estimation the levels equal to 30-35% in the dose range 1-5 rad and 5-10% in the range 5-30 rad can be adopted.
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STATUS OF THE SPACE RADIATION MONTE CARLO SIMULATION BASED ON FLUKA & ROOT

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The NASA-funded project to develop a Monte-Carlo simulation program for use in simulating the space radiation environment based on the FLUKA and ROOT codes that was reported on at the First International Workshop on Space Radiation Research is well into its second year of development, and considerable progress has been made. The general tasks required to achieve the final goals include the addition of heavy-ion interactions into the FLUKA code and the provision of a ROOT-based interface to FLUKA. In addition, the final program as presently planned will incorporate internal source simulations of the various types of incident space radiation selectable by reference to flight trajectory parameters. The most significant progress to date includes the incorporation of the DPMJET event generator code within FLUKA to handle heavy-ion interactions for incident projectile energies > 3GeV/A. The ongoing study intends to extend the treatment of these interactions down to 10 MeV, and at present two alternative approaches are being explored. One of these involves the use of the PEANUT model and the other is centered on a modification of the RQMD code. The ROOT interface is being pursued in conjunction with the CERN LHC ALICE software team through an adaptation of their existing AliROOT software. As a check on the validity of the code, a simulation of the recent data taken by the ATIC experiment is underway. Examples of the present capabilities will be demonstrated.

MEASUREMENT OF THE COSMIC-RAY ON THE GROUND

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In this study, we aimed to measure the directly ionizing component and the indirectly ionizing component of the cosmic-ray spectra and evaluate their dose rate distribution to the total equivalent dose rate of the cosmic rays on a ground level in Japan. Measurements were carried out in Tohoku University, Japan, from November 2000. The pulse-height spectra of the cosmic-ray photons and muons were measured with a 12.7 cm diameter and 12.7 cm long NaI (Tl) scintillation detector. In order to measure the energy spectra of cosmic ray photons and muons, the response functions of the detector to photons and muons were determined by the EGS4 and MARS simulation code, respectively. The dose of the cosmic-ray photons is evaluated directly from the measured pulse-height spectrum by using the spectrum weight function and the muon cosmic-ray dose was evaluated by converting the measured pulse height spectrum into deposited energy within the detector. The quantity of the cosmic-ray electron is estimated to be very small and is not taken into account in this study. The cosmic-ray neutron spectrum and the neutron dose were measured by using the Multi-moderator spectrometer (Bonner ball), a Rem counter and a 12.7 cm diameter and 12.7 cm long organic liquid scintillation detector NE213. The thus measured annual dose rates of the cosmic-ray muons, photons and neutron on the ground in Japan are about 314, 48, and 35 Sv/y, respectively.

RESULTS OF THE DOSIMETRIC MAPPING EXPERIMENT FLOWN AS PART OF NASA'S HUMAN RESEARCH FACILITY ON THE ISS

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The experiment Dosimetric Mapping flown as part of the science program of NASA's Human Research Facility (HRF) was designed to measure at different locations inside the U.S. Lab integrated total absorbed doses (ionising radiation and neutrons) and heavy ion fluences and its energy, mass and linear transfer (LET) spectra; time dependant fluence rates of charged particles and their corresponding dose rate.
The experiment consists of five nuclear track detector packages (NTDPs) (thermoluminescence dosimeters (TLD) and plastic nuclear track detectors), two DOSimetry TELescopes (DOSTEL) using two passive implanted planar silicon detectors per instrument, four Mobile Dosimetry Units (MDUs) using one passive implanted planar silicon detector per unit with an Control and Interface Unit (CIU) and an onboard TLD system consisting of a small weight TLD Reader and twelve TLD-bulbs, which have been reused after each measurement. Detectors are spread over the whole US-Lab
Up to now, dose rates and preliminary LET spectra are available. Dose rates of the ionizing part of the radiation field measured with TLD-bulbs at different locations vary between 123µGy/d and 226 µG/d. As example, the DOSTEL dose rate for quiet solar times of 194 µGy/d fits excellent to the TLD measurements. Weighted with the radiation quality factor received from measured preliminary LET spectra, the dose equivalent rate arrives at 504 µSv/d. Until the meeting more data will be available and presented.

VISUALIZATION OF PARTICLE FLUX IN THE HUMANBODY ON THE SURFACE OF MARS

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For a given radiation environment due to the Galactic Cosmic Rays (GCR), the calculated particle flux of protons, alpha particles, light, medium, and heavy ions, varies with respect to the topographical altitude on the Martian surface. The Mars Global Surveyor (MGS) mission with its Mars Orbiter Laser Altimeter (MOLA) instrument has been providing precise topographical surface map of the Mars. With this topographical data, particle flux at the surface level through the CO_2 atmospheric shielding for several GCR spectra that covers all predicted solar deceleration parameters was calculated. These particle flux calculations are then transported first through anticipated shielding of the conceptual shelter and then into the human body from skin level to deep organs using the HZETRN code. Several water equivalent shield values (up to 50 g/cm^2 of water in steps of 5 g/cm^2) were considered for the anticipated shelter and in the human body about 12 different locations were considered from skin level to the internal organs including the blood-forming organs (BFO). The description of the shielding variation in the human body as well as those due to different altitudes on the Martian surface will provide tools for assessing radiation environment on the Martian surface and the risk for human body in that environment. Visualization of the calculated particle flux, dose, and particle-hits per cell in side of the human body at various locations on the surface of Mars behind a conceptual shelter are presented.

EFFECTIVE DOSE ESTIMATION IN SPACE FLIGHT USING A SPHERE PHANTOM

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Complex nature of space radiation and radiation monitoring hardware restrictions make it difficult to determine an effective dose in space missions. Dose at every critical organ of a human body should be used with a corresponding weighting factor to calculate the effective dose. Depth-dose curve in space flight is known to be a result of galactic cosmic rays and trapped radiation contribution, at some periods solar cosmic rays are the most essential component of space radiation.
A sphere tissue equivalent phantom of 35 cm diameter with detector holes specially designed for the in-flight measurements will be used on board the Russian segment of the ISS. The phantom holes will be stuffed with passive thermoluminescent and solid state track detectors and a detector telescope with 3 Si detectors (Liulin-5). Energy deposition spectrum, dose rate and particle flux will be measured simultaneously with the Liulin-5 instrument with near real time resolution at 3 different depths of the phantom. Detector locations inside the sphere phantom at a given depths can be attributed to critical organs of a human body. Effective dose in a human body can be estimated based on the dose values measured at different depths inside the phantom. For the first estimation of the effective dose, measurements on board the Mir station with the sphere water filled phantom stuffed with thermoluminescent detectors can be used.

WORST CASE SOLAR ENERGETIC PARTICLE EVENTS FOR INTERNATIONAL SPACE

STATION MISSIONS.

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Solar particle events (SPE) have historically been of concern for manned space missions due to the potential for large doses. During the space age many large SPEs have been observed with approximately one to two such events occurring in each 11 year solar cycle. For planning purposes the worst case solar particle event provides an upper bound for these doses. In this work, human organ doses for several plausible worst case solar particle events are evaluated in the environment of the International Space Station. Five worst case SPEs spectra based on large historical events are calculated. Doses are calculated for these worst case events using the BRYNTRN transport code and the Computerized Anatomical Man (CAM) human geometry model along with detailed shielding distribution files for the International Space Station. The largest doses were observed for the February 1956 event normalized to August 1972 event fluences. The resulting doses from this event are 227.5 cGy for skin, 276.5 cGy for eyes, and 216.1 cGy for the blood forming organs (BFO). When the geomagnetospheric cutoffs are applied to the spectra for the worst case orbit the doses above become 78.5 cGy for skin, 78.2 cGy for eyes, and 61.8 cGy for BFO.

A LINEAR-QUADRATIC MODEL FOR MIXED IRRADIATION WITH MULTIPLE TYPES OF RADIATION OBSERVED IN SPACE

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We revised the model of Suzuki for mixed irradiation with multiple types of radiation, substituting a 'reciprocal-time' pattern of repair function for a first-order one in reduction and interaction factors of the model. The reduction factor, which reduces the contribution of the square of a dose to cell killing in the model, and the interaction factor, which also reduces the contribution of the interaction of two or more doses of different types of radiation, were formulated by using the 'reciprocal-time' pattern of repair function.
The newly modified models for mixed irradiation could express or predict cell survival more accurately than the older ones, especially when irradiation is prolonged at low dose rates. We present survival curves of cells calculated from the new and the old models of assumptive simultaneous mixed irradiation with two or three types of radiation.

PHOSWICH NEUTRON DETECTOR TO MEASURE NEUTRON ENERGY SPECTRUM, FROM A FEW MeV TO 130 MeV IN A SPACECRAFT

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Neutrons over 1 MeV inside aircrafts and human spacecrafts contribute a significant fraction of the total dose equivalent, however only insufficient data have ever been acquired. A flight neutron spectrometer is necessary to estimate the equivalent dose of neutron in those environments. We developed new type of phoswich neutron detector consisting of the NE115 and NE213 scintillators that can distinguish neutron and photon events from charged-particle events. Performance of particle discrimination between neutron and charged particle events was investigated in two neutron and charged-particle mixed fields in NIRS, which gave satisfactory results. Particle energy spectra in these environments were simultaneously obtained from measured data. We have developed the portable neutron detector system for neutron measurements on board spacecrafts. As the simple and compact system is indispensable to flight applications, a smaller photomultiplier than usual one was selected, and a data acquisition system was installed. Such can be used in aircrafts and spacecrafts very easily.

REQUIREMENTS FOR BIOSPECIMEN EXPOSURE FACILITY ON JAPANESE EXPERIMENT MODULE (JEM)

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The purposes of this study are considering the feasibility of equipment for examining effects of the solar radiations at low earth orbit, including the far ultraviolet (FUV), on biological specimens, and proposing a conceptual design of the hardware. We assume to attach the equipment to the Japanese Experiment Module Exposed Facility (JEM-EF). The equipment will be capable of exposing certain kinds of biological specimens, such as microbial spores, directly to the space environment, or holding live organisms such as cell cultures, insects, or small plants under controlled temperature and atmospheric conditions. The biological specimens will be accommodated inside the compartments on sample trays. Specific filters may be fitted onto compartment windows. Sample trays are to be placed in a sample holder box on the gimbaled stage for tracking the Sun. The sample holder with shatter lid will be attached to or detached from the stage by operating with the Remote Manipulator System. The sample holder may be retrieved into JEM pressurized module, where crew procedures are possible, through the JEM Airlock. This equipment will be useful in studying combined effects of the microgravity and the wide spectrum of solar radiations on living organisms when actualized.

SPACE RADIATION WEATHER FORECAST FOR SPACE TOURISM AND MARS EXPLORATION

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It is foregone conclusion that human activities in space will become more varied and more frequent as we move through the 21st century. Space tourism is now becoming practical realities, and manned mission to Mars is also now considered feasible. For the safety operations of these manned space activities, the forecast and nowcast of the space radiation weather (temporal and special changes in the high energy particle environment) is an important requisite. The prediction of the big storm in the radiation belt is essential for space tourism, and the prediction of the solar particle events has a vital importance for manned Mars mission. In this paper, we describe the cutting-edge of the space radiation weather forecast and future requirements for more detailed and quantitative forecast.

INTERCOMPARISON OF RADIATION ISNTRUMENTS FOR COSMIC-RAY WITH HEAVY ION BEAMS AT HIMAC (ICCHIBAN PROJECT)

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We present initial results from the first InterComparison for Cosmic-ray with Heavy Ion Beams At NIRS (ICCHIBAN) exposures made at HIMAC in Feb. 2002. The space radiation dosimetry community has long recognized the need to intercompare of spaceflight dosimeters and the Workshops on Radiation Monitoring for the International Space Station (WRMISS) has recommended that radiation instruments used aboard the ISS should be intercompared using well-known radiation fields on the ground. Following this recommendation, the HIMAC facility at the National Institute of Radiological Sciences has begun a series of exposures to intercompare radiation instruments designed for use in space as part of a newly initiated ICCHIBAN project. The initial series of measurements (1st ICCHIBAN run) was designed to establish the response of each detector to two well-characterized heavy ion beams; 400 MeV/nucleon ^{12}C and 400 MeV/nucleon ^{56}Fe. These beams are representative in charge and energy of two of the most significant heavy ion components present in the galactic cosmic radiation spectrum. The properties of the incident beam—such as intensity, profile, charge and total energy—were be characterized by several detectors, including silicon detectors, CR-39 plastic nuclear track detectors and plastic scintillation counters. Once the response of each detector to heavy ion beams of known composition is measured, the space radiation measurement instruments can be compared with one another, in future measurements at HIMAC and at other accelerators around the world. We conclude by discussing plans for future ICCHIBAN runs, including next 2nd ICCHIBAN run for passive detectors in early summer 2002.

A NEUTRON SPECTROMETER COMPOSED OF POSITION-SENSITIVE DETECTORS AND A SPHERICAL MODERATOR WITH RESPONSE OF WIDE ENERGY RANGE

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A neutron spectrometer has been developed to measure energy spectra of neutrons in the energy range from thermal to a few tens MeV. The spectrometer consists of a spherical polyethylene moderator with a diameter of 30 cm and three slender position-sensitive ^{3}He proportional counters or nineteen pairs of ^{6}Li- and ^{7}Li-glass scintillators arranged along the orthogonal x-, y-, and z-axes of the sphere. The detectors can obtain the thermal neutron flux distribution in the sphere. The energy spectrum of the incident neutrons can be extracted from the information on the thermal neutron flux distribution in the sphere. The detector characteristics have been studied with Monte Carlo simulations and experiments using monoenergetic neutrons at the AIST standard neutron field. The response obtained by the experiments and that by the simulations show good agreement. The energy spectra of the monoenergetic neutron beams have been obtained with an unfolding process. In spite of white initial guess spectra, the unfolded energy spectra agree well with the true ones. The energy spectra of neutrons in an isotropic neutron field can also be obtained with a proper unfolding process. The spectrometer can also determine directions of neutron incidence with an uncertainty of less than 28 degrees for 500keV and lower-energy neutrons and 10 degrees for 1MeV and higher. Although the spectrometer has been developed for measurements of neutrons in spaceship environments, it can be used for many other purposes.

THE THEORY AND METHOD OF SPATIAL 3-D DETECTING OF SOLITARY AND REMOTE SPACE RADIATION SOURCES BY CORRELATION OF RADIATION INTENSITY

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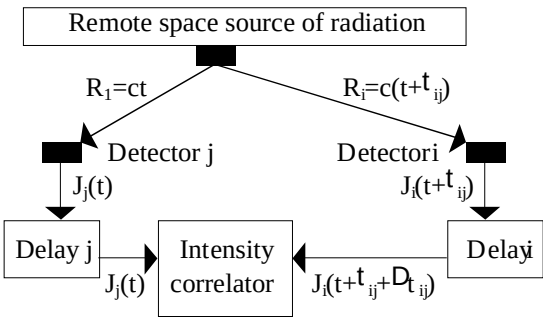
The intensity correlation method of spatial and angular (three-dimensional) location of solitary or remote space sources of radiation (X, gamma or neutrons) is studied. The main idea of the method is based on the phenomenon of pair correlation of intensities $J_j(t) = \varepsilon_j |\xi_j(t)|^2$ and $J_i(t+\tau_{ij}) = \varepsilon_i |\xi_i(t+\tau_{ij})|^2$ of radiation measured by two separated detectors i and j [1]. Here $\xi_k(t) = \Sigma_n \Psi_k(\mathbf{R}_k, t-t_{kn})$ are sums of pulse spherical waves $\Psi_k(\mathbf{R}_k, t-t_{kn}) \equiv F(t-t_{kn})\exp(i\mathbf{k}\mathbf{R}_k)/R_k$ of quanta coming from a remote source, location $\mathbf{r}_o$ of which is to be found. The pair correlation function $K_{ij}(\tau_{ij})$ of intensities $J_j(t)$ and $J_i(t+\tau_{ij})$ for two spatially separated independent detectors, situated at $\mathbf{r}_i = \mathbf{R}_i+\mathbf{r}_o$, $\mathbf{r}_j = \mathbf{R}_j+\mathbf{r}_o$ and having the effectiveness ε_i and ε_j of the quantum detecting, equals

$K_{ij}(\tau_{ij}) = < J_i(t)\, J_j(t+\tau_{ij})> - < J_i(t)> < J_j(t+\tau_{ij})>$.

Here $\tau_{ij} = (R_i-R_j)/c$ is the time-delay of measured intensities $J_j(t)$ and $J_i(t+\tau_{ij})$ in different detectors i and j from the same remote detected source.

For the case of quasi-stationary source of radiation and for the usual case of the random Gaussian process of quanta detecting $\xi_k(t)$ the correlation function of intensity has the form



$$K_{ij}(\tau_{ij}) = \varepsilon_i\varepsilon_j \{<\xi_i(t)\, \xi_i^*(t)> <\xi_j(t+\tau_{ij})\, \xi_j^*(t+\tau_{ij})> + <\xi_i(t)\, \xi_j(t+\tau_{ij})> <\xi_i^*(t)\, \xi_j^*(t+\tau_{ij})> + <\xi_i(t)\, \xi_j^*(t+\tau_{ij})> <\xi_i^*(t)\, \xi_j(t+\tau_{ij})>\} - <J_i(t)> <J_j(t+\tau_{ij})> = \varepsilon_i\varepsilon_j |<\xi_i(t)\, \xi_j^*(t+\tau_{ij})>|^2 = <n_i> <n_j>| \int_{-\Delta\omega/2}^{\Delta\omega/2} |F(\omega)|^2 \exp(-i\omega\tau_{ij})\, d\omega|^2.$$

Here $F(\omega) = \int_{-\infty}^{\infty} F(t)\exp(-i\omega t)\, dt$; $|F(\omega)|^2$ is the spectral intensity (having the spectral half-width $\delta\omega$) of the single detected quantum after detector (on the exit of detector);
$\Delta\omega$ is the spectral band of the intensity correlator (signal acquisition and processing system);
$\langle n_i \rangle$ and $\langle n_j \rangle$ are the averaged quantity of detected quanta in the detectors i and j.

For the usual case $\Delta\omega < \delta\omega$ we have the correlation function

$$K_{ij}(\tau_{ij}) \approx 4\langle n_i \rangle \langle n_j \rangle |F(0)|^4 |\sin(\Delta\omega\tau_{ij})/\tau_{ij}|^2.$$

The maximum value of this correlation function is equal $K_{ij}(0) = 4\langle n_i \rangle \langle n_j \rangle |F(0)|^4 |\Delta\omega|^2$ and corresponds to the additional delay $\Delta t_{ij} = -\tau_{ij}$ of the registered intensity signal $J_i(t+\tau_{ij})$ from one of the detectors (i) or both detectors (i and j) introduced in the correlator.

The maximal distance to an investigated source of radiation equals $L_{(max)} = \Delta\omega a^2/4c\sqrt{\delta}$.

Here a is the distance between two detectors, $\delta = |K_{ij}(0) - K_{ij}(\tau_{ij(min)})|/K_{ij}(0) \approx 10^{-5} - 10^{-6}$ is measurement accuracy of correlation function near its maximum value $K_{ij}(0)$,

$\tau_{ij(min)} = a^2/2L_{(max)}c$. At usual values $\Delta\omega = 10^9\ s^{-1}$, $a = 10^4$ km we have $L_{(max)} \approx 10^{14}$ km.

For three-dimensional location of the remote X-source of radiation it is necessary to use three or more spatially separated independent detectors, situated at $\mathbf{r}_1$, $\mathbf{r}_2$, $\mathbf{r}_3$,..., and three or more independent intensity correlators. For this case the position of the detected remote source $\mathbf{r_0}=\{x_0, y_0, z_0\}$ of radiation may be calculated using the system of equations

$$[(x_i - x_0)^2+(y_i - y_0)^2+(z_i-z_0)^2]^{1/2} + c\Delta t_{ij} = [(x_j - x_0)^2+(y_j - y_0)^2+(z_j-z_0)^2]^{1/2};$$

for maximum values of correlation functions $K_{ij}(0)$ for different pairs ij ($i \neq j$=1,2,3...) of detectors of investigated radiation.

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ACTIVITIES OF JAPANESE SPACE FORECAST CENTER IN COMMUNICATIONS REAEARCH LABORATORY

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There is an international organization for space weather forecasts under the International Union of Radio Science (URSI). It is called the International Space Environment Service (ISES). There are eleven forecast centers of the ISES in the world. Communications Research Laboratory is running the Japanese forecast center. We made forecasts of space environment everyday and deliver our forecasts via networks, fax, and answer phones. Our forecasts will be useful for human activities in space. Now solar activities are near maximum phase. We report several large disturbances of space environment occurred in 2001. Low-latitude auroras were observed several times in Japan associated with these large disturbances.

A CONSIDERATION ON CLASSIFICATION OF SPACE RADIATION MEASUREMENT

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The purposes of space radiation measurement can be classified into three major categories: (1) Validation

of transport codes, (2) Protection dosimetry for astronauts, and (3) Acquisition of radiation data for onboard experiments. Each category requires different instruments to measure radiations. Detail information on charges and energies of particles with incident angles are needed for strict validation of the models on space environment and radiation transport. Such precise data are not needed for conservative radiological protection, whereas the safety, small scale and simplicity in handling are critical in employment of personal dosemeters that have to be always attached on an astronaut's body. For possible onboard experiments, the radiation-detecting part should be as small as possible not to disturb the surrounding radiation field; the detectors must be chosen flexibly according to the size and density of a sample, the targeting endpoint in respect, and the accuracy requested from investigators. In any case, space radiation dose as equivalent for a specific endpoint has to be determined on the basis of sufficient data obtained on ground using various kinds of beams with a broad range of energy.

A SIMPLIFIED SYSTEM FOR MEASUREMENT OF TIME-RESOLVED PHOTOLUMINESCENCE INDUCED BY PULSED UV EXCITATION

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A simplified system that can measure the time-resolved photoluminescence (PL) afterglow was designed using a commercially available radiophotoluminescence reader (FGD-1000, Asahi Technoglass) coupled with a digital oscilloscope (Waverunner LT342, Iwatsu-LeCroy). The time-resolved PL after pulsed UV excitation using a N_2 laser (VSL-337, Laser Science) was measured continuously for 45μs with intervals of 10ns. The PL emission in the long-wavelength region was detected with a photomultiplier (R669, Hamamatsu) behind several band filters. The readout data were saved in to a built-in flash memory of the oscilloscope during measurement and analyzed on a computer. The good reproducibility was observed in the time-resolved PL afterglow from a phosphate glass irradiated with selected heavy ions. It is expected that this system will be applied conveniently for future PL studies, particularly for developing new PL materials.

2. Health effects expected in long space mission (include. Synergistic effects of microgravity)

DOSE RESPONSE FOR CATARACT INCIDENCE AMONG ASTRONAUTS

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The increased risk for cataracts from radiation exposure is often assumed to be a deterministic effect occurring only above a dose threshold. In contrast, evidence from animal studies as well as a previous investigation of cataract incidence among astronauts[#] suggest a linear response with no dose-threshold. However, there are unanswered questions related to the importance of stationary cataracts and the definition of "clinically significant cataracts," in light of epidemiological data suggesting that the probability of stationary cataracts to progress is highly dependent on the age of appearance of stationary cataracts. Here, we present analysis of the astronaut cataract data that consider models of the dose-response in relationship to age and time after exposure. Using parametric survival analysis and the maximum likelihood method, we estimate the dose- response for cataract induction by space radiation. We also consider the probability of cataract inductions in terms of the heavy ion and neutron component of space radiation exposures. Our results support a probabilistic model for the induction of stationary cataracts by space radiation. Future studies are needed to understand the possible progression of stationary cataracts to severe forms after low-dose exposures in space, and on Earth.

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EXPOSURES TO THE ATMOSPHERIC IONIZING RADIATION ENVIRONMENT: A COMPARISION BETWEEN ICELANDIC AND ITALIAN CIVILIAN AVIATION FLIGHT PERSONNEL

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All risk assessment techniques for possible health effects from low dose rate radiation exposure should combine knowledge both of radiation environment and biological response, whose effects (e.g. carcinogenesis) are usually evaluated through mathematical models and/or animal and cell experiments. Data on human exposure to low dose rate radiation exposure and its effects are not so readily available, especially with regards to stochastic effects, related to carcinogenesis, and therefore to cancer risks, for which the event probability increases with increasing radiation exposure. The largest source of such data may be airline flight personnel, if enrolled for studies on health effects induced by the cosmic-ray-generated atmospheric ionizing radiation, whose total dose, increasing over the years, may

cause delayed radiation-induced health effects, with the high-LET and highly ionizing neutron component typical of atmospheric radiation. A comparative study has been performed between the radiation exposure patterns of the Icelandic and the Italian civilian aviation flight personnel. These two populations represent two extremes within the group of worldwide airline personnel. The Icelandic crewmembers, like only in the world their Canadian colleagues, always fly over or very close to the geomagnetic pole, and are this way exposed to high doses within each flight leg, whereas the Italian crewmembers, apart from transatlantic flights, are always flying close to the geomagnetic equator or anyhow quite far from the geomagnetic pole, receiving a small dose rates for each flight. For both Icelandic and Italian flights the actual radiation dose calculations along the various flight legs have been performed taking into account the different flight profiles for different routes and the variations over the considered time period of the heliocentric potential and of the geomagnetic field, in order to take into account the whole atmospheric neutron spectrum. Average dose rate values for aircraft types and routes have been obtained, along with their variations with time, and the different exposure patterns have been put into evidence. The annual individual dose for each crewmember is obtained by multiplying the average dose rates by the number of block hours for aircraft type flown each year. In the future it will be possible to analyze dose rates and cumulative doses to crewmembers in relation with different health outcomes for the two considered aircrew groups. The data analysis in this respect is in progress, and the first exposure results are expected soon.

EXPOSURE TO THE ATMOSPHERIC IONIZING RADIATION ENVIRONMENT: A STUDY ON ITALIAN CIVILIAN AVIATION FLIGHT PERSONNEL

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A study of the effects of high-LET, low-dose and low-dose-rate ionizing radiation and associated risk analysis is underway. This study involves analyzing the atmospheric ionizing radiation exposure (including high-energy neutrons) and associated effects for members of civilian aviation flight personnel, in an attempt to better understand low-dose long-term radiation effects on human subjects. The study population includes all Italian civilian airline flight personnel, both cockpit and cabin crewmembers, whose work history records and actual flights (route, aircraft type, and date for each individual flight for each person where possible) are available. The dose calculations are performed along specific flight legs, taking into account the actual flight profiles for all different routes and the variations with time of solar and geomagnetic parameters. Dose values for each flight are applied to the flight history of study participants in order to estimate the individual annual and lifetime occupational radiation dose. An update of the study of the physical atmospheric ionizing radiation exposure is given here, in terms of environmental modeling, flight routes, radiation dose evaluation along different flight paths, and exposure matrix construction. The exposure analysis is still in progress, and the first results are expected soon.

RESEARCH IN METABOLIC PHYSIOLOGY ON SPACE FIELD BY USING THE MULTITRACER TECHNOLOGY

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The creatures on the earth fit themselves to various kinds of environment, and evolve and prosper. In recent years, it has been realized that mankind utilizes universal space. Information concerning changes of homeostasis of a creature in universal space is still much limited. Detailed physiological studies on this problem are a pressing need. Bio-trace elements can be an index reflecting various kinds of diseases. In certain diseases, some elements become a reliable source of information for diagnosis. The multitracer technology can analyze metabolism and behavior of different elements in the living bodies and cells simultaneously. We proved that this method is a powerful tool to obtain information on the behavior of bio-trace elements. In this article, we describe the usefulness of the multitracer technology in the studies of trace elements in living bodies and discuss possibility of its application to metabolic physiology in universal space environments such as low or zero gravity, low oxygen concentration, radioactive rays exposure and low atmospheric pressure.

HEAVY ION RADIATION ENHANCES DECREASE IN BONE MINERAL DENSITY BY CLINOSTAT-MICROGRAVITY

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The purpose of the present study is to examine the effects of heavy ion radiation combined with microgravity on bone metabolism in rats. Irradiated rats with doses of 0.5-5 Gy of heavy ion particle were exposed to microgravity by clinostat (90 min/ day) for 4 weeks. The total bone mineral density (BMD), cortical BMD, cortical thickness and strength strain index of tibia by a quantitative computed tomography (pQCT) were increased in the radiation alone group, while total and trabecular BMD was decreased and trabecular area was increased in the clinostat alone group. In the radiation combined with microgravity group, the trabecular BMD was decreased. By bone histomorphometry, increase in trabecular separation and osteoid thickness and volume were observed. It was concluded that space radiation stimulates bone metabolism and enhance the decrease in BMD under mirogravity enviroment, probably by each different action.

RADIATION MICROBIOLOGY IN SPACE ENVIRONMENT CONDUCTED USING SPACE SHUTTLE AND SPACE STATION MIR

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We participated in space experiments, parts of the NASDA project, conducted during the NASA and the Russian Space Agency (RSA) missions, *i.e.*, "FMPT (STS-47)" in 1992, "IML-2 (STS-65)" in 1994, "S/MM-4 (STS-79)" in 1996, "S/MM-6 (STS-84)" in 1997 and "JMIR (Mir mission 24 & 25)" in 1997. In these missions, we had purposes of studying the effect of HZE cosmic radiation and searching for radioresistant bacteria in space station, and we obtained the following results: (1) Procaryote *Escherichia coli* excision DNA repair-deficient mutants were sensitive to HZE cosmic radiation, and I speculated that the *pol* and *exo* genes contributed to the repair of cosmic radiation-damaged DNA. (2) Using agarose-gel electrophoresis method, it was found that the plasmid pZ189 and pKmK8 DNAs exposed to cosmic radiation did not cause the drastic damage, then the detection of minor damage on DNA was tried by the autoradiography method of end-labeled DNA. (3) The repair process of the cell and DNA damaged by heavy ion beam on *E. coli* B/r strain was inhibited in a microgravity environment on orbit. (4) Many microorganisms were isolated from condensed water, wiping and scratching of cabin wall and air sampler in Russian space station Mir. Further, UV resistant bacterium, *Sphingomonas paucimobilis* (90.8% identification) in the chemoheterotroph Pseudomonadaceae, was isolated by comparing with radioresistant *E. coli* B/r strain.

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PREVENTION OF SPACE RADIATION EXPOSURE ON BONE

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One of the major problems in space is the decrease of bone mineral density and bone volume. This is caused by microgravity and space radiation. Thus, it is important to conduct an experimental study to prevent space radiation exposure on bone.

At present, there are two kinds of compounds to improve bone metabolism and to maintain and increase bone volume. One has an inhibiting effect of bone absorption, acting on otsteoclast cells, for example, bisphosphonates, and the other has an enhancing effect of bone formation, acting on osteoblast cells like statins. NASA is investigating bisphosphonate medication for astronauts. However, the compounds may cause some unknown side effects if they are given for a long term.

In this experimental study, we focus on Milk Basic Protein, which is a product separated and purified from fresh milk. Three-month-old female rats and nine-month-old year female rats were given a 100mg/kg of Milk Basic Protein and a 2mg/kg statins by oral administration and also given a subcutaneous injection of 3mg/kg bisphosphonate after whole-body HIMAC irradiation for 6 weeks everyday. Then we measured tibial bone mineral density using peripheral quantitative computed tomography.

The results show that Milk Basic Protein was not able to increase bone mineral density in comparison with bisphosphonate and statins. Further studies must be conducted to find effects of pre-medication and long-term medication.

APOLIPOPROTEIN E EXPRESSION AND BEHAVIORAL TOXICOLOGY OF HEAVY PARTICLE IRRADIATION

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BACKGROUND: Previous studies have suggested that exposure of the central nervous system to high charge, high energy (HZE) particles such as those encountered in deep space triggers behavioral changes. None of this prior work has examined the effect of genotype on the behavioral toxicity of HZE radiation. Apolipoprotein E (ApoE) is a 34 kD protein which is expressed in high concentration in the central nervous system. Three different apoE gene alleles are found in humans, epsilon 3 (allelic frequency: 84%), epsilon 4 (allelic frequency: 12%), and epsilon 2 (allelic frequency: 4%). Possession of the epsilon 4 gene has been repeatedly shown in epidemiological studies to be a genetic risk factor for late onset Alzheimer's disease. It is also known that apolipoplotein E (ApoE) genotype affects CNS response to many types of injury, and that inability to produce ApoE protein increases the susceptibility to neurotrauma and cerebral ischemia. It is presently unknown whether ApoE expression affects brain response to radiation. In the present study, we investigated whether ApoE affects neurobehavioral abnormalities after HZE particle irradiation using a genetically engineered ApoE knockout mouse line.
METHOD: Sixteen male ApoE gene knockout (ApoE KO) mice and sixteen male genetically matched wild-type C57BL mice were used in this experiment. Half of the ApoE knockout and half of the wild-type animals were irradiated with 2 Gy in an ion particle beam (whole body radiation) at the Brookhaven National Laboratories. Neurological and neurobehavioral examinations were performed at regular intervals for up to 6 months after irradiation:
RESULTS: Rotarod latencies of irradiated-mice were significantly shorter than those of sham-irradiated mice in both Apo E KO and wild type groups as assessed 30 days after irradiation. Sixty days after radiation, the radiation effect was lost in wild type animals, but still observed in HZE irradiated Apo E KO mice. In the Morris water maze test of spatial reference memory, we observed a significant increase in latencies to find a submerged platform only in irradiated ApoE KO mice. In open field test, locomotor activity was significantly decreased in irradiated ApoE KO mice compared with sham-irradiated mice.
CONCLUSION: Our study suggests that ApoE expression may influence the neurobehavioral and cognitive deterioration that can occur after heavy particle irradiation.

INDUCTION OF MICRONUCLEI AND P53 EXPRESSION BY SPACE FLIGHT IN CULTURED MAMMALIAN CELLS

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To examine the possible synergistic effects of space radiation and microgravity on radiobiological responses, we sent four cultured mammalian cell strains into space by the Space Shuttle Discovery (STS-95 mission). After 9-day flight, we analyzed frequencies of micronuclei and cellular amounts of

stress-responsive proteins such as P53 and mitogen activated protein kinases (MAPKs). Cell strains used were; human tumor MCF7 cells, AT2KY cells derived from an ataxia telangiectasia patient, mouse m5S cells and Syrian hamster embryo (SHE) cells. Frequencies of micronuclei in flight cultures of MCF7, AT2KY and SHE cells were almost the same with those of ground controls. In m5S cells, micronucleus frequency in flight sample was slightly higher than control, but the difference appears to be within a limit of experimental variation. Cellular levels of stress-inducible proteins were measured with MCF7 and m5S cells by Western blotting. In MCF7 cells significant accumulation of P53 and P21 proteins were detected, however, no differences were observed between flight and ground control samples. Only small amounts of P53 were present in both flight and control m5S cells. Similarly, there were no marked differences between flight and control cultures of MCF7 and m5S in the amounts of three activated (phosphorylated) forms of MAPKs, SUPK/JNK, p38 MAPK, and extracellular regulator kinase (ERK1/2). Altogether, these results indicate that, at least under the present flight conditions, neither space radiation nor microgravity induced excess micronuclei and increased accumulation of stress-responsive proteins.

RADIATION-INDUCED GENOMIC INSTABILITY - INVOLVEMENT OF TELOMERE DYSFUNCTION

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Radiation induces genomic instability in the descendants of surviving cells. Delayed chromosome aberration is a sensitive biomarker for genomic instability. In the present study, we examined our working hypothesis that radiation induces delayed chromosome aberrations mediated by promotion of telomere dysfunction. Using irradiated mouse cells, we found that a dose-dependent increase of delayed formation of dicentrics that retained telomere sequences at a fused position, suggesting that radiation promotes telomere dysfunction. To know the stability of irradiated chromosomes, mouse A9 cells containing a human chromosome 4 or 11 were irradiated with 6 Gy or 15 Gy of X-rays, and then an irradiated human chromosome was transferred into unirradiated mouse m5S cells using a microcell-mediated chromosome transfer. The stability of the irradiated human chromosome was analyzed by whole chromosome painting specific for human chromosome 4 or 11. In the m5S cells transferred with 15 Gy-irradiated chromosome 11, all chromosomes 11 were fragmented and 45% of the chromosomes 11 was rearranged after chromosome transfer. Similarly, in the cells transferred with 6 Gy-irradiated chromosome 11, 24% and 43% of the chromosomes 11 were rearranged to form rings and telomeric-fusion chromosomes, respectively, possibly due to telomere dysfunction. These results suggest that the irradiated chromosome per se possesses unstable nature and indicate further that telomere dysfunction induced by radiation is involved in the induction of delayed chromosome aberrations.

MICRONUCLEI INDUCED BY LOW DOSE RATE IRRADIATION IN EARLY SPERMATIDS OF p53 NULL AND WILD MICE

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The major risks of low-level radiation are mutagenesis, teratogenesis and carcinogenesis. To obtain

evidence of the dose-rate effect on induction of micronuclei, we observed the frequencies of micronuclei in early spermatids of wild-type p53(+/+), heterozygous p53(+/-) and null p53(-/-) mice exposed to gamma rays at high (1,020 mGy/min) or low (1.2 mGy/min) dose-rates. The frequencies of micronuclei in spermatids were measured about 2 weeks after irradiation and later. The frequencies of micronuclei increased dose dependently in all strains when given at 1,020 mGy/min. These data were found to be best fitted by a linear-quadratic dose-response model. The frequencies at 1.2 mGy/min also increased dose dependently in all strains, however these were best fitted by a linear dose-response model. The yields at 1.2 mGy/min were significantly lower than that at 1,020 mGy/min in the same manner of all strains. Testis weight declined to the minimum levels 4 weeks after 3 Gy irradiation in the same degree for both p53(+/+) and p53(-/-) mice when given at 1,020 mGy/min, and gradually recovered. In our other studies, we observed the complete elimination both of malformation in fetuses and mutant T-lymphocytes defective in T-cell receptor gene expression in p53(+/+) mice. This indicates that concerted DNA repair and p53-dependent apoptosis are likely to completely eliminate mutagenic damage at low doses or dose-rates. In the germ cell, however, irradiation at1.2 mGy/min was mutagenic independent of p53 gene.

THE EFFECTS OF MICROGRAVITY ON LIGASE ACTIVITY IN DNA REPAIR OF DOUBLE-STRAND BREAKS DURING SPACE FLIGHT

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In recent years, some contradictory data about the effects of microgravity on radiation-induced biological responses in space experiments have been reported. The aim of the present study was to clarify whether enzymatic repair of DNA double-strand breaks is affected by microgravity using an *in vitro* enzymatic reaction system. We measured the DNA repair activity *in vitro* of T4 DNA ligase as a DNA substrate damaged by restriction enzyme digestion under microgravity (Discovery; STS-91). After the flight, the amount of ligated DNA molecules was measured using electrophoresis methods. In the space sample, the ligated products (closed circular DNA, open circular DNA and multimeric ligated products) were produced by T4 DNA ligase activity for double-strand break DNA, and increased with increasing T4 DNA ligase concentration (0-3 Units per μg of plasmid DNA). We detected almost no difference in T4 DNA ligase activity between the space experiments and the control ground experiments. No significant effect of microgravity on ligation of damaged DNA was found during space flight. Therefore, other mechanisms must account for the synergism between radiation and microgravity, if it exists.

THE EFFECTS OF MICROGRAVITY ON INDUCED MUTATION IN *Escherichia coli* AND *Saccharomyces cerevisiae* DURING SPACE FLIGHT

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We examined whether microgravity influences the induced-mutation frequencies (space shuttle Discovery, STS-91). We prepared dried samples of repair-deficient cells and the parental cells of *Escherichia* (*E.*) *coli* and *Saccharomyces* (*S.*) *cerevisiae* given DNA damage treatments of UV, X-ray and N-methyl-N-nitroso urea (MNU) before flight. To succeed the space experiment, we developed a new experimental apparatus to culture in space from freeze stocks of *E. coli* and *S. cerevisiae* cells. After

culture in space, the induced-mutation frequencies and SOS-responses were fixed under microgravity. The experimental findings indicate that induced-mutation frequencies and SOS-response activities of space samples were almost the same level as compared with the ground control samples in both strains. It is suggested that microgravity might not influence them. Therefore, we speculate that microgravity might affect not at all DNA replication and/or DNA repair in their all stages.

ESTABLISHMENT OF A HUMAN CELL STRAIN, GSA-1, WITH HIGH SENSITIVITY TO THE APOPTOTIC EFFECTS OF GRAVITY-CHANGING STRESS

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The induction of apoptosis by gravity-changing stress is considered as one of the important causes of cellular damage in spaceflight, although the molecular mechanisms of the apoptotic event remain unclarified. Therefore, it is valuable for the elucidation of the apoptosis mechanism to develop human cell lines which are easily cultured *in vitro* and characterized to be highly sensitive to gravity-changing stress. In this study, we tried to establish a cell line, in which apoptosis was significantly induced after a gravity-changing stress load. We developed cell lines from ethyl metanesulfonate-treated human RSa cells which were previously established by infection with SV40 and Rous sarcoma virus. From the cell lines, we selected GSA-1 as a cell line with high sensitivity to gravity-changing stress. Apoptotic events were observed in 20 % of GSA-1 cells exposed to gravity-changing stress alone, while RSa cells showed only 4%. Furthermore, the apoptosis was augmented by UV irradiation after exposure to gravity-changing stress. Treatment with caspase 3 inhibitor reduced the ratio of apoptotic events in GSA-1 cells. GSA-1 cells are suggested to be highly sensitive to the appoptotic effects of gravity-changing stress, possibly via caspase 3 induction. Comparative analysis of GSA-1 cells and the parent RSa cells may be useful to investigate the mechanism of apoptosis under gravity-changing stress.

DIFFERENTIATION OF *Dictyostelium discoideum* DURING SPACE FLIGHT

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We previously reported that the emerged amoebae of *Dictyosterium* (*D.*) *discoideum* grew, aggregated and differentiated to fruiting bodies with normal morphology in space. Here, we investigated the effects of space radiation and/or microgravity on the number, viability, kinetics of germination and mutation frequency of spores formed in space in a radiation-sensitive strain, □s13, and the parental strain, NC4. In □s13, there were hardly spores in the fruiting bodies formed in space. In NC4, however, we found about half amount of spores, a delay in germination of the spores and delayed start of cell growth of the spores formed in space when compared to the ground control. However, the mutation frequency of the NC4 spores formed in space was similar to that of the ground control. We conclude that the depression of spore formation might be induced by microgravity and/or space radiation through the depression of some stage(s) of DNA repair during cell differentiation in the slime mold.

MOLECULAR NATURE OF MUTATIONS INDUCED BY REPEATED LOW-DOSE OF X-RAYS IN DIFFERENT TISSUES OF LACZ-TRANSGENIC MICE

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Mutation induction is one of the radiation effects which are assumed to play important roles in long-term effects of radiation. Although it is well established that the biological effects of radiation differs significantly between a single acute exposure and a protoracted or fractionated irradiation, little is known about dose fractionation effects in mutation induction. Here we have examined molecular characteristics of mutations induced by repeated low-dose of X-ray exposure in somatic and germ line tissues. The results were compared to those induced by a single acute dose of radiation. The mice used were lacZ-transgenic Muta^{TM}. The tissues examined were spleen, liver, brain and testis. Ae dose of 0.15Gy was given 3 times a week on Mon, Wed and Fri, and repeated for 6 months, which resulted in 78 times of exposure and the total dose of 11.7Gy. After the completion of the irradiation, we waited 4 months and excised the tissues. Mutation in the lacZ gene was examined by positive selection in the presence of P-gal using E. coli lacZ$^-$, galE$^-$. The mutant frequencies in irradiated mice showed 1.5 to 2 times higher rates than those found in unirradiated age-matched control mice. DNA sequencing analysis of the mutants revealed that the irradiation created higher frequency of deletion type mutation in all of the tissues examined. The size of deletion was mostly a few bases or less. Approximately one half of the deletion had no repeat sequences at the break points. Although the incidence was low, some mutants showed complex changes, which could be explained by a simultaneous occurrence of deletion and insertion. These molecular characteristics of mutation were similar to those found with a single acute irradiation.

GENOMIC INSTABILITY OF MUTATION INDUCTION IN NORMAL HUMAN FIBROBLASTS IRRADIATED WITH CHRONICALLY LOW-DOSE RADIATION IN HEAVY-ION RADIATION FIELD

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We have been studying the induction of genomic instability in mutation induction irradiated with chronically low-dose radiation in heavy-ion radiation field. Normal human fibroblasts were cultured in a CO_2 incubator, which was set in the irradiation room of heavy ions in the Heavy Ion Medical Accelerator in Chiba (HIMAC). We estimated the exposure dose, which was determined by a thermoluminescence dosimeter (TLD), to be 1.4 mGy per day when operating the HIMAC machine. The life-span of the irradiated cell population reduced to 70～94% of non-irradiated control cell population. There is evidence that the exposure of chronically low-dose radiation in heavy-ion radiation field promotes the life-span reduction in cellular level. The mutation frequency of the low-dose accumulated cell population in HPRT locus, which was determined as the number of 6-thioguanine resistant colonies, was much higher than that of non-irradiated cell population, when irradiated with defined doses of the challenging X rays. On the contrary, there was no observation of enhanced effect on cell killing between the low-dose accumulated and non-irradiated cell populations irradiated with defined doses of the challenging X rays. These findings show that genomic instability was induced in mutagenesis by the chronically low-dose irradiation in heavy-ion radiation field.

PRE-IRRADIATION AT A LOW-DOSE-RATE BLUNTED TUMOR SUPPRESSOR P53 RESPONSE

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To estimate the effects of space radiation on health of space crews, we aimed to clarify whether -ray-irradiation at a low-dose-rate interferes in a *p53* centered signal transduction pathway induced by radiation in human cultured cells (SAS/*neo*) and C57BL/6N mice. *In vitro* experiments, we found that challenging irradiation with X-rays (5.0 Gy) immediately after chronic irradiation (1.5 Gy, 1 mGy/min) resulted in lower levels of apoptosis than those observed after challenging treatment only. In addition, the levels of *p53* centered apoptosis-related proteins after challenging treatments were strongly correlated with the above phenomena. *In vivo* experiments, accumulation of p53 and Bax, and the induction of apoptosis were observed dose-dependently in mouse spleen 12 h after challenging irradiation with X-rays (3.0 Gy). However, we found significant suppression of the accumulation of p53 and Bax, and induction of apoptosis 12 h after challenge irradiation at 3.0 Gy with high-dose-rate following chronic pre-irradiation (1.5 Gy, 1 mGy/min). These findings suggest that chronic pre-irradiation suppressed p53 function through radiation-induced signaling and/or p53 stability.

THE EFFECT OF MICROGRAVITY ON INDUCED MUTATION THROUGH DNA SYNTHESIS DURING SPACE FLIGHT

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In recent years, some contradictory data about the effects of microgravity on radiation-induced biological responses in space experiments have been reported. We prepared a damaged template DNA produced with an alkylating agent (N-methyl-N-nitroso urea; MNU) as a template to measure incorrect base-incorporation during DNA replication under microgravity. We examined whether mutation frequency is affected by microgravity during DNA replication for a DNA template damaged by an alkylating agent. Using an *in vitro* enzymatic reaction system, DNA synthesis by *Taq* polymerase or polymerase III was done during a US space shuttle mission (Discovery, STS-91). After the flight, DNA replication and mutation frequencies were measured. We found that there was almost no effect of microgravity on DNA replication and mutation frequency. It is suggested that microgravity might not affect at the stage of substrate incorporation in the induced-mutation frequency.

DOSE AND DOSE-RATE EFFECTS OF X RAYS AND NEUTRONS ON T-LYMPHOMA APOPTOSIS: DEPENDENCY OF TP53 STATUS AND MULTIPOLAR INDUCTION IN APOPTOSIS RESISTANCE CELLS

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Mouse thymic lymphoma cells, whose TP53-status is normal (p53+/+), are susceptible to X-rays-induced apoptosis. On the other hand, mutagenized clonal cells, whose TP53 is mutated in both allele (p53-/-), are highly apoptosis-resistant to X-rays. Here we analyzed dose and dose-rate effects of neutrons-induced thymic apoptosis. The p53+/+ cells were markedly susceptible to neutrons-induced apoptotic cell death. The relative biological effectiveness (RBE) of neutrons was >2. However, the thymic apoptosis induced by neutrons was a dose-rate independent event as well as by X-rays. In addition, the p53-/- cells were resistant to neutrons-induced apoptosis and the irradiated non-apoptotic cells had multiple centrosomes. Western blot analysis showed that the level of centrosome proteins, gamma-tubulin and pericentrin, were not increased. Therefore, it is likely that the multipolar cells produced by neutrons-irradiation are caused by abnormal centrosome separation.

MUTATION FREQUENCY OF PLASMID DNA AND *Escherichia coli* BY LONG-TERM SPACE FLIGHT ON MIR

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To elucidate the biological influence of the space radiation, we studied the effects of long-term space flight on mutation of the bacterial *ribosomal protein L* gene (*rpsL*). We prepared the dried samples of plasmid DNA and repair-deficient and parental cells of *Escherichia* (*E*.) *coli.* After a 40-day space flight on board the Russian space station Mir, the mutation frequencies of the *rpsL* gene were estimated by transformation of *E .coli* and by assessment of the conversion of the *rpsL* wild-type phenotype (Sm^S) to its mutant phenotype (Sm^R). The experimental findings indicate that mutation frequencies of space samples were almost the same level as compared with the ground control samples in plasmid DNA and both strains. It is suggested that space radiation might not influence them.

RADIO-ADAPTIVE SURVIVAL RESPONSE IN MICE

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It is important to estimate health effects of space radiation on astronauts in long-term space missions. The health risk estimation as well as weight of devices for radiation protection might be influenced if there were radio-adaptive health effects. Our present study suggests the presence of such adaptive response induced after low or small dose radiation. Pre-irradiation with 0.05-0.10 Gy or 0.3-0.5 Gy of X-rays induces radio-resistance in mice of ICR and C57BL/6 strains 9-17 days or 2-2.5 months afterwards, respectively. The 30-day survival rate of the animals after challenging high dose X-rays was significantly increased, indicating that so-called bone-marrow death was prevented by the conditioning irradiations. Expression of p53 in the spleen, which will lead to cell apoptosis after high dose X-rays, was decreased by a small dose pre-irradiation with 0.45 Gy. Recovery of endogenous spleen colonies after high dose exposure, an indication for blood-forming stem cells, was significantly enhanced by the pre-irradiation. The lifespan investigation after 30-day survival rate observation is now in progress. The death rate of the two groups, the pre-irradiated and its control, seems to be proportional till now (on day about 300 after challenging exposure). An old preliminary experiment also shows that the 30-day survival rate was significantly increased after high dose X-rays in mice continuously administered with ^{137}Cs (gamma emitter) and ^{90}Sr (beta emitter) in drinking water.

THE MOLECULAR MECHANISM AND TIME-DEPENDENT DYNAMICS OF SELF-INDUCED RADIOPROTECTIVE EFFECT, HORMESIS AND RADIATION ANTAGONISM AT COMBINED IONIZING IRRADIATION OF DNA

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The problem and modeling of radiation stability of DNA and living organisms at action of free radicals and ionizing irradiation in space are studied. Our considerations suggest that the energy V(L) of interaction between the two end-pairs of DNA nucleotides on the opposite sites of a double break with width L (owing to detrimental action of irradiation) are totally under the control of: 1) Coloumb interaction of charges, distributed on a surfaces of these nucleotides; 2) Kasimier-like forces and dispersion features of dielectric permeabilities of the nucleotides (**A**denine, **T**hymine, **G**uanine**, C**ytosine) and intermolecular salt-aqueous medium. It was shown [1] that at low (natural) concentration of hydrated electrons ($\eta \leq 10^{-9}$) in intercellular liquid the energy of interaction of two end-pairs (AT-AT, CG-CG) has the anti-repair barrier V(L)=(2-3)kT at L=7-8 A. If η is increasing the barrier is reducing. All other transversal end-pairs experience only attraction. Other results of irradiation are generation of additional hydrated electrons and heavy ions. The formation of these electrons and ions influences the energy of interaction in two ways - changing the permeabilities and changing the Coloumb interaction.
From one hand irradiation leads to additional DNA breaks.
From the other one it leads to the controlled reducing of anti-repair barrier and possible double breaks autorepairing.
The time-dependent dynamics of DNA depolymerization, self-repairing at separated and combined action of free radicals, slight and intensive irradiation and low-dose action is studied and calculated. There are some main results of this investigation.

1). For the case of short-time irradiation we have the usual linear (additive) radiation effect: the number of double breaks is proportional to any radiation doses and total action of free radicals.
2). For the case of long-time action of weak intensity radiation (e.g., chronic space irradiation) we have the phenomenon of “hormesis” - decreasing of concentration of double breaks of DNA caused by free radicals and irradiation action with increasing of intensity of weak ionizing radiation.
3). For the case of combined action of two different kinds of irradiation the phenomenon of radiation antagonism take place: the number of DNA double breaks caused by action of one kind of intensive irradiation is decreasing with growing the intensity of other kind of weak irradiation.

[1] Pinchuk A.O., Vysotskii V.I // *Phys. Rev*.E, v. 63 (2001) p. 31904-31910

3. Biological effects and biomarkers of charged particle irradiation

EFFECTIVE MUTATION METHOD FOR PLANTS USING HEAVY-ION BEAMS

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We found that the ion beam is very effective in causing the mutagenesis of seed embryos at a particular stage during fertilization without damage to other plant tissues. We have isolated albino, periclinal chimera, sectorial chimera, herbicide-tolerant and salt-tolerant mutants in tobacco. Intact embryos in the flowers were irradiated with ^{14}N ions (135-MeV/u). The LET of the N ion corresponded to 28.5 keV/um. The M_1 seeds were harvested one month after irradiation. The changes in the M_1 progeny obtained from this experiment indicate that ion beams are far more effective than EMS treatment for mutagenesis. An albino mutant (*ali*) was isolated from the M_2 progeny. We have determined that the *ali* mutant resulted from a nuclear mutation. The plastid ultrastructure in leaf mesophyll cells of *ali* showed that the leaves were devoid of developed chloroplasts, and stacked thylakoid membranes could not be detected in the plastids. The expression of plastid-encoded genes for the photosynthesis system was greatly reduced in *ali*, but at the transcript level. Transcription of the nuclear-encoded *Lhc* and *rbcS* genes was almost the same as in WT plants. These results suggest that *ali* is a novel albino mutant in which the chloroplast gene expression is affected.

PROBLEM OF OXIDATIVE HOMEOSTASIS DISORDERS UNDER RADIATION FACTOR IMPACT AND OPTIONS FOR ITS CORRECTION

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Oxidative homeostasis status studies held for 1992 - 1999 in persons exposed to ionizing radiation within extended dose range included evaluation of lipid peroxidation (LPO) products content, activity of superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, reduced glutathione content, lysosome enzymes activity - β-galactosidase & β-glucosidase.
Received data indicate the stable pro-antioxidative equilibrium disorders with primary and intermediate LPO products accumulation, antioxidative system functional capacity exhaustion, its enzymatic branch depression, glutathione content decrease and lysosome membranes permeability elevation. Under altered pro-antioxidative equilibrium the organism vital functions are preserved on the definite level at the cost of less valuable and less important biological structures destruction with nervous, endocrine and immune systems reactive response. Stated problem requires the adequate approach in pharmacological management of organism vital functions with taking into account oxidative homeostasis individual peculiarities. Long-term human presence in space under various factors impact including the radiation one requires the anti-oxidative remedies application with taking into account the genetically determined anti-oxidative status. We proposed, applied and clinically tested seafood products, bee-farming products and phyto-preparations with anti-oxidative properties.

THERMORADIOTHERAPY COMBINED WITH ADENOVIRAL P53 GENE THERAPY IN HEAD AND NECK CARCINOMA CELL LINES

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In general, malignant head and neck tumors are treated surgically, often in conjunction with postoperative radiation therapy. However, in the treatment of head and neck tumors, it is important to preserve aesthetic features and functions. Therefore non-invasive treatments and methods are necessary.
In the present study, we report on the use of thermoradiotherapy with adenoviral p53 gene therapy to treat head and neck carcinoma cell lines, with the aim of establishing a conservative treatment that can be used clinically.
Among 9 head and neck carcinoma cell lines, 8 had a negative relationship between irradiation and hyperthermia at 43 or 44℃. This finding indicates that the combination of radiotherapy and thermotherapy is good approach for these cell lines. In fact, theses two therapies had a synergistic effect in 6 of 9. However, only one cell line was resistance to both irradiation and hyperthermia. To overcome this resistance, we added adenoviral p53 gene therapy in the thermoradiotherapy. In radiotherapy combined with adenoviral p53 gene therapy, 3 of 9 head and neck cell lines had a decreased survival rate compared with radiotherapy alone. In thermotherapy combined with p53 gene therapy, 3 at 44℃ and 5 at 43℃ of 8 head and neck squamous cell lines had a decreased survival rate compared with thermotherapy alone. Adenoviral p53 gene therapy increased the effects of both radiotherapy and thermotherapy in 3 of 8 head and neck squamous cell lines. In conclusion, thermoradiotherapy combined with adenoviral p53 gene therapy is effective in the head and neck carcinoma cell lines.

CYCLIN-DEPENDENT-KINASE INHIBITOR EXPRESSION IN IRRADIATED DIFFERENTIATING HUMAN LENS CELLS IN VITRO

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The goal of our research is to investigate mechanisms underlying proton-induced cataractogenesis allowing the development of strategies to intervene with countermeasures. Recent evidence indicates that relatively low doses of space radiation are causative of an increased incidence and early appearance of human cataracts (Cucinotta et al., Radiat. Res. 156: 460-466, 2001). Protons are the most prevalent particle contributing to radiation doses in space, however concomitant exposures to small doses of neutrons or heavy ions are likely significant to cataract incidence in space travel. It is important to understand the mechanisms of action that trigger cataract by each radiation quality found in space. Lens cells continue to differentiate throughout the lifetime of an organism. The cyclin-dependent kinase inhibitors (CDKI) $p21^{CIP1}$ (CDKN1a), $p27^{KIP1}$ and $p57^{KIP2}$ negatively regulate entry into S-phase of the cell cycle. In vivo, p57 is one of the earliest genes expressed during lens fiber cell differentiation and is required for cell cycle exit for fiber cell differentiation. p27 is also upregulated as fiber cell differentiation begins and spatial and temporal expression patterns appear to be different from p57. p21 can be transiently induced by either p53-dependent or p53-independent regulation, DNA damage-induced growth arrest, and in the terminal differentiation of post-mitotic cells. We have investigated CDKI expression in our model of human lens epithelial (HLE) cells that show markers of differentiation during growth on extra-cellular matrix derived from bovine corneal endothelial cells (Blakely et al., IOVS 41:3898, 2000). We have investigated changes in the expression of the CDKIs in a time course after exposure to graded doses of Xrays or protons. Our evidence with immunofluorescence and Western

analyses indicate dramatic radiation-induced changes in the expression of the CDKIs leading to a disruption of normal lens cell differentiation. This work was supported by NASA Grant #T-965W.

DIETARY RETINYL ACETATE EFFECTS ON GENE EXPRESSION AND CANCER INHIBITION IN RAT SKIN.

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NYU School of Medicine, Department of Environmental Medicine, New York, NY.Ionizing radiation, including electrons, is a strong inducer of cancer in rat skin, and dietary retinoids have shown potent cancer preventive activity in the same system. As an approach to a better understanding of how retinoids might inhibit radiation-induced cancer, this work focussed on discovering how a non-toxic, dietary dose (300 ppm in lab chow) of a naturally-occurring retinoid, retinyl acetate (RA), alters gene expression levels 24 hours after exposure of rat skin to electron radiation. A method based on oligonucleotide microarrays containing probes to 5285 known rat genes was used to identify genes whose expression levels were strongly altered (up or down by at least 5 fold) by electron radiation and substantially reversed (at least 2.5 fold) by dietary RA. These genes were grouped according to their known cellular functions *in vivo* as a means of identifying possible pathways involved in the radioprotective action of the retinoid. Versus control the radiation significantly altered 188 genes, and the retinoid altered 231 genes. Of the 188 genes altered by the radiation, 8 were strongly reversed by the retinoid. While radiation strongly affected the expression of differentiation, stress response, immune/inflammation and nucleic acid metabolism genes, primarily differentiation-related genes, including, keratin 14, ornithine decarboxylase (ODC), involucrin and Ca^{++} binding protein, were strongly reversed by the retinoid. These results point to differentiation genes, rather than stress response or other categories of genes, as the basis for the anti-radiogenic effect of dietary RA in rat epidermis. (Work supported by NASA and NIEHS)

LIGHT FLASH MEASUREMENTS ON BOARD MIR WITH SILEYE-2 EXPERIMENT

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We report on Light Flashes (LF) observations performed on board Mir space station with the SilEye-1 and -2 experiments. LF observations with the two SilEye experiments consist of the longest LF observation program ever performed in space. LF were originally predicted by Tobias in 1952 and observed for the first time on Apollo 11 mission; subsequently there were studied on Apollo, Skylab, and Apollo-Soyuz missions. LF consist of visual sensations in the eye of subjects exposed to relativistic particles. A number of dedicated observations in space and on ground accelerators have provided a wealth of data which however – due to the elusive and subjective nature of this effect – could not provide a clear answer to this phenomenon. In this work we report on observations performed on board Mir by six cosmonauts in the years 1995-1999. A total of 18 hours of observation in 19 sessions resulted in the observation of 145 LFs. LF rate is significantly lower than what observed in previous

experiments but consistent with an increased shielding (geomagnetical and hull) of Mir; in addition there is evidence of a reduction of LF observation with time of permanence in Space.

PROTON RADIATION-INDUCED MUTATIONS IN LACZ TRANSGENIC MICE

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The goal of our research is to quantify and characterize mutation events in tissues using a plasmid-based lacZ transgenic mouse mutation model system. In this system, multiple copies of the reporter transgene are inserted into every cell of the animal, allowing us to examine early and late radiation-induced responses in tissues that are not easily accessible using conventional methods. C57 lacZ mice were exposed to 0.1 – 4 Gy protons and tissues were harvested at 1, 8 and 16 weeks post irradiation. Dose-dependent proton-induced genetic alterations in the spleen at different times after exposure was evaluated by measuring the mutation frequencies (MF) in the surrogate lacZ transgene. We noted that there was a modest dose-dependent increase in MF at 1 week after exposure - 1.2 fold above spontaneous level after 0.5 Gy of protons, and 1.8-fold above spontaneous level after 4 Gy protons. The levels of induced MF were significantly higher (> 2-fold above spontaneous) at 8-weeks post irradiation after 0.5 Gy and 1 Gy of protons. Preliminary evidence also shows that doses higher than 2 Gy did not result in higher MFs. We hypothesize that, at high doses, damaged cells may be eliminated from tissues and therefore do not contribute to increased MF in late responses in the spleen. Work is now in progress to examine the spectrum of damage in the mutant transgenes as a function of dose and time after irradiation. Our findings highlight the importance of examining both the temporal and dose-dependence in radiation responses in vivo. This work was supported by NSBRI through NASA Cooperative Agreement NCC 9-58.

CLUSTERIN IS A LOW DOSE IONIZING RADIATION INDUCED PROTEIN THAT IS TRANSCRIPTIONALLY REGULATED BY THE TUMR SUPPRESSOR PROTEIN, p53.

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Clusterin (CLU) has been implicated in a multitude of biological and pathological processes. The function of clusterin is still unknown. Our laboratory identified CLU as a x-ray induced protein/transcript that could interact with the DNA double strand break repair protein, Ku70, implicating a possible role for CLU in DNA repair. This led us to propose the existence of a nuclear form of this protein (nCLU). While secretory clusterin (sCLU) is thought to be cytoprotective, nCLU is cytotoxic. We have shown sCLU to be induced by as low as 2 cGy IR, suggesting a role for sCLU in possible bystander effects after low dose IR exposures and its potential utility as a biomarker for low dose exposures. Determining the transcriptional regulation of sCLU will allow us to better understand its function after IR. The p53 protein is stabilized in response to genotoxic stress and acts as a transcription factor for genes resulting in either cell cycle arrest or apoptosis. Several lines of evidence suggest that sCLU is transcriptionally repressed by p53. (A) HCT116 colon cancer cells that are p53 null show a dramatic induction of sCLU after IR as compared to cells that contain wild-type p53; (B) MCF-7 cells that contain the HPV-16 E6 protein have an earlier induction of sCLU after IR as compared to cells without E6; and (C) administration of leptomycin B completely abolishes the induction of sCLU after IR. Current work is focused on better understanding the mechanisms underlying p53 suppression of the gene, as well as transcription factors needed for IR induction.

IMPLEMENTATION OF GY-EQ FOR DETERMINISTIC EFFECTS LIMITATION IN SHIELD DESIGN

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In addition to the career exposure limits, the space program has dose rate limitations for three critical tissues to control deterministic effects. In a farther past, dose rate limitations were put on absorbed dose rates, although a more conservative approach of limiting dose equivalent rates was recommended in NCRP 98. More recently, NCRP 132 recommended that dose rate limitations be made on Gy-Eq rates using field dependent RBE for specific components. We address a consistent method of application of the RBEs, as defined by the NCRP. A problem in the application of the defined RBE is the inadequate definition of the neutron RBE across the spectrum in the space environment and the lack of a defined computational procedure for evaluation of Gy-Eq. The neutron RBE as given by the NCRP is shown in Table 1. We make a suggestion on the application of Table 1 to space exposures, although the NCRP recommendations cannot be applied without some ambiguities. We assume the RBE above 25 MeV to be 3.5, the same as that assumed by the NCRP on the range of 25 to 50 MeV. This leaves the suggestion for less than 1 MeV as follows:

$$\mathrm{RBE}(<1\ \mathrm{MeV}) = C/(B-A)$$

$$A = \int_0^1 C_T(E)\, \varphi_n(E)\, dE, \quad B = \int_0^\infty C_T(E)\, \varphi_n(E)\, dE, \quad C = \int_1^\infty \mathrm{RBE}(E)\, C_T(E)\, \varphi_n(E)\, dE$$

where $C_T(E)$ is the specific tissue neutron conversion factor, $\varphi_n(E)$ is the neutron fission spectrum, and RBE(E) is given in table 2. We assume the skin conversion factors to be similar to the ocular lens. We have evaluated RBE(<1 MeV) for U^{235} and Cf^{252} fission spectra and give results in table 2 for skin, lens, and BFO. An RBE value of 5.0 for neutrons below 1 MeV is considered well consistent with table 2.

Within the space program, the local tissue exposure field changes in composition with penetration depth and dosimetry is augmented with computational models to define the local tissue environment There is an added complication in applying field related quantities to local tissue exposures in a deterministic calculation, since the discontinuous nature of the associated field weighting factors (for example, see table 1) requires a discontinuous representation of the field related boundary conditions which rely on numerical interpolation in the computational procedure. In the case of neutrons, we can use the neutron conversion factors to evaluate an average neutron RBE for each specific neutron environment and evaluate the associated neutron Gy-Eq from the single field averaged RBE value as follows:

$$\mathrm{RBE}_{n,T} = \int dE\, \mathrm{RBE}_n(E)\, C_{n,T}(E)\, \varphi_n(E) / \int dE\, C_{n,T}(E)\, \varphi_n(E)$$

where $\varphi_n(E)$ is the neutron field spectra, $C_{n,T}(E)$ is the specific tissue conversion factor, and $\mathrm{RBE}_{n,T}$ is the field averaged RBE for the specific tissue. In the computation we find little difference in the average $\mathrm{RBE}_{n,T}$ for different tissues and take the largest value of the various tissues as the average RBE_n for the field averaged quantity. The computations are implemented by scaling the local particle fields into effective fields scaled according to the field RBE and determine the correspond effective absorbed dose resulting from these effective fields which is numerically the Gy-Eq for the tissues as required.

Table 1. Neutron RBE(E) for Deterministic Effects (from NCRP 132).

Energy region	RBE value
Less than 1 MeV	RBE (fission neutrons)
1 to 5 MeV	6.0
5 to 50 MeV	3.5

Above 50 MeV	Not more than 1-50 MeV

Table 2. Values for RBE(< 1MeV) from Current Evaluation.

Tissue/Fission source	U-235	Cf-252
Skin, Lens	5.14	4.96
BFO	5.01	4.82

COSMIC RADIATION INDUCED CHROMOSOMAL ABERRATIONS IN HUMAN LYMPHOCYTES

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Since decades, elevated frequencies of dicentric chromosomes (DIC) in human lymphocytes have successfully been used as a biological dosimeter in cases of *acute*, often accidental exposures to ionizing radiation. As long as duration and time lags after exposure are small compared to the lifetime of DIC, their frequencies can also be used to assess doses from protracted, *chronic* irradiation. E.g., within the substantial range of uncertainties, the frequencies of DIC observed in cosmonauts are compatible with the frequencies expected from doses of low and high LET radiation to which they were exposed in LEO. On the other hand, frequencies of DIC detected in lymphocytes of civilian aviation crewmembers rarely correlate with the doses accumulated all along their professional career. For such long duration exposures with relatively low induction rates, the concomitant decay of DIC frequencies due to the removal during exposure of lymphocytes carrying DIC has to be taken into account. We present temporal profiles of frequencies of DIC during the exposure calculated with a model of exponential decay of DIC for some scenarios of chronic exposure to cosmic radiation. E.g., even after a 'heavily' shielded Mars mission, the expected frequencies of DIC in lymphocytes of astronauts will be 10 to 40 times higher than the terrestrial control levels. For air flight personnel we calculated the time profiles of frequencies of DIC in lymphocytes of a 'typical' pilot, a male cabin attendant and a female cabin attendant whose professional radiation exposures were recalculated for the actual flight routes flown during their entire flight career as recorded in detailed duty logs. These results demonstrate that experimental (epidemiological) studies concerning DIC in air or space flight personnel must explicitly take into consideration the temporal exposure profiles in the prospective study population and that the point in time at which blood samples are to be drawn must be selected accordingly.

THE EFFECT OF SINGLE HEAVY ION HIT ON THE MAMMALIAN CULTURED CELLS

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Considering the risk of space radiation environment, the effect of single heavy ion radiation becomes more important. Nevertheless less are known about this subject. Thus, to analyze the single ion effect

of heavy ion beam radiation on individual cells, we established a method for irradiating individual cells with heavy ion microbeam. CHO-K1 cells in exponential growth phase were used for irradiation. The cells were attached to the cell dish made by ion track detector CR-39 (100 µm thick). The position of the cells on CR-39 was pre-detected by fluorescent staining and registered to the position database. Thereafter the cells were irradiated with 17.5 MeV/u ^{20}Ne or 11.5 MeV/u ^{40}Ar ion beams semi-automatically according to the position in the database. After irradiation, the position and the number of ion tracks traversed the cell was detected with just in time etching of CR-39 with alkaline ethanol etching solution at 37ºC. The growths of the cells were observed individually up to 60 hours after irradiation. The continuous observation of the individual cell growth indicated that a single ion traversal of cell nucleolus resulted to the complete growth inhibition of the irradiated cells. The effect of cytoplasmic irradiation and, also, the bystander effect will be discussed.

ANALYSIS OF COMPLEX-TYPE CHROMOSOME EXCHANGES IN ASTRONAUTS' LYMPHOCYTES AFTER SPACE FLIGHT AS A BIOMARKER OF HIGH-LET EXPOSURE

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High-LET radiation induces a higher percentage of complex-type chromosome exchanges then low-LET radiation, and this can potentially be used as a biomarker of radiation quality. However, difficulties may arise in accurately estimating radiation-induced complex chromosome damage at first mitosis post irradiation. Previous studies have indicated that there is a delay in the expression of chromosome damage in metaphase that is mostly related to the late emergence of complex-type damage. It was suggested that the yield of complex chromosome damage could be underestimated when analyzing metaphase cells collected at one time point after irradiation, and chemically-induced PCC may be a more accurate system since problems with complicated cell-cycle delays are avoided.

Although heavy particles contribute only a few percent of an astronauts' over all radiation dose during space flight, the effect on biological damage and health risk may be significant. An increase in the ratio of complex to simple type exchanges post flight could estimate the degree of exposure to heavy particles.

We have obtained direct *in vivo* measurements of chromosome damage by comparing frequencies of exchanges in astronauts' blood lymphocytes before and after their respective flights. Chromosome damage was assessed by an *in situ* hybridization technique with a cocktail of 2 or 3 different chromosome painting probes. Although the frequency of total chromosome exchanges increased significantly after long-duration flights of approximately 3 months, there were few complex exchanges detected in either PCC or metaphase samples. However, pooled data for 9 astronauts revealed a significant increase in the frequency of complex exchanges detected shortly after flight, which could indicate the biological effects of exposure to charged particles. Results from this study will improve health risk estimations for astronauts.

DENSELY LOCATED DNA DAMAGE CAUSED A DELAY IN CELL-CYCLE PROGRESSION IN HUMAN LYMPHOBLASTOID CELLS EXPOSED TO FE-ION

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Human crew members are exposed to extraterrestrial radiation, consisting of protons and heavier charged particles in space. To develop the scientific basis for the protection of human from spaceradiation, it is important to investigate cellular effects of heavy-ion exposure. After heavy-ion, such as C-ion (22keV/µm) and Fe-ion (1000keV/µm) exposure, human lymphoblastoid cells (TK6) demonstrated a delay in accumulation of G2/M phase cells compared to X-ray. After particularly Fe-ion exposure, any

increase in the proportion of G2/M phase cells was not shown. To determine stalling at or passing through the particular phase of cell-cycle after Fe-ion exposure, S phase's cells pre-labeled with BrdU before exposure were chased after the irradiation. Only 6.3% of cells in S phase at the time of Fe-ion exposure, moved to G2/M phase until the period when 34% of cells moved there after X-ray exposure. The DNA damage densely occurred after Fe-ion exposure, are considered difficult to be repaired than those after X-ray exposure.
Therefore, we investigated DNA repair machinery after the radiation exposures. Phosphorylated H2X is shown to be localized at DNA double-strand break site, and Rad51 protein at recombination repair site. In contrast to the X-ray or 22keV/µm C-ion exposure, phosphorylated H2X and Rad51 foci were densely localized immediately after Fe-ion exposure. This striking result indicates that densely localized DNA damage occurs immediately after Fe-ion irradiation. Delayed cell-cycle progression after Fe-ion exposure is probably due to the difficulty in repair of such damage. These results suggested that cellular response after Fe-ion exposure would different from X-ray exposure.

CYTOSKELETAL AND FUNCTIONAL CHANGES IN BIOREACTOR ASSEMBELED THYROID TISSUE ORGANOIDS EXPOSED TO GAMMA RADIATION

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Tissue grown under microgravity was utilized to evaluate various aspects of complex tissue interactions. Thyroid tissue analogs were developed under conditions of very low-shear stress (bioreactor) with controlled replacement and removal of spent medium. FRTL-5 cells were grown to a stage of organization that was composed of multiple, integrated follicles resembling small thyroid glands prior to exposure to 3 Gy gamma radiation. Reactor vessels and control cells were harvested at 24, 48, 96 and 144 hours post exposure. Tissue samples were fixed and immunocytochemically labeled for actin, microtubules, integrins, integrin-□2, 3, V and □ 1 and 3. Tissues were assessed for changes induced by radiation and quantified by laser scanning cytometry. Supernatants were tested by ELISA to quantify changes in various protein products. Tissue architecture was disrupted by exposure to radiation. The structural organization of actin was the most obviously affected with a lack of orderly assembly. The levels of actin and microtubules were decreased more than 20% with time post irradiation and was more pronounced in the tissue analogs than in tissue grown in control flasks. The constitutive low-level expression of interferon-□ was unchanged. Active TGF-□1 was higher in the supernatants from the bioreactors, whereas total TGF-□ was not significantly different. Thyroxin release paralleled cell survival in the bioreactors and control tissue. Thus, the engineered tissue responses to radiation differed from those of conventional tissue culture conditions making it a potentially better mimic of the in vivo situation.

GENETIC CONTROL OF RADIATION SENSITIVITY

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The dose limits proposed for astronauts in space flight are different from those on the ground, though the basic philosophy of limiting the life-time risk of stochastic effects to 3% is preserved. Nevertheless the purpose of radiation protection remains to prevent deterministic effects of clinical significance and limit stochastic effects to acceptable levels. The levels proposed are based on the assumption that the human

population is uniform in its radiosensitivity. If sub-populations exist that are genetically predisposed to be radiation sensitive, then it would clearly be undesirable to choose individuals with such a background for long-term missions in space where substantial doses may be accumulated in a short time.
In humans, the only gene so far proven to have a major impact on sensitivity to ionizing radiations is the gene for Ataxia Telangiectasia (AT). Individuals with a defect in both copies of this gene are cancer prone, exquisitely radiosensitive and suffer from debilitating clinical problems. However, approximately 1 to 3% of the US population are AT heterozygotes, which are not readily identifiable except by direct sequencing of the gene involved. It would be expensive and time-consuming to discover in human subjects if AT heterozygotes are radiosensitive and so we resorted to the use of AT knock out mice.

We have shown that these animals are significantly more radiosensitive than their wild-type litter-mates for two biological endpoints:
a) Cataracts as an important and relevant deterministic effect
b) Oncogenic transformation in cultured embryo cells as a surrogate for carcinogenesis, the most relevant stochastic effect.

The other candidate genes that we are in the process of studying, using knock-out mice, include NBS, BRCA1 and HRAD 9.

COMPARISON OF BIOLOGICALLY BASED MULTISTAGE MODELS FOR ANALYSIS OF LUNG CANCER INCIDENCE ASSOCIATED WITH LOW DOSE EXPOSURE TO IONIZING RADIATION IN THE NATIONAL DOSE REGISTRY OF CANADA COHORT

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A new class of nested multistage models with exact multi-stage Armitage-Doll initiation followed by (one or more) clonal expansion stages prior to malignant conversion allows efficient optimization of continuous dose-response models using piecewise constant individual exposure patterns in cohort analysis, direct likelihood based comparison of models with and without clonal expansion, and subsequent exploration of “what if” situations. These methods are demonstrated in an analysis of lung cancer incidence in a cohort of over 190,000 individuals in the National Dose Registry of Canada with low-dose exposure to gamma and tritium ionizing radiation. We optimized a range of models including models with one to 10 Armitage-Doll initiation stages followed by a single clonal expansion stage, with transition rates tested for dose-responsiveness. The exact Armitage-Doll model (with one more stage but without clonal expansion) is nested within this class of models when the initiated cell birth and death rates are set to zero in the clonal expansion stage. Likelihood ratio tests utilizing a broad range of dose-response models indicate that the cell birth-death process (promotion) is necessary to provide good fits to the data. The apparently significant effects of low dose exposure to ionizing radiation on promotion may be associated with bystander effects in the irradiated tissue. We are extending the analysis to models with more than one clonal expansion stage.

SENSITIVITY TO ULTRAVIOLET-B RADIATION CORRELATES WITH THE LOW ABILITY IN CYCLOBUTANE PYRIMIDINE DIMER PHOTOREPAIR IN PLANT

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Ultraviolet-B (UV-B) radiation can damage plants, decreasing biomass and productivity. There is a great difference in the inhibitory effect of growth to UV-B among rice cultivars. We found that UV-B can suppress genes expression and protein synthesis of Rubisco, which is carbon assimilation enzyme of photosynthesis, in UV-sensitive cultivars more than UV-resistant one. These results indicated that plants with a decreased resistance to UV damage could show severer damage under increased UV-B accompanied by stratospheric ozone depletion. The aim of our study is improving UV-B resistance in plants by bioengineering or breeding programs. In order to make it, there is need to find the molecular origin of the sensitivity to UV-B.
UV-B radiation can induce photodamages in DNA. Cyclobutane pyrimidine dimer (CPD) that is major UV-induced DNA lesions can be lethal or mutagenic to organisms impeding replication and transcription. Plants possess two mechanisms to cope with such DNA damage. The first is the accumulation of UV-absorbing compounds, resulting in protection of the underlying tissue against UV-induced damages. Our previous data showed that the steady-state CPD levels in leaves of rice grown under chronic radiation in any culture were not so greatly influenced by the increased amounts of UV-absorbing compounds, although there was a significant positive correlation between the CPD levels induced by challenge UV-B exposure and the amount of UV-absorbing compounds. The other mechanism is the repair of DNA damage. Photorepair is the major pathway in plants for repairing CPD. We found that the sensitivity to UV-B could seriously correlate with the low ability in CPD photorepair in rice plants, and the photorepair deficiency in UV-sensitive Norin 1 rice resulted from a functionally altered photolyase. These results suggest that the photorepair capacity is a principal factor for determining UV-B sensitivity and the photolyase might be an excellent candidate for restoration by way of selective breeding or engineering in plants.

REPAIR SYSTEM FOR DNA DAMAGES IN MEIOTIC CELLS OF CAENORHABDITIS ELEGANS

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Sensitivity of meiotic cells to DNA damaging agents is little understood. The nematode Caenorhabditis elegans is a useful experimental organism for studies on the several processes of development and differentiation including meiosis. We have demonstrated that the meiotic pachytene nuclei are hyper-resistant to X-ray irradiation, but not to UV irradiation, whereas the early embryonic cells after fertilization and the full grown oocytes are not. The hyper-resistance in the meiotic nuclei is also observed against heavy ion-beam (carbon) irradiation. It is reported that the irradiation of heavy ion-beam caused 10bp- to 10kb-deletions. Following silencing of the Ce-rdh-1 (rad51/dmc1 (lim15) homolog 1) gene, which is a single recA-like gene in the C. elegans genome, by RNA interference, the meiotic cells become more sensitive to X-ray irradiation than the early embryonic cells. These results suggest that the meiotic cells are hyper-resistant to DNA strand breaks and gaps due to the high level of expression of enzyme(s) involved in meiotic homologous recombination. We have also found that the Ce-atl-1 (ATM/ATR like gene 1) is involved in the DNA repair system for both radiation and UV damages during meiosis.

REPAIR OF DNA DOUBLE STRAND BREAKS IN HUMAN CELLS INDUCED BY RESTRICTION ENZYME I-SCEI

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DNA double strand breaks (DSBs) spontaneously occurring or induced by ionizing irradiation are usually repaired in mammalian cells through either of two pathways: end-joining (EJ) or homologous recombination (HR). Although the former is predominant in mammalian cells, the relative contribution of each pathway is unclear. We introduced the restriction enzyme site I-SceI into the thymidine kinase (tk) gene of human lymphoblastoid cell line TK6 and established a system to investigate the fate of DSBs quantitatively and qualitatively. TK6 is heterozygous (tk+/-) for a point mutation in exon 4. We produced TSCE5 and TSCER2 cell lines from TK6 by gene targeting. We inserted into both cell lines a 31 bp DNA fragment containing an18 bp I-SceI site in intron 4 of the tk+ allele and, in TSCER2, a point mutation in exon 5, making it a compound heterozygote (tk-/-). When a DSB at the I-SceI site is repaired by EJ in TSCE5, it causes a deletion, permitting the cell to be isolated as a TK-deficient mutant. In TSCER2, on the other hand, when the DSB is repaired by HR between tk alleles, a tk+ allele is generated and the phenotype reverts. With introduction of the I-SceI expression vector (pCBASce), mutants from TSCE5 and revertants from TSCER2 appeared at the frequency of 10^{-4} and 10^{-6}, respectively, suggesting that EJ contributed to the repair of DSBs 100 times more frequently than HR. Analysis of the tk gene revealed that EJ mainly caused 100 to10,000 bp deletions with a 2 or 4 bp microhomology at the joint. Moreover, almost all revertants generated by HR were produced by gene conversion. This system should be useful as a model for repair of a single DSB induced by low-dose irradiation and as a tool to investigate the factors associated with DSB repair in mammalian cells.

FREQUENT REARRANGEMENT OF GENOMIC DNA BY AN ENDOGENEOUS RETROVIRUS IN RADIATION-INDUCED MYELOID LEUKEMIA CELLS OF C3H/HE INBRED MICE.

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Mouse genome contains 1000 copies of intracisternal A-particle (IAP) DNA element that is closely related with endogeneous retrovirus. The IAP RNA is reversely transcribed and the cDNA is inserted into genomic DNA by the retrotransposition mechanism. Since functions of the gene at or nearby the novel insertion site of IAP cDNA are modified, the IAP element is presumable as endogenous mutagen. We found that genomic DNA rearrangement by the IAP-mediated retrotransposition is augmented in the myeloid leukemia cells in C3H/He inbred mouse.
Radiation-induced tumors are originated from cells in regenerated tissues after serious damages by ionizing radiation. In the regenerated myeloid cells following irradiation of sublethal doses at 3Gys of x-ray, the transcription level of a limited type among structural variants of the IAP elements in the genome were increased. Rearrangements of genomic DNA by unique insertions of the limited type of IAP cDNA are found in all the cell lines of acute myeloid leukemia induced by the radiation. This type of retrotransposition was observed in limited cell lines of radiation-induced thymic lymphoma and was hardly detected in the cells of non-hematopoietic tumor including skin carcinoma and hepatic tumors. Similar activation was not observed in the most types of IAP element. These findings indicate that an activation of the limited type of IAP element by radiation damage contributes to the genomic instability in the myeloid cells in C3H.

INDUCTION OF AGE-RELATED CHANGES IN HIPPOCAMPAL NEUROGENESIS BY EXPOSURE TO ^{56}FE PARTICLES

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Exposure to particles of high energy and charge has been found to disrupt the dopaminergic system as well as the motor and cognitive behaviors mediated by this system in a similar fashion to that seen during the aging process. In the hippocampus, the proliferation of new neurons can be modulated both by aging and irradiation with ionizing particles. Likewise, the migration of newly formed cells to the granular cell layer is also affected by these processes. Thus, the present study was designed to investigate the effects of 2.5 Gy of 1GeV/n ^{56}Fe particles on neurogenesis in the dentate gyrus of rats using the nuclear proliferation marker 5-bromodeoxyuridine (BrdU). 10 male Sprague-Dawley rats (n=5 irradiated and n=5 controls) were exposed to whole-body irradiation, were sacrificed 28 days after the last BrdU injection (50mg/kg X 3days) and their brains were processed for immunohistochemistry. PSA-NCAM, a migration marker, was used to determine the migration pattern of precursor cells to the granular cell layer of the dentate gyrus. Results illustrate a decrease in the number of BrdU-positive cells, as well as different distribution of these cells, in the dentate gyrus of irradiated animals. Moreover, there is a decrease in PSA-NCAM expression in irradiated subjects when compared to non-irradiated controls. These changes are similar to those found in aged subjects.

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CHARACTERISTICS OF THYMIC LYMPHOMAS INDUCED BY CARBON IONS IN B6C3F1 MICE

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Biological effects of heavy ions have been extensively investigated using HIMAC synchrotron, and generally large RBEs for cell killing and mutation induction have been shown. One of major concern about heavy particles is its carcinogenic potential, but the data are still scanty. We investigated the induction of and cellular and molecular characteristics of thymic lymphomas (TLs) of B6C3F1 mice induced by carbon-ions and X-rays. The incidence of and latent period for the induction of TLs were similar between two TLs, although the size was distinctively smaller for carbon-ion-induced TLs. FACS analysis revealed little difference in the surface expression of T-cell differentiation antigens. However, molecular analysis revealed that high frequency of LOH was found on chromosomes 4, 11 and 19 in both two TLs, while that on chromosome 12 was much higher in X-ray-induced TLs than in carbon-ion-induced TLs. These results indicate that mechanistic differences exist between carbon-ion- and X-ray-induced lymphomagenesis.

ROLE OF p53 GENE IN APOPTOTIC REPAIR OF GENOTOXIC TISSUE DAMAGE IN MICE

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Experimental studies with mice have established that fetuses at midgestational stage are highly susceptible to malformation at high, but not low, doses of radiation. This suggests that when DNA damage is produced by a small amount of radiation, it is efficiently eliminated by DNA repair. However, DNA repair is not perfect. There must be defense mechanisms other than DNA repair. In order to elucidate the essential role of p53 gene in apoptotic tissue repair, we compared the incidence of radiation-induced malformations and abortions in wild-type p53(+/+) mice and null p53(–/–) mice. For p53(+/+) mice, an X-ray dose of 2 Gy given at a high dose-rate (450 mGy/min) to fetuses at 9.5 days of gestation was highly lethal and considerably teratogenic whereas it was only slightly lethal but highly teratogenic for p53(–/–) fetuses. However, when an equal dose of 2 Gy given at a 400-fold lower dose-rate (1.2 mGy/min), this dose became not teratogenic for p53(+/+) fetuses exhibiting p53-dependent apoptosis, whereas this dose remained teratogenic for p53(–/–) fetuses unable to carry out apoptosis. Similarly, after gamma-irradiation of p53(+/+) mice with 3 Gy, the mutation frequency of mice T-lymphocytes defective in T-cell receptor (TCR) gene expression was higher than the control level for acute exposure. However, when an equal dose of 3 Gy was given at a low dose-rate, the frequency of mutant T-lymphocytes did not increase at all for p53(+/+) mice whereas it remained mutagenic for p53(–/–) mice. Hence, complete elimination of teratogenic and mutagenic damage from irradiated tissues requires a concerted cooperation of two mechanisms; proficient DNA repair and p53-dependent apoptotic tissue repair.

FINE MAPPING OF LOH EVENTS IN SPONTANEOUS TK$^-$ MUTANTS OF THE HUMAN LYMPHOBLASTOID CELL LINE TK6

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Loss of heterozygousity (LOH) is the major chromosomal mutational events of thymidine kinase (TK)-deficient human lymphoblastoid cell line TK6, which harbors the heterozygous thymidine kinase locus. Analysis of the LOH events with 10 microsatellite markers spanning over the whole chromosome 17 showed the LOH extended over half of 17q toward the terminal end (Honma, M., et al, Molecular Carcinogenesis, 28: 203 – 214, 2000). Here we report an improved system which allows to map more precisely the LOH events on the chromosome 17 of TK6 cells. To map the LOH events in more detail, 38 microsatellite markers were selected from NCBI Gemome Database. The set of LOH markers allows us to map the LOH events on the chromosome 17 at average interval of 1.2 Mb. With the system, LOH events in 139 tk$^-$ mutants from the wild type cell line (20C) and 77 tk$^-$ mutants from the cell line deficient in p53 function (5E) have been determined. The results can be summarized as follows; i) there was a hot region of LOH events showing ~3 times higher incidences than that of the over all average, ii) the p53 function did not affect the spectrum of LOH, though the frequency of LOH was much higher in the p53 deficient cell line (5E) than in the wild type cell (20C), iii) an unique hot-spot of LOH was found at the site 47.3 to 48.4 Mb, which is specific to the wild type cell line 20C. The results may suggest that there

are preferred sites for LOH occurrence on the chromosome 17 which are independent of the cellular p53 function.

HEAVY-ION INDUCED ISOCHROMATID BREAKS AND ITS INFLUENCE ON G2 REPAIR KINETICS

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We report initial chromatid breaks in prematurely condensed G2 chromosomes following exposure to heavy ions of different LET, and the rejoining kinetics of chromatid and isochromatid breaks. Human fibroblast cells AG1522 were irradiated with γ-rays, energetic carbon (13 keV/□m, 80 keV/□m), silicon (55 keV/□m) and iron (140 keV/□m, 185 keV/□m, 440 keV/□m) ions. Chromosomes were prematurely condensed using calyculin A. Chromatid-type and isochromatid breaks in G2 cells were scored. The dose response curves for total chromatid breaks were linear. The RBE showed a LET dependent increase, peaking around 2.7 at 55 to 80 keV/□m and decreasing at higher-LET. The dose response curves for isochromatid-type breaks were linear for high-LET radiations, but linear-quadratic for γ-rays and 13 keV/□m carbon ions. The rejoining kinetics of isochromatid breaks was determined in G2-PCCs after several post-irradiation incubation times, ranging from 0 to 600 minutes. G2-fragments, the results of isochromatid break induction, decreased quickly with incubation time. The curve for kinetics of chromatid-type break rejoining showed a slight upward bowing with time after exposure to 440 keV/□m iron particles, probably due to isochromatid-isochromatid break rejoining. The formation of chromatid exchanges after high-LET irradiation appeared to be underestimated because isochromatid-isochromatid exchanges can not be detected.

BIOPHYSICAL ANALYSIS OF RISK BY LOW ION FLUENCES

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Both DNA double strand break formation and mutation induction after heavy ion exposure were measured were measured over a large range of energies and LET. Cross sections can be parametrised by a linear-quadratic dependence on LET. The data were used to evaluate the efficiency of DNA double strand breaks for cell killing and mutation induction. The resultant curves peak around an LET-value of around 100 keV/micron. This analysis can be used to assess the risk by low fluences of heavy ions as encountered in space. The basic assumption is that radiation leads to the formation of double strand breaks which are the starting points for mutations which in turn may lead to the initiation of tumour cells. It is shown that the probability for tumour initiation increases with LET passing a maximum around 100 keV/micron. The use of equivalent doses leads to a reduction of the number of cells hit but essentially not to a decrease of initiated cells. It is thus calculated that with an equivalent dose of 1 mSv the fraction of initiated cells lies around 1 in 100 000 000 000 and varies with LET by not more than a factor of 5. An extension of this way of reasoning has to take into account the number of potential tumour stem cells in the human body and has also to consider the possible influence of bystander effects.

CHARGE TRANSFER IN ION-BIO-MOLECULES INTERACTIONS AT KEV ENERGY REGION

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Theoretical investigation on charge transfer in collisions of Cq+, Oq+ ions (q = 1-6) with bio-molecules including H2O has been carried out in the energy region from a few tens of eV to several keV. Particular emphasis was placed on to carry out a careful study on the molecular orientation effect, and resulting molecular fragmentation analysis.

SYSTEM OF CELL IRRADIATION WITH A PRECISE NUMBER OF HEAVY IONS

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A single cell irradiation system has been developed for targeting cells individually with a precise number of high-LET heavy ions to elucidate radiobiological effects of exactly one particle and to investigate the interaction of damages produced by separate events. The system has been installed at high-energy collimated heavy ion microbeam apparatus under a vertical beam line of the JAERI-Takasaki AVF-cyclotron accelerator. Using the heavy ion microbeam apparatus, mammalian cells were irradiated in the atmosphere with a single or precise numbers of heavy ions, 13.0 MeV/u ^{20}Ne or 11.5 MeV/u ^{40}Ar, with a spatial resolution of a few microns. Positional data of the individual cells were obtained at the off-line microscope before irradiation, then the targeting and irradiation of the cells were performed semi-automatically at the on-line microscope of the microbeam apparatus according to the obtained data. The number of ions traversed the cells attached on the ion track detector CR-39 were counted with a plastic scintillator-photomultiplier tube assembly and a constant fraction discriminator. Immediately after irradiation, the ion track detector CR-39 was etched to check the spatial distribution of the irradiated ions.

ANALYSIS OF LOW DOSE RATE EFFECT OF RADIATION AND THE SYNERGISM WITH HIGH GRAVITY BY A NEW MUTATION ASSAY SYSTEM

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It is known that transformation and mutation induced by high LET-radiation were enhanced with decreased dose-rate (so-called, inverse dose-rate effect), while cell toxicity was unchanged. This evidence implies that radiation risks would be elevated under occupational conditions in space, since astronauts would be exposed to high LET-radiation, known as cosmic-rays, over a long period of time. However, it is difficult to obtain the statistical significant data of the inverse dose-rate effect, which usually occurs at an exposure to low dose. To overcome this difficulty, we developed a new mutation

assay system with high sensitivity to radiation, and analyzed the inverse dose-rate effect and also the interaction between high gravity and radiation effect.
HPRT deficient hamster cells containing an exogeneous X-chromosome were irradiated with gamm-rays or neutrons, and after appropriate expression time, 6-TG-resistant clones were counted for HPRT mutation frequencies. Our new mutation assay system was appeared to be approximately 100-fold higher sensitive than that of conventional mutation assay system using rodent cell lines, such as V79 and m5S. These hybrid cells were exposed to neutrons of 1 Gy at dose rates ranging from 0.025 cGy/min to 1.5 cGy/min. The mutation frequencies were significantly increased with a decreased dose rate, namely, inverse dose-rate effect, especially below 0.1 cGy/min, and the frequencies at 0.025 cGy/min was 2-fold higher than that at 1.0 cGy/min. Subsequently, the types of mutation were analyzed with multiplex PCR of HPRT gene and the EST markers on X-chromosome. Elevated ratios of deletion type were observed in radiation-induced mutants, while this type was decreased at a lower-dose rate and close to the level of spontaneously occurred mutation. On the other hand, the interaction of high gravity and radiation was tested with 33.5G, which was generated by 500 rpm centrifugation. Significant synergism of mutation frequencies were observed with high gravity before or after irradiation, while modification of cell lethality was not detectable.

THE INDUCTION OF POINT AND DELETION MUTATIONS IN BACTERIAL CELLS BY HEAVY IONS

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The study of regularities and mechanisms of point (fepA$^-$, ton B$^-$) and deletion (ton B$^-$trp$^-$) mutation induction in E.coli cells by radiation with broad region of linear energy transfer (LET) was accomplished. It was shown that the frequency of point mutations as a function of the □-ray and heavy ion dose (helium and carbon ions with LET 20 - 200 keV/□m) is described by the linear-quadratic curves. The quadratic part of these curves is parallel shifted from the dependence with □-irradiation. The relative biological effectiveness (RBE) depends on LET as a function with a local maximum. The maximal biological effect reveals after helium ion irradiation with LET ≈ 20 keV/□m. The induction of deletion mutations by helium and carbon ions (LET = 20-200 keV/□m) is described by the linear function. The helium ions with LET=50 keV/□m are more effective in induction of deletion mutations than the carbon ions. The induction of mutagenic SOS repair in E.coli cells after irradiation by deuterons, helium and carbon ions was studied by using the SOS lux test. A genetically controlled luminescent bacterial reporter assay was developed for detection of cell SOS response. The bioassay is based on the recombinant plasmid pPLS-1, which was constructed as a derivative of pBR322, carrying the promoterless luxCDABFE genes of Photobacterium leiognathi downstream of a truncated cda gene from ColD with a strong SOS promoter. E.coli strain containing this construction are inducible to high levels of light production in the presence of agents that cause damage to the DNA of the cells or after irradiation. It was shown that the relationship of SOS induction potency (SOSIP) on LET has a local maximum in region of 50–60 keV/□m. The results that were obtained with bacterial cells indicate on the important role of cluster DNA damages in formation of point mutations. On the other hand, the formation of deletion mutations is connected with induction of direct and enzymatic double strands breaks of DNA.

APOPTOTIC REGULATION AND MUTAGENESIS IN HUMAN CELLS EXPOSED TO FE IONS OR PROTONS

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Exposure to ionizing radiation can elicit two modes of cell death – necrosis or apoptosis. In human lymphoid cells, the predominant mechanism of radiation-induced cell death is apoptosis. The most likely exposure of individual human cells to heavy ions (e.g. Fe) during spaceflight will result from single particle traversals. Here we report the fluence-response for apoptosis in human TK6 B-lymphoblasts and provide preliminary evidence that single Fe ion traversals can stimulate an apoptotic response. We have also explored the importance of apoptotic regulation on the frequency and spectrum of mutations arising after exposure to charged particles. We used isogenic derivatives of TK6 cells stably transfected with pSFFV-neo-bcl-x_L (encoding the anti-apoptotic gene BCL-X_L and the neomycin resistance gene) or with pSFFV-neo (encoding only the neomycin resistance gene). TK6-bclx_L cells were more susceptible to Fe ion-induced mutations at the TK1 locus than TK6-neo cells. Molecular analysis demonstrated that most Fe-ion-induced mutations arose by loss of heterozygosity (LOH). In TK6-bclx_L cells, more of the LOH occurred via mitotic recombination than in TK6-neo cells where the predominant mode of LOH was via deletion. We are currently mapping the LOH tracts to further define the biological bases for the differential sensitivity to Fe-ion-induced mutagenesis as a function of the genotype of the cell at risk. Experiments are underway to assess the sensitivity of TK6-bclx_L cells and TK6-neo cells to the cytotoxic and mutagenic effects of moderate doses of protons, the predominant charged particle radiation in space.

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ASSIGNMENT OF LONG-LIVED RADICALS WHICH INDUCE MUTATION IN THE IRRADIATED MAMMALIAN CELLS AS EXTRA-DNA BYSTANDER EFFECTS

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Although most of researchers in radiation biology have been interested in the relationship between biological phenomena and reactive oxygen species in the irradiated cells, we have studied long-lived radicals (LLR) in irradiated mammalian cells directly measured by electron spin resonance (ESR) spectroscopy. We have found that LLR are not responsible for cell death or chromosomal aberrations but for inducing mutation and transformation in the irradiated cells. The LLR were produced in mammalian cells by □- or X-ray irradiation at room temperature, and the half lifetime of the LLR is around 20 h after the irradiation. LLR are scavenged by the addition of L-ascorbic acid (AsA) and (-)-epigallocatechin-3-O-gallate (EGCG) at 20 min and 6 h after the irradiation, respectively, accompanying with the suppression of mutation simultaneously. No reactive oxygen species are remain when the additives were introduced to the cells because lifetimes of ROS are less than 1 ms. Therefore, LLR are responsible for inducing mutation. It is very interesting to know where the LLR are produced in the cells. Very recently we have assigned that LLR are not produced in DNA but in protein as sulfinyl radicals. This is a new kind of extra-DNA bystander effect that the radicals in protein induce DNA mutation.

THE FORMATION OF BRAGG PEAK AND THE INCREASED BIOLOGICAL EFFICIENCY OF STRONGLY SCATTERED LOW-ENERGY IONS

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The relative biological efficiency (RBE) of accelerated ions in different parts of Bragg peak is usually related to a corresponding LET (linear energy transfer) value at a given distance from the beam range limit. The LET value being established as an average energy transfer per one ion to a unit layer perpendicular to the original beam direction; i.e., per one ion having reached the corresponding layer.
It is evident that inactivation efficiency of different ions depends on energy transferred by an individual particle to a cell nucleus (or to its chromosomal system). The actually energy transferred to individual nuclei may not be, however, determined by LET values derived with the help of macroscopic measurements, especially when a strongly scattered ion moves approximately along a mentioned perpendicular layer.
The RBE established experimentally by Barendsen for alpha particles at different LET values have been analyzed and interpreted with the help of a mechanistic model taking into account the mentioned strong scattering of slowly moving ions. A greater number of cell nuclei in a perpendicular layer may be hit, but all energy transferred to these nuclei may be significantly lower than the energy transferred to the given layer by a corresponding particle. The hit numbers and the values of energy transferred to individual nuclei in different layers have been derived by fitting the mentioned experimental data. The given model enables to correlate the RBE and LET values to the values of absorbed dose at given positions of Bragg peak. The given mechanism predicts also that ion types should influence the RBE-LET dependence, which is indicated by some experimental data, as well.

IMPACT OF THE P53 STATUS ON THE EFFECT OF REACTOR NEUTRON BEAM IRRADIATION ON INTRATUMOR TOTAL AND QUIESCENT CELL POPULATIONS

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Human head and neck squamous cell carcinoma cells transfected with mutant p53 (SAS/mp53) or with neo vector as a control (SAS/neo) were inoculated subcutaneously into both the hind legs of Balb/cA nude mice. Mice bearing the tumors received 5-bromo-2'-deoxyuridine (BrdU) continuously to label all proliferating (P) cells in the tumors. After sodium borocaptate-^{10}B (BSH) or *p*-boronophenylalanine-^{10}B (BPA) administration, the tumors were irradiated with neutron beams. The tumors were then excised, minced and trypsinized. The tumor cell suspensions thus obtained were incubated with a cytokinesis blocker, and the MN frequency in cells without BrdU labeling (= quiescent (Q) cells) was determined using immunofluorescence staining for BrdU. Meanwhile, 6 h after irradiation, tumor cell suspensions obtained in the same manner were used for determining the frequency of apoptosis in Q cells. Without ^{10}B-compounds, in both tumors, relative biological effectiveness (RBE) of neutrons was larger in Q cells than in total cells. With ^{10}B-compounds, both frequencies were increased for each cell population, especially for total cells. BPA increased both frequencies for total cells more than BSH. Nevertheless, the sensitivity of Q cells treated with BPA was lower than that in BSH-treated Q cells. These sensitization patterns in combination with ^{10}B-compounds were more remarkable in SAS/mp53 than in SAS/neo tumors. The p53 status had the potential to influence on intratumor ^{10}B distribution.

INDUCTION OF RADIORESISTANCE TO ACCELERATED CARBON-ION BEAMS BY A NITRIC OXIDE-MEDIATED BYSTANDER EFFECT IN HUMAN GLIOBLASTOMA

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PURPOSE: To investigate whether nitric oxide (NO) excreted from the irradiated cells with accelerated carbon ion beams (C-beams) modulates cellular radiosensitivity against C-beams in human glioblastoma A-172 and T98G cells.
MATERIALS AND METHODS: Western blot analysis of inducible NO synthase (iNOS), hsp72 and p53, the concentration assay of nitrite in medium and cell survival assay after irradiation with C-beams were performed.
RESULTS: The accumulation of iNOS was caused by C-beam irradiation of T98G cells but not of A-172 cells. The accumulation of hsp72 and p53 was observed in A-172 cells after exposure to the conditioned medium of the irradiated T98G cells with C-beams, and the accumulation was abolished by the addition of an inhibitor for iNOS to the medium. The radiosensitivity of A-172 cells was reduced in the conditioned medium of the irradiated T98G cells with C-beams compared with conventional fresh growth medium, and the reduction of radiosensitivity was dissolved by the addition of a specific iNOS inhibitor to the conditioned medium.
CONCLUSIONS: NO excreted from the irradiated donor cells with C-beams could modulate radiosensitivity of the recipient cells against C-beams. These findings indicate the importance of an intercellular signal transduction pathway initiated by NO in the cellular response to accelerated heavy ions.

MUTANT FLOWER OF DAHLIA (*Dahlia pinnata* Cav.) INDUCED BY HEAVY-ION BEAMS

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Dahlia is one of the important crop for cut flower industry during winter time in Horoshima City. However, the number of the varieties, which are adapted for winter production, is quite limited. Radiation has been conducted as an easy and reliable method to induce artificial mutations in the breeding of many plant species. We conducted an experiment using treatments of heavy-ion beams for the induction of mutations in agronomic traits with marketability. Irradiation treatments were conducted on the small shoots (approximately 1 cm in length) of the pink-flower dahlia cv. ‘Miharu’, which were grown in vitro in a modified Murashige and Skoog medium, in the dose range of 5, 10, 20, 50 and 100 Gy for N-ions. More than 10 mutated clones were selected as promising strains for the market, such as clones with the change in flower colors or change in the number of flower petals. A change in flower traits in a given species is sometimes attributable to their chimeric characteristics. Thus, further experimentation should be conducted to evaluate the stability of these promising strains.

THE EFFECT OF COSMIC RADIATION ON SILKWORM EGGS

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We investigated the lethal and mutageneic effects of cosmic radiation on silkworm eggs, using the Radiation Monitoring Container and Dosimeter in the Russian space station "Mir" as part of the first MIR

utilization space experiment. In hatching and pupation, there was difference in survival rate between the launched eggs and the eggs on the earth. But, in emergence, there was no difference in it between them. In order to detect the mutation frequency, we used the specific locus method using the egg-color gene pe and re located on the fifth chromosome. The mutation frequency was 12.4×10^{-3} in space, as compared with controls, it was very high. We think that the cause is the effect of cosmic rays and micro gravity.

CELL-CYCLE DEPENDENT EXPRESSION AND RADIATION INDUCED PHOSPHORYLATION OF HISTONE H2AX IN MAMMALIAN CELLS

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The mouse histone H2AX has unique C-terminal Ser residues, which are phosphorylated by ionizing radiation, implicating its role in the maintenance of genomic stability in response to DNA double strand breaks. We found that the gene was expressed in thymus, spleen, testis, intestine and in cell-cycle dependent manner. The mRNA level was high in S-phase. We found CCAAT box and E2F element in the promoter. Gel-shift and CAT assay revealed the importance of these element for transcription. Thus, the transcription was cell-cycle dependent, however, histone H2AX protein was rather stable and detected most of cells in various tissues and in every cell-cycle stage without phosphorylation. In contrast, by X-ray irradiation, histone H2AX protein was phosphorylated in thymus, spleen and intestine. In testis, spermatocytes in leptotene stage were stained by anti-phosphorylated H2AX antibody indicating its binding to the meiosis-specific DNA double strand break for synapsis and meiotic recombination. Thus we think that histone H2AX may have some roles in non-phosphorylated form as well as phosphorylated form in response to DNA damage and meiosis.

RADIATION MODULATED GENE EXPRESSION IN THE NEMATODE C. ELEGANS

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We use the nematode C. elegans to characterize the genotoxic and cytotoxic effects of ionizing radiation with emphasis on determining the specific effects of charged particle radiation as functions of its charge and specific energy. This model has proven useful and efficient in describing the fluence vs. response relationships for mutation, chromosome aberration and certain developmental errors. These endpoints, however, quantify the biological reactions in their end stages after complex repair and compensation pathways have completed their work. In order to address these reactions and their control we have turned to gene expression profiling. Using this approach, our goal is to detect the component genes in the radiation response and to identify those components that uniquely respond to high LET species or respond differentially as a function of radiation properties. Previously, we demonstrated by differential display RT-PCR that 90% of 222 radiation regulated mRNA sequences responded in a LET-specific reaction to gamma, proton or iron ion radiation; some of these genes were identified by sequencing the PCR products. In order to gain a more complete understanding of this observation we turned to DNA microarray techniques because the entire C. elegans genome could be profiled simultaneously.
In collaboration with the Stanford Microarray Consortium we are examining the gene expression profiles for worms exposed to gamma rays, accelerated protons and accelerated ion and silicon ions. Using statistical methods such as clustering, the expression profiles are being compared to each other and to profiles determined by the consortium for developmental stage, gender, and environmental stresses. As an example of observations from one gamma ray exposure condition we found that 5.4% of 19,600 genes

satisfied a signal to noise criteria for significant radiation induced regulation. Of the 100 most up-regulated genes we found that: 1) chromosome distribution was uniform except for the X chromosome, 2) identified genes tended to be associated with late larval stage regulation, and 3) there was a 2:1 gender bias in terms of male specific gene expression. Of these 100 genes the distribution amongst cellular functions was as follows: 15 kinases and phosphatases, 8 proteases, inhibitors, or elements of ubiquitin metabolism, 5 lipid and sterol enzymes, 6 major sperm proteins, 5 cytoskeleton components and 3 collagens, 7 nucleic acid or chromatin processing and binding proteins, 1 cell cycle and 1 apoptosis protein, 5 translation and transcription complex proteins, 2 transcription factors, 3 G-protein family members, 1 steroid hormone receptor, 3 transport proteins and 1 ion channel, 2 metabolic enzymes and 32 proteins of unknown function or insufficient data. The emerging picture is clearly complex and lists such as that above must be synthesized into potential pathways and functional responses to guide further investigation. We will present the most updated account of this analysis.

PARTICLE RADIATION EFFECTS OF MOUSE BRAIN CELLS IN VITRO

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Central nervous system or CNS is organized from several cell components of which radiosensitivity differ to each other (Nojima 1999). We have reported that irradiation with X-ray and 290MeV/n carbon ions, 400MeV/n neon ions, 490MeV/n argon ions, 500MeV/n silicon ions and 500MeV/n ion ions preferentially suppressed the growth of microglia, astrocyte and neurons in primary culture of mixed brain cells. We here investigated that low dose radiation induced apoptosis of brain cells in vitro. Brain cells of neonatal C3H, B6 and Scid mice were monodispersed to single cells and plated into culture bottles. Apoptotic cells were identified as Hoechst 33342 staining; they appeared 12hrs after irradiation. Apoptotic cells indicated the dose dependence in 5-200cGy reagion. We are also investigating significance of mouse strain and of particle's LET dependence of radiation-induced apoptosis of brain cells in vitro.

PARTICLE RADIATION EFECTS OF MICE HEMATOPOIETIC STEM CELLS IN VIVO.

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Radiation-indused myeloid leukemia resulted from the whole-body X-ray irradiation of C3H/He mice (Seki 1991). Three was most effective dose for hematopoietic tissues, and induced leukemia attained maximal incidence within 2 years after the irradiation. The hematopoietic stem cells were radiation sensitive cells, located in spleen and bone marrow in mice, and they differentiated mature peripheral blood cells. The peripheral blood cells and granulocyte-monocyte colony forming unit (GM-CFU) disapeared after the whole-body 3Gy X-ray irradiation, and recovered 3 weeks after the irradiation (Nojima 1995). We investigated here the effects of whole-body irradiation with beams of carbon-ions, neon-ions, silicon-ions, argon-ions, and iron-ions. We have recognized the regeneration of mouse peripheral blood cells and GM-CFU both in spleen and bone marrow after the irradiation.

EFFECTS OF THE X-IRRADIATION ON ENDOGENOUS ANTIOXIDANTS IN THE LIVER OF ACATALASEMIC MICE

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Changes in antioxidative capacity in response to irradiation would provide useful information to estimate the risk in space environment. We previously reported the increase in the level of endogenous antioxidants, including catalase (CAT), and glutathione (GSH) and the decrease in lipid peroxide level in the liver of C3H/HeN mice after irradiation with 0.5 Gy of X-rays. In the present study, we examined changes in the antioxidants and lipid peroxides in acatalasemic mice, which have low level CAT activity. Acatalasemic mice (C3H/AnLCs^{b}Cs^{b}) and the control mice (C3H/AnLCs^{a}Cs^{a}) were exposed to X-rays (125 kVp, 10 mA, Cu 0.5 mm-Al 1.0 mm) at a single dose of 0.5 Gy. Mice were sacrificed 3, 6 or 24 hr after exposure, and the livers were removed and examined. The lipid peroxide level in both the acatalasemic and the control was decreased significantly after irradiation. The CAT activity in acatalasemic mice was significantly increased after irradiation. GSH content of acatalasemic mice decreased though the content of the control mice increased. These results indicated that, although the mechanism might be different, 0.5 Gy of X-rays increased the antioxidative capacity regardless of the difference in the generic background.

HYPERGRAVITY MODIFIED THE SIGNAL OF IONIZING RADIATION THROUG p53

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Space environment mainly consists of microgravity and space radiation. But it is difficult to make the condition of microgravity on earth. Then we used hypergravity by centrifugal machine. We also used ionizing radiation by using X ray machine instead of space radiation. The signal transduction of p53 is very sensitive to ionizing radiation. Low dose radiation (0.5Gy) accumulated p53 at 1.5h and then, induced Waf-1or Bax in human glioblastoma cell line, A172. There was no report whether hypergravity may affect the p53 signal. We found that hypergravity (20g) also accumulated p53 at 3h and induced Waf-1 slightly in the cells. Then we investigated that hypergravity may modify the signal of ionizing radiation through p53. After the irradiation of low dose, the cells were incubated under the condition of hypergravity. The peak of accumulation of p53 shifted from 1.5h to 3h, and the induction of Waf-1 and Bax were suppressed entirely. We considered that the hypergravity modified the signal pathway of p53 by low dose of radiation.

RADIOADAPTIVE RESPONSE FOR PROTECTION AGAINST RADIATION-INDUCED TERATOGENESIS AND APOPTOSIS IN MOUSE SPLEEN AND THYMUS CELLS

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To clarify radioadaptive response in mice, we compared the incidence of radiation-induced malformations in ICR, and the frequencies of apoptosis in p53 (+/+) and p53 (+/-) mouse spleen and thymus cells. The ICR mice were exposed to an adapting dose of 0.02 Gy at the mid-gestational period and subsequently to a challenging dose of 2 Gy at 4 hours, and sacrificed on day 18.5 of gestation. The incidence of malformations, prenatal death and their body weights were studied. In the second

experiment, p53 (+/+) and p53 (+/-) mice were pre-exposed to 0.02 Gy and challenged with 2Gy at intervals of 0 to 168 hours, and the frequencies of cells dying by apoptosis in spleen and thymus measured 4 hours after challenged irradiation. The incidence of external anomalies was significantly lower (by approximately 20%) in the primed (0.02 + 2 Gy) mice compared to the unprimed (2Gy alone) mice. However, there were no differences in the incidence of prenatal death, the skeletal anomalies and body weights between the primed and the unprimed mice. In p53 (+/+) mice, the frequencies of apoptotic cells in spleen and thymus were lower in the primed mice at the time intervals of 2 to 168 hours than those in unprimed mice, whereas it was only suppressible at the time intervals of 2 to 48 hour for p53 (+/-) mice. These results suggest that primary conditioning low doses irradiation suppresses the radiation-induced teratogenesis and induction of apoptosis. p53 has an important role in radioadaptive response.

THE ACTION OF HEAVY CHARGED PARTICLES TO THE VISUAL PIGMENT RHODOPSIN AND ISOLATED FROG RETINA.

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The solubilized rhodopsin and isolated frog retina have been irradiated by deuterons (15.5 MeV).

a) **Rhodopsin**. Irradiation induces the bleaching of rhodopsin (500nm) and appearance of its stable product metarhodopsin II (380nm). In contrast to the light-induced bleaching, the deuterons-induced bleaching leads to partly fall of rhodopsin's capability to be regenerated after 11-cis retinal adding. It means that the native state of rhodopsin molecule is damaged as a result of deuterons irradiation

b) **Isolated frog retina.** The light-induced and deuterons-induced electrical activity of the retina – electroretinogram (ERG) has been recorded. The ERG itself and it behavior are similar in both cases. However, in contrast to light, the long lasting irradiation of the retina by deuterons leads to decrease and then lose both the light-induced and deuterons-induced ERG.

So, both light and deuterons are able to induce rhodopsin bleaching and ERG of isolated retina, but deuterons are able to damage both rhodopsin molecule and retina in comparison with physiological action of visible light.

The similar results were obtained with alpha-particles irradiation (30 MeV).

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EFFECTS OF EXPOSURE TO ^{56}Fe PARTICLES OR PROTONS ON FIXED-RATIO OPERANT RESPONDING IN RATS.

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On long-duration trips outside of the magnetosphere, astronauts will be exposed to protons and to heavy particles, such as ^{56}Fe, which have the capacity to affect their ability to perform required tasks. It is therefore essential to determine the range of behaviors that might be affected by exposure to these types of radiation in order to understand the nature of irradiation-induced behavioral deficits and to develop effective countermeasures. The present experiment examined the ability of rats to make an operant response (pressing a lever in order to obtain food) following exposure to protons (250 MeV, 4.0 Gy) or ^{56}Fe particles (1 GeV/n, 1.0 or 2.0 Gy). Following irradiation, rats were trained to press a lever in order to obtain food reinforcement. Once the response was learned, the rats were placed on an ascending fixed-ratio (FR) schedule from FR-1 (every lever press is rewarded with a food pellet) through FR-35 (35 lever presses are required to produce 1 food pellet). In general, as the ratio increases, rats increase their rate of responding. The rats exposed to 4.0 Gy of protons or 1.0 Gy of ^{56}Fe particles

responded similarly to controls increasing their rate of responding as the ratio increased. However, rats exposed to 2.0 Gy of ^{56}Fe particles failed to increase their rate or responding at ratios greater than FR-20. These results indicate that rats exposed to 2.0 Gy of ^{56}Fe particles cannot respond appropriately to increasing work requirements. Additional experiments will be necessary to determine the factors that are responsible for this deficit.

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EVALUATION OF RADIATION RISK BY THE USE OF CHROMOSOME ABERRATIONS

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There is increasing evidence that the frequency of aberrations detected by the classical metaphase assay is strongly affected radiation-induced cell cycle delays. To contribute to this issue human lymphocytes of one donor have been exposed in vitro to either X-rays or 200 MeV/u Fe ions (LET: 500 keV/μm) and aberrations were scored in G_2-cells after Calyculin A induced premature chromosome condensation (PCC) as well as in classical metaphase spreads. Additionally apoptosis was measured. The data clearly demonstrate that at the standard fixation time, i.e. 48h post-irradiation, metaphase analysis underestimates the radiation efficiency. Heavily damaged cells have been found to be arrested in G_2 and thus, can be only detected by the PCC-technique: After X-irradiation 2 times more aberrations were found in G_2 - than in metaphase-cells, while after Fe ion irradiation 20 times more aberrations were observed. Because the rate of apoptosis was low in both experiments and did not depend on LET an additional effect of apoptosis on the yield of chromosome aberrations can be ruled out. In summary, our data indicate that for a meaningful quantification of radiation induced chromosomal damage and consequently reliable risk estimates modified protocols have to be developed. In particular, when the action of heavy ions is studied, cell cycle transition delays of heavily damaged cells have to be considered. (SR was supported by JST, Japan, grant 399026)

CYTOKINE GENE EXPRESSION IN BONE MARROW OF MICE IRRADIATED CHRONICALLY WITH LOW DOSE RATE γ-RAYS.

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The results in preliminary experiments on CFU-S assay of bone marrow of SPF C3H/HeN female mice (8 w.o.) irradiated chronically with low dose rate ^{137}Cs □-rays (20 mGy/day-22hrs) showed that the number of hemopoietic stem cells significantly reduced, while that of peripheral blood cells did not change significantly. In order to investigate its regulation in molecular level, the change in expression of five cytokine genes (IL-1□, IL-6, IL-11, GM-CSF and SCF) in bone marrow cells of the mice by chronic low dose rate and acute dose rate (0.59 Gy/min) ^{137}Cs □-rays was measured by the method of TaqMan Real-Time PCR. The results showed no change more than two times (detection limit) of control level in the expression of the genes tested. Therefore, probably, the expression of these five genes is not related directly to the above-mentioned phenomenon.

EFFECTS OF CHRONIC LOW DOSE RATE GAMMA-IRRADIATION ON THE PROCESS OF CARCINOGENESIS IN MICE

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For the estimation of health effects of the space environment, information on the effects of chronic irradiation on the process of carcinogenesis should be useful.
Thirty-five female ICR mice, 6 weeks old, were irradiated with 137 Cs gamma rays for 35 days at a dose rate of 0.95 mGy/hr. The mice were then injected with 0.5 mg of methylcholanthrene (MC) in the groin. The irradiation was continued until tumors appeared. It was 126 days after MC injection when the cumulative tumor incidence reached 50 % in the irradiated mice, while 105 days in non-irradiated control mice. Similar delay in the timing of tumor appearance in MC injected mice was also observed in B6C3F1 mice.

EFFECTS OF HIGH-ENERGY CARBON ION IRRADIATION ON NEGATIVE GRAVITAXIS OF EUGLENA GRACILIS Z

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Flagellate Euglena gracilis Z(Euglena) has the behavioral property of swimming against the gravity (negative-gravitaxis). Negative gravitaxis is needed to move to and stay at a position in a water column which is optimal for growth. Organic and inorganic toxic compounds affected the negative gravitaxis of Euglena, but there has no report on effects of space-radiation in negative gravitaxis of Euglena. Thus, the aim of this paper was to investigate the relation between exposure to 290MeV/amu carbon ion simulated space-radiation and negative gravitaxis in Euglena. R-value, a statistical index of convergence of swimming directions of the group of Euglena, was adopted in this study as an endpoint. The r-value ranges from 0 (swim to random directions) to 1 (swim to upward direction). In general, around 70 - 80 % of all Euglena swim upward in a water column, and mean of r-value ranges from 0.4 to 0.5. The r-value was estimated at 28 hours after irradiation of 290 MeV/amu carbon ion at the dose of 0, 1, 5, 7.5, 10, 15, 20, 50, 75, 100, 150 and 200 Gy for water (Gy). The r-value ranged from 0.46(±0.08) at 0 Gy to 0.27(± 0.06) at 200 Gy (values in the parenthesis are standard deviations). Decrease of r-value from non-irradiated samples (0 Gy) were significant statistically at the exposures of more than 7.5 Gy ($p<0.05$), that restored to the control level at a few days after irradiation.

EFFECTS OF HEAVY IONS ON THE VISUAL FUNCTION AND ELECTROPHYSIOLOGY OF RODENTS: THE ALTEA-MICE STUDY

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ALTEA-MICE is a multidisciplinary international project sponsored by NASA and by the Italian Space Agency (ASI) and Institute of Nuclear Physics (INFN) to investigate the effects of heavy ions on the visual system of mice. Both normal and mutant mice with gene defects affecting photoreceptor or bipolar cell function will be studied, with the scientific focus spanning from *in vitro* models to *in vivo* approaches and from cell to system physiology. Experiments will be performed at the Brookhaven National Laboratories with application of standardized electrophysiological techniques. The retina and visual cortex of adult mice and *in vitro* (retinal or cortical) cell preparations will be radiated with short (2-5 msec) bursts of heavy (e.g. iron) ions, delivered by a collimated 1-3 mm beam. Mice will be anesthetized and implanted with acute or chronic electrodes (retina; visual cortex) during pulsed radiation. Preliminary experiments performed with the GSI accelerator (Darmstadt, FRG) allow to record transient electrophysiological responses of the mouse visual cortex to bursts of particles in an order of magnitude of ~2 GeV, comparable to an energy loss of a bragging Fe in the eye, with 100-350 ms latency from pulsed radiation. The study protocol, experimental set-up, and preliminary results will be presented. The results of the GSI study will be outlined. The ALTEA-MICE project is expected to provide the scientific background needed to supplement the ALTEA project on astronauts and to yield information about the (electrophysiological correlates) of the functional brain impairment eventually induced by heavy ions in specific instances (e.g. during long-term operations in microgravity).

A MODEL CALCULATION FOR SINGLE-PARTICLE TRAVERSE: DIFFERENCE BETWEEN MICROBEAM AND BROAD-BEAM EXPERIMENTS

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For a high-LET region of 30-500 keV/μm, we propose here a new model that has been developed for analyzing the difference in single-particle traverse between microbeam and broad-beam experiments. When L(k) is the track-average LET in cells required for a 37% survival response, and is expressed as a function of k, which is the number of particle traversals per cell nucleus, the expression $L(k)=L_1(k^{-1})^{1/2}$ gives a reasonable agreement with two recent data sets in microbeam experiments with α particles, where L_1 is a critical value for inducing lethal damage by a single track. L_1 has been found to be 152 keV/μm for Chinese hamster V79 cells. Another expression, $L(n)=L_1(n^{-1}+n^{-2}/2+n^{-3}/3+ - - -)^{1/2}$, n>1, is also applicable for broad-beam experiments with light ions, where n is the average number of particle traversals per cell nucleus. Under n=k, L(n) is always larger than L(k), suggesting that many over-killed cells with several traversals are involved in broad-beam experiments. The fluctuation in radiosensitivity of individual cells is a primary stochastic property in a microbeam case, while that in particle hits is further added in a broad-beam.

RADIATION RESPONSES OF SURVIVAL AND SPLENIC LYMPHOCYTE APOPTOSIS IN ROLLING MOUSE NAGOYA FOLLOWING LOW-DOSE PRE-IRRADIATION

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Rolling mouse Nagoya (RMN) is an ataxic mutant that carries the mutation in the gene coding for the $\square_{1A}$ subunit of P/Q-type Ca^{2+} channel. We examined the role of the P/Q-type Ca^{2+} channel in radiosensitivity and radioadaptive response induced by pre-irradiation with a low dose using RMN. Survival of RMN following 4, 5 or 6.75 Gy X-irradiation was slightly radiosensitive compared to a control (C3Hf/Nga). In both RMN and the control, Bax- and TUNEL-positive lymphocytes in the splenic white pulp increased 12 hours after 3 Gy irradiation. They had been apparently suppressed by pre-irradiation with a low dose (0.45 Gy) in both RMN and controls. The mutated Ca^{2+} channel $\square_{1A}$ subunit immunoreactivity was not found in the white pulp lymphocytes of RMN. Their expression was not induced by irradiation with or without pre-irradiation. These results suggested that the mutation in P/Q-type Ca^{2+} channel might modify the radiosensitivity. This phenomenon may support a radioadaptive response resulting in the depression of apoptosis in splenic white pulp lymphocytes, but not in the expression of the mutated Ca^{2+} channel.

PROBING DNA LESION COMPLEXITY WITH PLASMID ASSAYS

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The existence of complex DNA damage and its relationship to radiation quality has important implications for predicting risks of space travel. We have investigated the use of a plasmid model system to define experimental parameters, which correlate with the level of clustering in complex DNA lesions. The advantage of such a system is that it can be prepared and studied in a well-defined chemical environment that simulates the OH radical scavenging capacity of a cell without interference from cellular repair processes. Complex DNA lesions are classified as SS lesions, characterized by at least one strand break on opposing DNA strands; BB lesions, with at least one damaged or lost base but no strand break on opposing DNA strands; and SB lesions, with at least one strand break on one strand and at least one damaged or lost base but no strand break on the opposite strand. These different forms of damage may be distinguished by studying the action of DNA glycosylases or endonucleases on irradiated plasmid DNA. This can be done either in vitro by incubating irradiated DNA with purified enzymes and scoring double strand breaks with gel electrophoresis or, alternatively, in vivo by transforming *E. coli* bacteria with irradiated plasmids and measuring the loss of bacterial resistance to suitable antibiotics. Using binomial statistics and making a realistic assumption about the ratio of damaged or lost bases and strand breaks, it is shown that the inverse ratios of the frequencies of each complex lesion form and all complex damages depend strongly on the number of lesions per damage cluster. To verify this experimentally, we studied the ratio of frequency plasmid lesions leading to loss of bacterial resistance and the frequency of SS lesions (double strand breaks) for low-LET gamma rays, intermediate-LET protons, and high-LET alpha particles, and found the expected LET dependence. Possible applications of these new parameters for validation of mathematical models of the response of DNA to ionizing radiation will be discussed.
This work was supported by USPHS grant CA46295 and the National Medical Technology Testbed Inc. (NMTB) under the U.S. Department of the Army Medical Research Acquisition Activity, Cooperative Agreement Number DAMD17-97—2-7016. The views and conclusions contained in this presentation are those of the authors and do not necessarily reflect the position or the policy of the U.S. Army or NMTB.

NITRIC OXIDE-MEDIATED BIFUNCTIONAL BYSTANDER EFFECT INDUCED BY HEAVY-ION RADIATION IN HSG CELLS

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Purpose: To investigate the medium-mediated bystander effect and its induction factor by co-cultivating unirradiated HSG neoplastic cells with HSG cells irradiated by a 290 MeV/u carbon beam.
Results: An increase in cell proliferation relative to an unirradiated recipient HSG was found in the co-culture and its subculture, as well as micronucleus (MN) induction, which occurred in unirradiated recipient cells. 100 keV/□m carbon ion irradiation was found to be a much more efficient inducer of the medium-mediated bystander effect compared to 13 keV/□m carbon ion irradiation. The treatment of cells by PTIO, a specific scavenger to nitric oxide (NO), resulted in the elimination of such effects, which supports a role for NO in the medium-mediated bystander effect. As an oxidization product of NO, nitrite was indeed detected in the co-culture medium, and the dose response of its formation was also measured. Moreover, sper/NO, a NO generator, was used to directly examine the effect of NO on HSG cells. When the HSG cells were treated by sper/NO with a concentration of less than about 20 □M, cell proliferation was enhanced. However, MN was concurrently observed in the cells.
Conclusions: This research first show that radiation-induced bystander effect was relative to LET; and NO, excreted from the heavy-ion irradiated HSG cells, as an important signal factor, played an dominate role in the medium-mediated bifunctional bystander effect.

EFFECTS OF EXPOSURE TO ^{56}Fe PARTICLE IRRADIATION ON SPATIAL LEARNING AND MEMORY BEHAVIOR AND NEURONAL SIGNALING

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Our laboratory has been studying behavioral and neuronal effects following exposure to particles of high energy and charge (HZE particles) such as those that might be encountered by astronauts on future flights outside the magnetic field of the earth. In these previous experiments we have shown that whole-body exposure of rats to ^{56}Fe irradiation disrupts the functioning of the dopaminergic system and causes deficits in behavior mediated by this system. In this study we attempted to determine the mechanisms involved in these deficits. Thus, ^{56}Fe-exposed rats (1 GeV/n, 1.5 Gy) were tested in an 8-arm radial maze (RAM), a test of spatial memory, and the relationship between this behavior and markers of neuronal signaling were examined. Radiation exposure impaired cognitive behavior, since irradiated rats committed more errors than control rats in the RAM and were unable to adopt a spatial strategy to solve the maze. To determine whether these findings relate to the brain-region-specific alterations in sensitivity to oxidative stress, inflammation, and neuronal plasticity, three brain regions (striatum, hippocampus, and frontal cortex) linked to behavior were isolated and measured from control and irradiated rats. The levels of oxidative stress, inflammation, and neuronal plasticity were significantly adversely affected by irradiation as reflected through the levels of dichlorofluorescein (DCF), heat shock and synaptic proteins (e.g., synaptobrevin and synaptophysin), respectively. Changes in these factors consequently altered cellular signaling [e.g., calcium-dependent protein kinase C (PKC), protein kinase A (PKA)]. Furthermore, these changes in brain responses significantly correlated with reference and working memory errors in the RAM. Our results show differential brain-region-specific sensitivity induced by ^{56}Fe irradiation. These findings are similar to those seen in aged rats, suggesting that increased oxidative stress and inflammation may be responsible for the induction of both radiation- and age-related cognitive deficits. Our results also show that future research should focus on a more thorough evaluation of the behavioral and neurochemical effects of HZE particles, continue to explore the mechanisms by which HZE particles affect behavior, and possible nutritional modification procedures (e.g., antioxidants or anti-inflammatories) to offset the deleterious effects of heavy particles in space.

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A REVIEW OF DNA OXIDATIVE DAMAGE MECHANISMS AND DOUBLE-STRAND BREAK PRODUCTION BY IONIZING RADIATION

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Evidence is presented suggesting that the predominant mechanism by which ionizing radiation produces double-strand breaks (DSBs) is misrepair of clustered single-strand breaks (SSBs). Electron spin resonance suggests that electron scattering by ionizing radiation does not produce unpaired electrons in the hydration layer or in the ribose phosphate backbone of DNA, but does produce specific radical bases, especially thymine and guanine. Evaluation of acid/base equilibria reveals that these radical bases are relatively stable and that the guanine radical is readily oxidized to 8-oxo-guanine. The oxidatively-damaged bases that are caused by ionizing radiation are identical to those caused by normal cellular metabolism, and DNA repair mechanisms already exist for the lesions produced by ionizing radiation. However, an examination of the repair mechanisms reveals that they induce SSBs during the repair process. Characterization of the DNA lesions produced by ionizing radiation suggests that the majority of the damage is oxidation of bases virtually adjacent to each other on the same or opposite strand, as opposed to the lesions produced by normal cellular metabolism, which are distributed homogeneously along the DNA strands. Evidence is presented to show that repair of adjacent lesions on opposing strands incises both strands, thereby producing a DSB. Evidence is presented to suggest that DSBs produced by this mechanism are far more common than DSBs that occur too fast for an intermediate lesion to be detected. The mechanism whereby DSBs might be produced directly, without involvement of DNA repair enzymes is questioned, and evidence is presented to suggest that high-Z particles may produce DSBs almost exclusively through misrepair of clustered DNA damage.

MUTAGENIC CHARACTERISTIC OF RICE SEEDS INDUCED BY SPACE ENVIRONMENT

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To understand the radiation in space can be utilized as a special resource to mutate plant seeds. We have done quantitative analysis of space radiation on plant seeds inside recoverable satellite. We also observed the germination percentage, seedling survival rate and seed setting rate of first generation, and observed the plant height and heading date of second generation after collected rice seeds form recoverable satellite in comparison with 300 Gy r-ray irradiation on the ground.
The results indicated the seeds received average dose rate in 0.177mGy/d and integral dose in 2.656mGy/15days. The average stopping power is estimated about 5MeV/cm. There were 1.5? 0.5 heavy nuclear particles/cm^{2}of $Z/\beta \geq 50$ and the numbers of $Z \geq 3$ heavy nuclear particles reached 29.7 ? 0.5 particles/cm^2 in satellite cabin. The physiological damage of rice seeds after space flight was much smaller than that treated with r-ray irradiation. Mutation frequency and mutagenic efficiency varied with different genotype of rice.
Therefore the recoverable satellite is probably a good experimental system for studying the effect of space that indicted potential uses of crop improvement that can be highly mutagenic and can induce some regulatory mutation effectively.

CLUSTERED DNA DAMAGES INDUCED BY LOW DOSES OF IONIZING RADIATION[A]

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Ionizing radiation induces clusters of DNA damages—oxidized bases, abasic sites and strand breaks—on opposing strands within a few helical turns. Such damages have been postulated to be difficult to repair, as are double strand breaks (one type of cluster). We have shown that low doses of low and high linear energy transfer (LET) radiation induce such damage clusters, as well as isolated damages, in DNA in solution and in human cells. In DNA in solution irradiated with low LET radiation, double strand breaks comprise only about 20% of such complex damages, with other cluster types being about 80%; in human cells, DSB are about 30% of the total of complex damages. The dose responses for cluster induction in cells are linear, implying that even low doses of ionizing radiation can produce clustered damages. Studies are in progress to determine whether clusters can be produced by mechanisms other than ionizing radiation, as well as the levels of various cluster types formed by low and high LET radiation.

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MUTATIONAL BREEDING OF VERBENA WITH LARGE NUMBER OF FLOWERS USING HEAVY-ION BEAMS IRRADIATION

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Long blooming period with large number of flowers is the important characteristic of floricultural crops. Suntory Ltd. has developed a new type of Verbena cultivar 'Temari' (Verbena hybrida), which has many characteristics superior to common verbena cultivars. 'Temari Coral Pink' which is the variety of coral pink flowers of Temari occasionally shows the decrease number of flower clusters compared to other varieties. Sixty-four single nodes containing two lateral meristems at each base of two opposite leaves of 'Temari Coral Pink' were cultured in one plastic dish under *in-vivo* conditions, and irradiated with 0, 1, 2, 5 and 10 Gy of the ^{14}N heavy-ion beam at 135 MeV/u. All shoots developed from lateral meristems after irradiation were planted in soil, and grown in a green house. Four mutant lines with stable sterility were successfully selected. These sterile mutants continuously grew well compared to the host plant in the field trials, especially in the end of blooming season, autumn, when the host plant start senescences probably due to continuous reproductive state with seed setting. It was observed that the sterile mutant always had larger number of flower clusters than the host plant in the pot-planting test for three months. It is noted that the host and its mutants had identical characters other than sterility. We conclude that heavy-ion beams irradiation is an excellent tool for sterile mutational breeding with high frequency, because the resultant sterility increases the number of flower clusters with improved growth from self-seed setting plants.

DNA STRAND BREAKS INDUCED BY VACUUM-UV PHOTONS IN AQUEOUS SOLUTION

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The effects of vacuum-ultraviolet radiation on biological systems should be considered seriously, if humankind becomes to have its activity in outer space. Vacuum-ultraviolet photons can get easily in laboratory by using synchrotron radiation (SR). In this study, DNA strand breaks induced by VUV photons from SR were investigated using plasmid DNA in aqueous solution. Radiobiological effects in aqueous system are known to be mediated mainly by water radicals such as OH. Those water radicals produced by vacuum ultraviolet (VUV) photons are confirmed in previous studies. [1, 2]. As the next step, the yields of strand breaks especially double strand breaks in plasmid DNA by VUV photons in aqueous condition were aimed to observe. For this purpose we developed a new apparatus, which consists of a MgF_2 window and a rotating quartz disc. Irradiation was done at BL-20A, Photon Factory, Tsukuba, Japan. Photon flux was around 10^{12} photons per sec. Irradiated samples were analyzed with electrophoresis and strand breaks were quantified. Induced number of strand breaks was plotted against the absorbed energy in the sample, and the yield was calculated from the slopes of the linear fitting, although small quadratic components were observed. Yields were 3.1×10^{-5} Gy^{-1} for dsb and 1.9×10^{-3} Gy^{-1} for ssb at 160 nm (7.7 eV). Interestingly, wavelength dependence of the ssb yield was different from that of dsb, indicating that different mechanisms contribute to the induction of strand breaks.

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ROLE OF DROSOPHILA TLS DNA POLYMERASE ON RADIATION INDUCED MUTATION

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Recently, a new family of DNA polymerases was identified called the UmuC/DinB/Rev1/Rad30 superfamily. Several of these polymerases participate in translesion synthesis (TLS). cDNA sequences were identified and isolated that encode Drosophila homologues of human Rad30A, Rad30B and Rev1, called drad30A, drad30B and drev1 respectively. The drad30A and drad30B gene products, designated dpol□□C and dpol□□C, respectively, exhibit DNA polymerase activity on non-damage DNA template. dpol□□C also exhibited bypass synthesis of various types of DNA damage which include UV-photoproducts, AP site, AAF adduct and cisplatin. dpolh□C efficiently bypass a cis-syn cyclobutane thymine-thymine dimer (TT-CPD) in a mostly error-free manner, while it shows limited ability to bypass a (6-4)photoproduct at thymine-thymine (TT-(6-4)PP) or at thymine-cytosine (TC-(6-4)PP) in an error-prone manner. These results suggest a critical role on DNA-damage induced mutagenesis of the TLS polymerases. To determine the role of these TLS polymerases on radiation induced mutation, we have made transgenic-fly lines in which the level of drad30A, drad30B and drev1 expression can be regulated developmentally and in a tissue-specific manner. For the regulation of the expression of each gene, we have used UAS-GAL4 system. We have made two types of transgenic lines; 1) full-length cDNA of each gene under control of UAS, 2) inverted repeat construct of each gene under control of UAS. The former construct is predicted to be an over-expression line and the latter a reduced expression line (effects of

RNAi). In this paper we will discuss about the possibility whether these transgenic-fly lines can be a sensitive detector for mutation induced by various type of radiation.

BEHAVIORAL EFFECTS OF HEAVY IONS AND PROTONS AND POTENTIAL COUNTERMEASURE AGENTS

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Space travel beyond the Earth's protective magnetic field (for example, to Mars) will involve exposure of astronauts to irradiation by high-energy nuclei such as ^{56}Fe, which are a component of galactic cosmic rays. These particles have high linear energy transfer (LET) and are expected to irreversibly damage cells they traverse. Exposure to HZE radiation may therefore cause progressive deterioration of brain function, adding to other inescapable damage involved in normal aging. We propose a study of the hypothesis that long-term behavioral alterations are induced after exposure of the brain to 1 GeV/n iron and silicon particles with fluences of 1 to 8 particles/cell targets. Previous studies support this notion but are not definitive, especially with regard to long-term effects. Our principal goal is to examine the neurological effects of high-LET radiation on C57BL/6 mice using a series of behavioral tests to unveil the temporal expression of altered behaviors in the radiation response, as well as the means, which can modulate these responses. The studies planned in this project are designed to: 1) Characterize the behavioral consequences after exposure to low-fluences of heavy ions and protons on C57BL/6 mice. The main behavioral endpoints to be used in these studies are locomotor activity to evaluate the integrity of striatal dopaminergic pathways, and spatial reference memory to probe hippocampal cholinergic pathways. 2) Characterize the neurochemical and structural changes induced by heavy ions and protons. 3) To develop countermeasures to protect neural cell populations exposed to low fluences of heavy ions and protons. The project will test methods to protect injured neural cells based on their molecular and cellular mechanisms that may regulate neural cell survival in the central nervous system. Among the methods that will be studied is the direct administration of neuroprotective molecules as well as the modulation of apoptotic pathways by pharmacological manipulation. The effects of 3 different neuro/radioprotectors (GM1, melatonin and PTF-∝) on the levels of radiation induced neurochemical and structural damage will be compared with the level of behavioral alterations to determine a cause/effect relationship

EFFECTS OF HIGH-LET RADIATION ON NEURAL CELLS IN CULTURE: APOPTOSIS INDUCTION, CELL TOXICITY AND GENE EXPRESSION

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Despite the fact that some *in vivo* studies suggest that chronic low-dose exposure to HZE particles might produce effects similar to aging and neurodegeneration, the basic mechanisms of HZE particle neurotoxicity remain to be elucidated. The goal of these experiments is to establish neural cellular models to evaluate the capacity of low- and high-LET radiation, to induce cell damage and apoptosis. In the present study we measured apoptosis, cell toxicity and gene expression induced by low fluences-doses of heavy ions, protons and photons using neuronal precursor cells (NT2, STRATAGENE) and post-mitotic neurons as models for adult neural cell system. Using heavy ions accelerated at AGS (BNL) and HIMAC (Chiba, Japan), and protons (Loma Linda) we study the neurotoxic effects of a variety of heavy particles (1 and 0.6 GeV/n Fe, 580 MeV/n Si, 290 MeV/n C, 550 MeV/n Ar; LET ranging from 13 to148 keV/μm), and 255 MeV/n protons. Apoptosis Induction: We measured the induction of apoptosis by flow cytometry using a FACSCalibur to detect the expression of Annexin V, as an early marker in the apoptotic

pathway, in NT-2 cells. The ApoAlert Annexin V assay is based on the observation that soon after initiating apoptosis, most cell types translocate phosphatidylserine (PS) from the inner face of the plasma membrane to the cell surface. Once on the cell surface, PS can be easily detected by staining with a FITC conjugate of Annexin V, a protein that has a strong natural affinity for PS. Externalization of PS occurs earlier than the nuclear changes associated with apoptosis, so the ApoAlert Assay detects apoptotic cells significantly earlier than do DNA-based assays. Exposing NT-2 cells to Fe ions and protons induced a strong dose- and time-dependent induction of apoptosis with the peak of apoptosis appearing at 72 hours post-irradiation. It was determined that Fe ion exposure were more effective to induce apoptosis in comparison to protons and gamma rays, suggesting an high RBE values for apoptosis in exposed NT2 cells at 72 hr post-irradiation. Cell Toxicity: Cell damage at different time points after exposure to charge particle radiation was determined by using the Live/Dead Viability/Cytotoxicity Kit on attached cells from 4 well plates. The LIVE/DEAD Kit provides a two-color fluorescence-based cell viability assay that allows the simultaneous determination of live and dead cells. Results obtained from BNL-7 indicated a dose- and time dependent increase of cell damage. Doses as low as 0.1 Gy were able to induce a significant increase of cell damage in comparison to controls. Colorimetric (XTT) assays and the evaluation of the number of attached and floating cells confirmed this trend. Gene Expression: Conventional western blot techniques were employed to monitor p53 and WAF-p21 gene expression. A subset of NT2 cell samples were lysed at different time points for the determination of p53 and WAFp21 expression using monoclonal antibodies against human p53 and p21. In BNL-7 we observed that p53 is over-expressed as a function of dose of particle exposure and time post-exposure. Doses as low as 0.25 Gy were able to up-regulate p53 and as early as 24 hours post-exposure. Doses of 0.75 Gy were able to up-regulate p53 as early as 12 hours post-exposure. Similar results were obtained when NT-2 cells were exposed to gamma or proton exposures, although higher doses were required to obtain similar degree of expression. These results appear to confirm that p53 gene is involved in the stress pathway induced by low- and high-LET radiation exposures. Up to this point we were not able to confirm changes in the expression of WAFp21 after radiation exposure in NT2 cells.

DETECTION OF DNA DAMAGE IN THE INDIVIDUAL CELLS INDUCED BY HEAVY ION IRRADIATION WITH COMET ASSAY.

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Determining the biological effects of high-LET heavy ion irradiation at low fluence is important to evaluate the risk of radiation in space. Especially it is necessary to detect the radiation damage induced by a precise number of heavy ions in the individual cells. Thus we compared the number of ions traversing the cell and the DNA damage produced by the hit ions. We applied comet assay to measure the DNA damage in the individual cells. Cells attached on the ion track detector CR-39 were irradiated with 17.3 MeV/u ^{12}C, 15.7 MeV/u and 10.4 MeV/u ^{20}Ne ion beams at TIARA, JAERI-Takasaki. After irradiation, CR-39 was covered with 1 % agarose. The agarose was allowed to solidify on the slide glass and then the electrophoresis was performed. After electrophoresis the CR-39 was taken off from the slide glass. the agarose gel on the CR-39 was stained with ethidium bromide and the opposite side of the CR-39 was etched with KOH-ethanol solution at 37℃. We observed that the heavy ions with higher LET value induced the heavier DNA damage, even by the same number of ion-hits within the irradiated cells. The result indicated that the amount of DNA damage induced by one particle depended on the LET value of the heavy ions.

HERITABLE NONLETHAL DAMAGE TO CULTURED HUMAN CELLS IRRADIATED WITH HEAVY IONS

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It has been noted that, during interplanetary space flights, the nuclei of all of a crew member's cells are expected to be traversed by high -LET(Linear Energy Transfer) cosmic-ray particles unless extraordinary shielding measures are implemented. Scientists have shown, from studies done *in vitro* , that 1 in 10,000 of the surviving cells traversed by heavy particles are transformed to malignancy or are mutated. The question remains, what, if anything, happens to the remaining >99% of surviving cells? A retrospective analysis of archived data and samples from heavy-ion irradiation experiments with cultured human cells was undertaken to answer this question. We used a computerized image analysis system and a colony-size percentile method to evaluate clone-size distributions to seek evidence for reduced growth rate (a heritable effect) and division delay (a transient effect) of surviving irradiated cells. The results showed that heavy ions caused division delays and a dose- and LET-dependent reduction in multiplication rates of cultured human cells. The maximum action cross section for this effect is about 200 μm^2. This is at least as large as the cell nuclear area and at least 6 times the cross section for cell killing. Thus, heritable slow growth is the most prevalent effect of high-LET radiation on cultured animal cells, with implications for radiation effects on crew members during deep space travel.

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ANALYSIS OF UNREJOINED CHROMOSOME BREAKAGE IN HUMAN FIBROBLAST CELLS EXPOSED TO LOW- AND HIGH-LET RADIATION

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Reported studies of DNA breakage induced by radiation of various qualities have generally shown a higher fraction of unrejoined residue breaks after high-LET exposure. This observation is supported by the argument that DNA breaks produced by high-LET radiation are more complex and, thus, less likely to be repaired. However, the dose used in these studies was usually very high. We studied unrejoined chromosome breakage by analysis of chromosome aberrations using a fluorescence *in situ* hybridization (FISH) technique with both whole chromosome specific probes and telomere probes. Confluent human fibroblast cells (AG1522) were irradiated with γ rays, 490 MeV/nucleon Si, 200 MeV/nucleon Fe and 500 MeV/nucleon Fe ions, and were incubated at 37 ^{0}C for 24 hours after exposure. A chemically induced premature chromosome condensation (PCC) technique was used to condense chromosomes mostly in the G2 phase of the cell cycle. Results of the study showed that the frequency of unrejoined chromosome breaks was higher at high-LET, but the ratio of unrejoined to misrejoined breaks remained low for LET values up to 440 keV/μm. Therefore, for both low- and high-LET most chromosome breaks were either rejoined or misrejoined, when observed in the G2/M phase of the cell cycle. Unrejoined chromosome breaks associated with incomplete exchanges were also analyzed with an m-FISH technique where human

chromosomes were painted in 24 different colors. As with the telomere analysis, the m-FISH analysis also resulted a higher fraction of unrejoined chromosome breaks. It was also shown that the ratio of unrejoined to misrejoined chromosome breaks, or of incomplete to complete interchromosomal exchanges, was a potential biomarker for radiation quality for a wide range of LET values.

A NEW METHOD FOR INDUCTION OF MUTATION IN RICE USING HEAVY-ION BEAMS

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Heavy-ion irradiation is a new method for mutation breeding to produce new cultivars. We established the application of this method in rice plants to obtain mutants. Rice seeds (Oryza sativa) were soaked for 3 days in water at 30˚C under dark. The imbibed seeds were irradiated by ^{12}C or ^{20}Ne ion (135 MeV/u) within a dose range of 5 to 160 Gy. The LET of the ^{12}C and ^{20}Ne ions were 22.7 and 63.4 keV/um, respectively. M_2 seeds from selfed M_1 strains were harvested approximately four months after the irradiation. M_2 seeds were sown on seed beds, and grown in a greenhouse. After 3-weeks, the number of chlorophyll mutants was recorded. Chlorophyll mutants segregated in M_2 progeny were the albino, pale green or the striped-leave phenotypes. The heigher frequencies of chlorophyll mutants were obtained by the irradiation of C ions; 40 and 20 Gy and also Ne ions; 20 and 10 Gy. Ion-beams irradiation on rice imbibed seeds can give a higher mutation rate and a wider range in the type of mutants compared to the case of r-ray irradiation. We used the RLGS (Restriction Landmark Genomic Scanning) method to analyze DNA deletion in an albino mutant genome. Not I-landmark RLGS profiles were detected about 2000 spots in rice. There were several polymorphic spots derived from 2,2kbp deletion in an albino mutant.

CHANGES OF GENE EXPRESSION IN DEVELOPING MOUSE BRAIN – A COMPARATIVE STUDY BETWEEN EXPOSURE TO CARBON PARTICLES AND TO X-RAYS

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Prenatal exposure to ionizing radiation of low doses in rodents induces deceleration of neuronal migration during cortical histogenesis, and results in disorganized cortical architecture in mature brain. On the contrary, exposure to heavy ion beams during fetal period mainly affects cell survival, viz., induction of apoptosis. However, the molecular mechanisms underlying to produce such difference in the effects between exposure to heavy particles and exposure to X-rays remain unknown.
We have attempted to elucidate whether the changes of gene expression after exposure to heavy ions differ from those after X-rays in fetal brains. We thus applied two molecular biological techniques, i.e., the Restriction Landmark cDNA Scanning method and the suppression subtractive PCR method. Approximately 13,000 cDNA species have been scanned and it turned out that more than twenty genes among the genes scanned are differentially expressed between X-irradiated embryos and non-irradiated ones. One of the genes showing up-regulation is Rab6A which is known to be associated with vesicle transport from *trans*-Golgi network. In addition, expression of some genes encoding RAB6A-interacting proteins was up-regulated. When expression of these genes was compared between animals after heavy-ion irradiation and those after X-irradiation, the changing pattern was different.

Taking our previous observation that prenatal exposure to carbon particles induces apoptotic cell death in developing cerebral cortex into consideration, the difference in gene expression herein reported may contribute to the difference in effects found between exposures to heavy-ion particles and to X-rays. In conclusion we ide ntified Rab6A and its interacting proteins as candidates for the migration-associated genes, whose expression in fetal brain is up-regulated by carbon beam irradiation.

RADIATION-INDUCED GENE EXPRESSION ABOUT APOPTOSIS-RELATED GENES BY DNA ARRAY ANALYSIS

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We previously reported that the genetic and functional status of *p53* tumor suppressor gene might be an important factor as the predictive indicator in cancer therapy, because cancer cells harboring *p53* mutations were resistant through the depression of apoptosis induced by X-ray, anticancer agents and hyperthermia. However, we think that it raises predictability of radiotherapy effect for patients widely to search a background of apoptosis-related genes induced in neoplastic cell. Therefore, we analyzed a difference of an expression of apoptosis-related genes using DNA array. We extracted mRNA from X-ray irradiated human cancer cultured cells. After labeling with [α-^{33}P]-dCTP and hybridization in DNA array (Human Apoptosis Expression Array, R&D Systems), we scaned the profiles of the spots with phosphorimager (BAS5000, FUJI FILM) and calculated using the public domain NIH Image program. The data of each DNA array were normalized with eight kinds of house keeping genes. mRNA from non-irradiated cells was treated as a control. We are studying on the difference in the expression level of apoptosis-related genes which contains cell cycle regulator, *p53*-related, *Bcl-2* family, *Caspase* family and *Fas*-relate genes.

THE DEVELOPMENT IN SENSITIVE DETECTION OF GENETIC ALTERATIONS CAUSED BY SPACE ENVIRONMENTAL RADIATION

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It is very important to develop the sensitive methodology for estimation of genetic influences by space environmental radiation, in which high-energy heavy-ion particles largely contribute to total absorbed dose. First we succeeded to establish the system to detect the effect of low-dose such as 10 cGy of X-ray irradiation by analyzing LOH (loss of heterozygousity) events of thymidine kinase (TK)-deficient mutants of human lymphoblastoid cell TK6-20C. This methodology can distinguish two classes of LOH mutants, being either hemizygous or homozygous for the nonfunctional *TK* allele. Further, the multi locus PCR analysis by using 12 microsatellites on chromosome 17 allows us to determine extent of LOH. As a result, we observed an incidence of radiation-specific hemizygous LOHs even under the condition of low-dose X-ray exposure, which did not show a significant increase in *TK* mutation frequency. These hemizygous LOHs are considered as a result of endjoining repair of DNA double-strand breaks (DSBs). Following this striking finding, we recently found an approximately 3–fold increase in *TK* mutation frequency after 10 cGy C-ion (22 keV/um)-beam exposure, which also accompanied such radiation-specific hemizygous LOHs. This increase is probably due to the enhanced occurrence of DSBs and/or difficulty in repair of such DSBs, compared to X-ray exposure case. These results suggest that the

developed LOH-analysis is promising to detect genetic alterations at chromosome level, caused by space environmental radiation.

4. Physical countermeasures for space radiation risks to human exploration

INFLUENCE OF THE SHIELDING ON THE SPACE RADIATION BIOLOGICAL EFFECTIVENESS. I DNA DAMAGE

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In the framework of the research collaboration aimed at investigating the influence of the shielding on the biological effects of heavy ions, we studied the production of DNA Double Strand Breaks (DSB) in human fibroblasts irradiated with iron ions of different energies. 1 GeV/u beams were obtained from the Alternate Gradient Synchrotron (AGS) of the Brookhaven National Laboratory (USA) while 500 MeV/u and 200 MeV/u were obtained from the Heavy Ion Medical Accelerator (HIMAC) of the National Institute for Radiological Sciences, Chiba (Japan). Different shieldings of PMMA or aluminium were also used.
Plateau phase AG1522 cells were irradiated in agarose plugs and DSB induction was determined by DNA fragmentation analysis after Pulsed/Constant Field Gel Electrophoresis.
The results until now obtained show that the number of DSB increases linearly with the fluence. Among the unshielded beams, the highest DSB induction per incident ion is observed for 200 MeV/u. A marked protective effect of 190 mm PMMA is found for 1 GeV/u, while an increased damage is observed after shielding of 500 MeV/u beam with 56 mm PMMA or 30 mm aluminium. No significant difference is detectable between the two types of shielding.
When the number of DSB is plotted as a function of the dose at the sample position, the higher effectiveness is shown by the 1 GeV/u unshielded beam. After PMMA shielding, the DSB yield decreases and is slightly higher than those obtained with the other beams, with and without shieldings.

INFLUENCE OF THE SHIELDING ON THE SPACE RADIATION BIOLOGICAL EFFECTIVENESS. IV. MODELLING

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Monte Carlo transport codes can be of great help in predicting the role played by shielding structures in modulating the spectra of space radiation; this problem is extremely relevant for radiation protection applications in long-term manned missions, such as activities on the International Space Station and possible missions to Mars. Within this context, the development of the FLUKA code is in progress. FLUKA is a "condensed-history" Monte Carlo code able to transport electromagnetic and hadronic particles of different energies in different materials, taking into account also nuclear interactions; development efforts are now focussed on the extension of nuclear interactions of heavy ions to energies below 5 GeV/u, an energy range of major importance for radiation protection in space. The results of

preliminary simulations of the effects of different shielding conditions will be presented, also including the use of an anthropomorphic phantom for the estimation of physical and "biological" dose distributions to different organs.

INFLUENCE OF THE SHIELDING ON THE SPACE RADIATION BIOLOGICAL EFFECTIVENESS. III. DELAYED REPRODUCTIVE DEATH

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In the framework of the research collaboration on space radiation shielding, we have studied early and delayed reproductive death in human fibroblast cells (AG1522) exposed to ^{56}Fe accelerated beams at the heavy-ion medical accelerator in Chiba, HIMAC. Cell killing is a common endpoint to quantify relative biological effectiveness, and delayed reproductive death (lethal mutations) provides information about late biological effects, which are important for estimating late stochastic effects. We used 200 MeV/n and 500 Mev/n beams. The 500 MeV/n was also shielded with 56 mm lucite or 30 mm aluminum. Plateau phase AG1522 cells were exposed at five dose levels from 0.25 Gy to 2 Gy for initial and delayed inactivation assays. Our data indicate that: a) the unshielded Fe 500 MeV/n beam effectiveness for inactivation of AG1522 cells is higher than any other iron beams, b) the progeny of irradiated AG1522 cells show the presence of delayed damage in the form of the reproductive cell death for all iron beams, c) fluence-response curves for the survival of irradiated AG1522 cells and the delayed reproductive cell death of their progeny show an increased effectiveness per incident ion induced by the shielding.

ADVANCES IN RADIATION SHIELDING

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We discuss methods to achieve the goals of having a Monte Carlo method and a 3D deterministic solution of the Boltzmann radiation transport equation (HZETRN) with efficient linkages to spacecraft geometry/material database and biological models. We have formed a consortium to leverage from ongoing DOE HZE ion transport research with respect to specific Monte Carlo codes and the latest research versions of HZETRN. *Revolutionary methods* are proposed herein *to move* Monte Carlo methods beyond the 30-year impasse to provide efficient linkage to spacecraft geometry and enable useful spacecraft design evaluation. The approach to reach a full 3D deterministic code is discussed in terms of asymptotic corrections of the forward components and a combination of analytic/numerical approach to the diffuse components. The associated research groups forming the consortium and their code versions will serve as the most cost-effective way of starting the presently proposed development of standardized methods. In addition, the most-complete nuclear models, which even now provide the

database in NASA shielding and astronaut risk assessment will be advanced through inclusion of cluster wave functions, in-media modifications of the two-body interaction amplitudes, and addition of meson production processes. Critical issues in developing a NASA standard shielding code will be outlined in this report and approaches for their resolution addressed. The ultimate test on code development will be the ability to predict shielding effectiveness in the known space environment using real vehicles with instruments in space and ability to lead to reliability-based optimized spacecraft shield design methods.

INFLUENCE OF THE SHIELDING ON THE SPACE RADIATION BIOLOGICAL EFFECTIVENESS

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A research program in space radiobiology has recently started in Italy. The program is focused on the effect of the shielding on the biological effects of heavy ions. Both experiments and models are included in the research program. Experiments aim to determine genetic effects of heavy ions with or without shielding. Mathematical models, based on Monte Carlo codes, will be used to interpret the biological results. The final goal is to predict the radiation-induced biological damage in space, given the free-space radiation field and the space vessel shielding. The grant is supported by the Italian Space Agency (ASI), and involves Italian radiation biophysics groups (Universities of Milan, Pavia, and Naples, National Institute of Health in Rome), in collaboration with NASA (USA), NIRS (Japan), CERN (Switzerland), BNL (USA), and TERA (Italy). In this overview of the project, we will briefly summarize the results obtained in human cells exposed to swift iron ions accelerated at the HIMAC (Japan) or AGS-BNL (USA) using lucite or aluminum shielding. Detailed results about DNA fragmentation, chromosomal aberrations, and delayed reproductive death will be presented in separate posters at this workshop.

(for poster presentation)

INFLUENCE OF THE SHIELDING ON THE SPACE RADIATION BIOLOGICAL EFFECTIVENESS. II. CHROMOSOMAL ABERRATIONS

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In the framework of the project on space radiation shielding supported by the Italian Space Agency (ASI), we measured chromosomal aberrations in human peripheral blood lymphocytes exposed to accelerated iron ions. Blood was exposed at the HIMAC accelerator to 500 MeV/n or 200 MeV/n ^{56}Fe beams, 20-100 cGy. The high-energy iron beam was also shielded with either 56 mm PMMA (lucite) or 30 mm aluminum. After 48 h in culture, chromosomes were prematurely condensed by calyculin A and painted with DNA whole-chromosome probes specific for human chromosomes 1, 2, and 5. Symmetrical and asymmetrical chromosomal exchanges were scored at an epi-fluorescent microscope. Dose-response curves were linear in this low-dose range. The effectiveness per unit dose at the sample position was similar for the 500 MeV/n shielded with PMMA, Al, and no shield. These beams were more effective than the 200 MeV/n beam. However, when plotted as a function of the number of ions hitting the shield, the curves are separated and the shield increases the effectiveness per incident ion. The difference is caused by nuclear fragmentation of the beam in the shield.

HEAVY ION TRANSPORT MONTE CARLO CODE HETC-CYRIC

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We have developed a Heavy Ion Transport Monte Carlo Code, HETC-CYRIC. The HETC-CYRIC was made by combining some existing codes and formula, HETC-3STEP, HIC, SPAR, and Shen's formula. The accuracy of the HETC-CYRIC has been evaluated by comparing with the experimental data of the angular spectra of secondary neutrons from thick-targets (carbon, aluminum, copper, and lead) bombarded by the heavy ions (helium, carbon, and iron of energies 100 MeV/nucleon, 180 MeV/nucleon, 400 MeV/nucleon). The calculated results agree well with the experimental results in all cases. We are now checking the accuracy of the code for the heavy ion transport by comparing the other heavy ion experimental data, and we are also planning to combine the QMD + JAM model for the heavy ion nuclear reaction with the HETC-CYRIC.

MEASUREMENTS OF THICK TARGET NEUTRON YIELDS FROM 100 TO 800 MEV/NUCLEON HEAVY-IONS

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We measured angular and energy distributions of neutrons produced by 100 and 180 MeV/nucleon He, 100, 180 and 400 MeV/nucleon C and Ne, 400MeV/nucleon Ar and Fe, and 800MeV/nucleon Si ions stopping in thick carbon, aluminum, copper and lead targets using the HIMAC of NIRS, Japan by using the time-of-flight method coupled with the □E-E counter system. The neutron spectra in the forward direction have broad peaks of about 60 to 70 % of the incident particle energy per nucleon due to the break-up process and spread up to almost the twice of the projectile energy per nucleon. They are much harder for a target of lighter nucleus like carbon. This means that the momentum transfer in the forward direction from incident particle to lighter nucleid is much higher than that to heavier nucleus. The total neutron yields above 5MeV that were integrated over a hemisphere from 0 to 90 degrees become slightly larger with increase of the target mass, but their dependence on the target mass is very small compared with the difference of neutron numbers of the target. The difference of neutron yields between He, C and Ne incidences is also very small and this much smaller difference of neutron yields than that of the nucleon numbers of He, C, Ne ions might be caused by the fact that the larger thin target yield for Ne ions than for He and C ions is compensated with additional neutron production due to multiple collisions from the thicker target for He and C ions than for Ne ion. From these data, we obtained that the total neutron yields are approximately proportional to the square of incident particle energy per nucleon. The phenomenological hybrid analysis, based on moving source model and the Gaussian fitting of break-up process, could well represent the measured thick target neutron spectra. The experimental results are also compared with the calculations using the HIC code, and the calculated results agree with the measured results.

IMPROVED THIN POLYMER FILMS FOR SPACE STRUCTURES AND RADIATION SHIELDING and the MISSE EXPERIMENT

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The incorporation of organometallic and submicron metallic additives into polymers has been investigated to improve their space-environmental durability and to improve their radiation shielding effectiveness. These improved polymers will ultimately increase the lifetime of space structures and microelectronic components, as well as increase the protection of astronauts when used in an improved spacesuit. The incorporation of nanometer-sized particles into high performance polymers was also studied theoretically for the design and optimization of ultra-lightweight polymer films with improved durability to the space environment, improved radiation-shielding effectiveness, and improved electrostatic control. A detailed computational model developed at the NASA Langley Research Center has been used for radiation exposure evaluation studies. The model-predicted transmission factors will be compared with an experimental test using a 34-MeV proton beam and high-resolution detectors. Films have been exposed to simulated space environmental parameters and are currently being exposed to actual space flight environments on the MISSE (Materials International Space Station Experiment).

EXPERIMENTAL STUDIES AND MODEL CALCULATIONS OF THE FRAGMENTATION OF HIGH ENERGY HEAVY IONS IN ISS MATERIALS

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Accelerator measurements and model calculations have been used to study the heavy ion radiation transport properties of materials in use on the International Space Station (ISS). Samples of the aluminum ISS outer hull were augmented variously with crew quarter wall material and polyethylene in several configurations and bombarded with 1037 MeV/nucleon ^{56}Fe ions. ^{56}Fe is the heaviest galactic cosmic ray (GCR) ion that contributes significantly to radiation dose, and the beam energy is characteristic of the trailing edge of the peak of the GCR heavy ion spectrum. Transmitted primary ions and charged fragments produced near the beam axis were measured, and a Monte Carlo nuclear fragmentation model was used to extrapolate from the data to lower beam energies and to a lighter ion, ^{28}Si. It was found that for the materials and ions studied, at incident particle energies down to at least 600 MeV/nucleon, nuclear fragmentation reduces the average dose and dose equivalent per incident ion, and it is thus advantageous to add material to fragment the incident ions, even at the expense of slowing the fragments and surviving primaries and making them somewhat more ionizing. At energies below 400 MeV/nucleon the calculation predicts that, as material is added, increased ionization energy loss produces increases in some dosimetric quantities. On balance, the results suggest that the addition of modest amounts of polyethylene or similar material to the interior of the ISS will reduce the radiation dose to crewmembers from GCR heavy ions; however the radiation transport properties of ISS materials should be evaluated with a realistic simulation of the entire flux of GCR and trapped particles.

MEASUREMENT OF NEUTRON PRODUCTION CROSS SECTIONS BY HIGH ENERGY HEAVY IONS

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The double differential cross sections of neutron production by high energy heavy ions have been measured by using the RIKEN Ring Cyclotron of the Institute of Physical and Chemical Research, and the Heavy Ion Medical Accelerator in Chiba (HIMAC) of the National Institute of Radiological Sciences. The incident particles were He, C and Ne ions of 135 MeV/nucleon, and Ar ions of 95 MeV/nucleon at RIKEN, and C of 290, 400 MeV/nucleon, Ne of 400, 600 MeV/nucleon, Ar of 400, 560 MeV/nucleon, and Xe of 400 MeV/nucleon at HIMAC. The target thicknesses are 1 mm of C, 0.6 mm of Al, 0.3 mm of Cu, 0.3 mm of Pb at RIKEN, and C of 0.15 to 5 cm, Cu of 0.05 to 1.5 cm, Pb of 0.05 to 0.8 cm at HIMAC. The neutron energy was measured by the time-of flight method using the ΔE-E counter system. The detection angles were 0, 15, 30, 50, 80, 110 degrees at RIKEN, and at 5, 10, 20, 30, 40, 40, 60, 80 degrees at HIMAC. The measured neutron spectra were compared with the calculation using the two heavy ion Monte Carlo codes of internuclear-cascade and evaporation model, HIC, and the quantum molecular dynamics model, QMD.

PROTECTION OF THE ASTRONAUTS FROM THE SOLAR AND GALACTIC COMPONENTS OF THE IONISING COSMIC RADIATION IN THE INTERPLANETARY SPACE

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In the very long travels through the interplanetary space the astronauts need to be protected from the solar component of ionising cosmic radiation (SCR), as well as from the galactic one (GCR). In the protection from the SCR component it could play a role active systems based on magnetic lenses as well as passive systems based on absorbing materials. The high energy of the galactic component and its isotropy makes the use of passive absorbers ineffective, and only superconducting magnetic systems can produce the very intense magnetic fields that could significantly reduce the high radiation dose due to the GCR component inside the spaceship module where the astronauts spend most of their time. We evaluated the reduction of the dose due to the GCR inside this module as a function of the strength of the magnetic field for a few configurations of the superconducting magnetic system. Furthermore for each configuration and for a number of values of the volume to be protected it has been evaluated the minimum needed mass of the system and the minimum required energy for its cooling.

RI BEAM FACTORY PROJECT AT RIKEN

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The radioisotope (RI) beam factory project is in progress at RIKEN. In this project a new cyclotron cascade consisting of three ring cyclotrons with K=510 MeV, 980 MeV and 2500 MeV in each is constructed. It will boost the heavy-ion beams' energies obtained by the existing K540-MeV ring cyclotron up to 350 MeV/nucleon. Intense RI beams are produced mostly via the projectile fragmentation of these energetic heavy ions or partially via in-flight fission of uranium ions. The first RI beam experiment is scheduled for 2005.

FRAGMENTATION OF HEAVY ION BEAMS IN SHIELDING MATERIALS

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Protection of astronauts from the deleterious health effects of space radiation is both a legal and ethical requirement for NASA. The large uncertainty in biological response to high-LET radiation is a particularly troubling issue, because much of the dose-equivalent for astronauts on long-duration missions comes from heavy ions in the galactic cosmic radiation (GCR). This will be particularly important when missions are undertaken outside the geomagnetosphere. A program of experimental measurements and model calculations of heavy-ion transport through various materials has been ongoing for several years. Here, we present current results from analysis of data obtained at the AGS and HIMAC accelerators using beams of iron and silicon nucle at energies comparable to those found in the GCR. The beams were incident on a variety of thick targets, all of which are either currently used or contemplated for use as shielding materials on future spacecraft. Fluences of fragments and surviving primaries were obtained using silicon detectors placed downstream of the targets. Because the targets were thick, allowing the possibility of several generations of nuclear interactions, these data present a challenge to the transport models. Comparisons are made to one specific model, in which the NASA Langley Research Center code NUCFRG2 is used in a Monte Carlo program that also performs a detailed simulation of energy loss.

5. Medical countermeasures for space radiation risks to human exploration

IMMUNE AND OXIDATIVE PATHWAYS ALTERATION IN HUMAN EXPOSED TO SPACE ADVERSE EFFECTS

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Recommendations elaboration for the immune system and oxidative equilibrium protection under space flight adverse effects was the study purpose. Study followed the objectives of 1) immune state and oxidative balance evaluation in human under various doses of ionizing radiation impact and 2) immune-modulating and anti-oxidative tools identification for space flight negative impact prevention and correction. Peripheral blood mononuclear cells study was conducted with flow cytometry and antibodies application. Enzymatic and non-enzymatic indices of antioxidant system state both with primary and final products of lipid peroxidation were assayed. Recommendations for immune system state and anti-oxidative capacity improvement in astronauts are proposed.

PREVENTIVE EFFECTS OF RUNNING EXERCISE ON BONE FRAGILITY OF HEAVY ION IRRADIATED RATS.

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The study was performed to examine the preventive effects of running exercise on bone fragility and bone mineral loss in rats. Rats were running at speed of 15m/min, 90 min per day for 5 weeks after exposed to heavy ion particle with doses of 0, 0.5. 1.0 and 5.0 Gy and the results were compared to those of radiation alone group. Compared with radiation alone groups, the trabecular bone mineral density (BMD) of tibia in the 0.5 + and 1.0 Gy +running groups was increased compared to those of radiation groups. The weights of muscles in the radiation +running groups were heavier than those of radiation groups. The data indicate that running exercise is effective to prevent the decrease in BMD and fragility induced by radiation

GENOMIC INSTABILITY IN THOROTRAST-INDUCED INTRAHEPATIC CHOLANGIOCARCINOMA

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Compared with terrestrial conditions, spaceflight can affect the body with cosmic rays especially with long-term exposure to heavy particles at low dose-rate. The liver is the largest visceral organ and central to whole-body metabolism. Thorotrast, a colloidal suspension of radioactive $^{232}ThO_2$ that emits □-particles, was used as a radiographic contrast during World War II. Thorotrast is known to induce liver cancers particularly intrahepatic cholangiocarcinoma (ICC) after decades of injection. Therefore, analysis of ICC induced by Thorotrast contributes to prevention of human body from cosmic rays.

We could analyze microsatellite instability (MSI) in 25 cases of Thorotrast ICC. DNA was extracted by phenol-chloroform method from paraffin-embedded archival sections and MSI was determined by PCR at 10 loci such as D2S123, BAT-26, D3S1029, D3S1611, BAT-25, D5S346, D8S87, D13S175, D16S402 and D20S100 which are popularly determined for evaluation of MSI. We defined MSI+ as tumors more than 3 loci showed MSI among the cases more than 5 loci were successfully amplified. The frequency of MSI positive phenotype (MSI+) was 56% in Thorotrast ICC whereas 23% in non-Thorotrast ICC. Since the hMLH1 gene and the hMSH2 gene are responsible for DNA mismatch repair, methylation status of the promoter region of these genes were determined by methylation specific PCR after Na-bisulfite treatment. The promoter region of the hMLH1 gene was highly methylated in tumor part compared with adjacent non-tumor part of Thorotrast ICC. However, frameshift mutations of mononucleotide repeats were not observed in Thorotrast ICC. These findings suggest that MSI induced by exposure to Thorotrast mainly reflects clonal expansion of cancer cells and is partly due to inactivation of the hMLH1 gene by hypermethylation.

GENETIC CHANGES INDUCED IN HUMAN CELLS IN SPACE SHUTTLE EXPERIMENT (STS-95)

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Cultured HCT-116 cells were loaded on the Space Shuttle Discovery (STS-95) and grown during the 9-day mission. After landing, many single-cell clones were isolated, microsatellite repetitive sequences in each clone were amplified by PCR, and mutations in the microsatellite loci were detected as changes in the length of PCR fragments. We also analyzed mutation frequencies of ouabain-resistant phenotype. The frequencies of microsatellite mutations as well as ouabain-resistant mutations in the flight sample were similar to those of the ground control samples. Some cells were treated in space with bleomycin which mimics the action of radiation, but the frequencies of microsatellite mutations were not significantly different between the flight and the ground control samples. Under the present flight conditions, neither space radiation (about 20 mSv during this mission) nor microgravity caused excess mutations in human cells.

WATER SOLUBLE VITAMIN E DERIVATIVE AS A RADIOPROTECTOR

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[Purpose]:
This is the summary of our work on the radioprotection by water soluble Vitamin E derivative presented mainly at the Satellite Symposium [Radioprotector for Human Health] after International Symposium on [Radiation and Homeostasis] held in Kyoto Japan on July 13-16, 20001.

1. Radiation inactivation constant of P. Radiola O 1 increased with the G value of the formation of hydroxylated thymine such as thymine glycole in the radiation chemical study of aqueous thymine solution. The effect of various gases and alcohols was explained by free radical mechanism with OH radical formed by the irradiation(Kagiya,1982).
2. TMG , 2-(alfa-D-glucopyranosyl) methyl-2,5,7,8-tetramethylchroman-6-ol), as a water soluble Vitamin E derivative showed excellent antioxidant activity (Murase,1998).

3. TMG inhibited radiation conversion of supercoiled plasmi DNA to open circular linear form and thymine conversion to thymine glycole in aqueous solution(Nair,2001).
4. Radioprotective effects of various water soluble Vitamin E derivatives such as TMG inhibited radiation damages of cells in vitro and in vivo (Kunugita , 1996).
5. Post i.p.infusion of TMG (0.6g/kg) inhibited radiation damage on bone marrow chromosomes of the mice in sublethal whole body irradiation (Satyamitra,2001).
6. Both of pre-oral administration of TMG(2.0g/kg) and post i.p. infusion of one (0.6 g/kg) inhibited the radiation death of mice (Shimanskaya, 2001).
7. The death of embryonic mice was inhibited by TMG (0.6g/kg, i.p.). The death , malformation, skeletal anomality, micronuclei and apoptosis in organogenesis stage of embryonics were inhibited by the TMG as well(Gu. 2001).

[Conclusion]:
TMG as a radical scavenger is expected to use as an effective radioprotector for not only high dose acute exposure to radiation source but also low dose chronic one for the workers in space and radiation field and the patients in radiotherapy .

PROTECTIVE EFFECTS OF CIMETIDINE ON RADIATION-INDUCED MICRONUCLEUS AND APOPTOSIS IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES

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Radioprotective effects of cimetidine, which has been used clinically as an antagonist of H2 receptor, on radiation-induced apoptosis in human peripheral blood lymphocytes prepared from healthy donors were studied. Cells were treated with cimetidine before or after X-irradiation, and then cytokinesis-blocked micronucleus assay and flow cytometry for measurement of phosphatidylserine externalization were utilized to evaluate the radiation-induced cytogenetic damage and apoptosis. The protective effect of pre-irradiation treatment of cimetidine on radiation-induced micronuclei was dependent on the concentration. The maximum protection rates of cimetidine (1 mM) on frequencies of micronuclei were 38.8% and 30.2% treated before and after X-irradiation (5 Gy), respectively. Protective effects of pre- and post-irradiation treatment of cimetidine on radiation-induced early apoptosis and decreased activity of caspase-3 were observed. The study of electron spin resonance-spin trapping with 5,5'-dimethyl-1-N-oxide revealed that the rate constant of cimetidine with radiation-induced OH radicals is about 4.5 x 10^9 (liter/mol/s). Cimetidine did not significantly increase the intracellular concentration of glutathione. These results suggest that cimetidine suppresses radiation-induced micronucleus and apoptosis via OH radicals scavenging and intracellular antioxidation mechanism. Cimetidine appears to be a useful candidate for the future development of post-irradiation radioprotectors.

DECREASED RADIATION SUSCEPTIBILITY IN RESIDENTS OF HIGH BACKGROUND RADIATION AREAS: POSSIBLE IMPLICATIONS IN LONG-TERM HABITATION IN SPACE

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In the past millenium, man successfully experienced relatively long time space missions. No doubt, in a near future deep space journeys as long as a few years would be inevitable. Despite current advances,

there are still some great problems that limit the duration of such long-term space missions. Radiation risk due to exposure to high levels of cosmic ray clearly is among these main problems. The high LET component of space radiation, neutrons especially, make the major contribution to the genetic risks. It has been reported recently that pre-exposure to low doses of neutrons may induce a radioadaptive response in cells received subsequent high neutron doses. We have previously shown that in high level natural radiation areas, cultured human lymphocytes of the inhabitants who received annual whole body doses as much as 170 times more than those of a control area (2635.4 mSv and 15.5 mSv respectively) when subjected to 1.5 Gy challenge dose, were significantly more radioresistant compared to the residents of the control area. Furthermore, our preliminary results indicated that there was no difference between the frequencies of chromosome aberrations in the non-irradiated cells of high-level natural radiation areas and those from the control area. Based on our data, we believe that studies on radiation susceptibility and radioadaptive response may play an important role in evaluating the health risks of future long-term deep space missions.

RADIATION RISK STRUCTURE IN APPLICATION TO SPACEFLIGHT RADIATION HAZARD ESTIMATION.

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The impact of ionizing radiation causes health deterioration of a man and the increase of the probability of his death per time unit (death probability rate) or within some fixed time interval (radiation risk). The additional increase of death probability rate taking into account both the direct death probability and the probability of specific and non – specific diseases results in decreasing the expected life span that can be used as the individual detriment caused to a cosmonaut by space radiation impact. If to determine radiation risk as probability of causing detriment expressed by the established value of expected life span caused by acute (deterministic) and delayed (stochastic) radiobiological consequences, it is possible to obtain a more precise criterion for space hazard estimation. With the help of this criterion it is possible to take into consideration the radiation induced probability of change of the majority of health components and not only additional death probability caused by radiobiological consequences as it is being realized at present.

EXPLORING NOVEL GENES INDUCED BY LOW-DOSE IONIZING IRRADIATION BY RETROVIRUS-MEDIATED GENE TRAP SCREENING

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A modified gene-trap method has been developed to examine transcriptional up-regulation of genes upon specific cellular signaling. We used this screening method to detect novel genes induced by low-dose ionizing radiation in human tumor cells. After transfection of ROSA-nGBT retrovirus, we treated A549 a human lung cancer cell line by 2-5 Gy of ionizing radiation or bleomycin. Transfected cells were first

selected in the medium contained with BLA-S. In the second screening of isolated trap lines, we performed X-gal staining to analyze reporter gene expression using ionizing radiation or bleomycin. For positively stained trap lines, we compared isolated DNA sequences using 5'- and 3'- RACE, and then studied on radiation-responsiveness of the promoter/enhancer by the dual luciferase assay. Among 1450 BLA-S resistant trap lines, we specified several clones. One of the screened clones was identical to upstream flanking sequences of c-IAP2 gene. c-IAP2 inhibits apoptosis and hence c-IAP2 gene may play a significant role in cellular protection against ionizing radiation. To examine radiobiological significance of the other clones, we are currently examining several candidates in searching for novel radiation-inducible genes. To decrease space radiation risks to human exploration, biological intervention should be considered as well as physical protection.

NEW STRATEGIES FOR THE PREVENTION AND TREATMENT OF RADIATION INJURY: POSSIBLE IMPLICATIONS FOR COUNTERING RADIATION HAZARDS OF LONG-TERM SPACE TRAVEL

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New strategies for the prevention and treatment of radiation injuries are currently being explored. The ultimate aim of this effort is to develop globally effective, nontoxic pharmacologics that significantly enhance resistance and repair of injured tissues. The preventive treatments under review encompass such diverse pharmacologic classes as novel immunomodulators, organ-specific stimulants, repair-enhancers, polyfunctional radical-trapping agents, nutritional antioxidants, and cytokines. The first treatment group that shows promise includes the androstene steroids, whose archetype is 5-androstenediol (AED). AED is a well-tolerated, long-acting steroid with broad-spectrum radioprotective attributes that include not only protection against acute tissue injury, but also reduced susceptibility to infectious agents, as well as reduced rates of neoplastic transformation. Other potentially useful radioprotectants are currently under study include vitamin E, genistein, and phenylacetate. The second treatment group includes two well-defined hematopoietic growth factors (cytokines), G-CSF and IL-11. Both of these agents have proven, but limited efficacy when given singly in treating the severe, life-threatening myelosuppression that often accompanies acute, high-dose radiation and/or chemical exposures. Given as single agents in a series of daily doses following exposure, G-CSF and IL-11 can help minimize the intensity and duration of granulocytopenia and thrombocytopenia, respectively. In combination (G-CSF + IL-11) the therapeutic effect is supraadditive. Blood granulocyte and platelet levels, and progenitorial marrow compartments are increased by several-fold during the post-irradiation recovery period, thereby reducing risk of fatal sepsis and uncontrolled bleeding. Risk of blood sepsis following acute radiation injury can also be reduced by the therapeutic targeting of the gastrointestinal system with another recombinant cytokine, keratinocyte growth factor (KGF). KGF exerts significant reparative action on injured epithelia of the gastrointestinal tract, thereby serving to block the translocation of intestinal bacteria into the interstitial spaces and, in turn, into the blood. Our results suggest that a new paradigm is evolving for preventive treatments of radiation injuries and is based on a combined treatment approach using newly identified, nontoxic, broad-spectrum prophylactic agents followed by postexposure use of cytokines with organ-specific reparative functions.

RIBCYS AND VITAMIN C APPEAR TO ALTER THE SPECTRUM OF MUTATIONS GENERATED BY LET=100 CARBON IONS EVEN WHEN ADDED 30 MINUTES AFTER IRRADIATION

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We here provide evidence that non-toxic concentrations of RibCys or vitamin C can alter the spectrum of $CD59^{-}$ mutations induced by carbon (290 MeV : LET = 100 KeV/□) in A_L cells even when added ½ hour after irradiation. The major change was to reduce the incidence of small mutations without much affecting the incidence of large (>3 mbp) mutations. Our hypothesis is that **L**ong **L**ived **R**adicals (LLR) as described by Watanabe and colleagues[A] , which are disarmed by vitamin C or RibCys are responsible for delayed mutagenesis. The ability to affect delayed mutagenesis has important implications for travel in space. Supported by NASA/NSCORT to CSU& LBL (W19133),NIH/NCI 36447 and the Walab Discretionary Fund. [A]Ayoshimura et al., Rad. Res 136 (1993)

BRACHYTHERAPY FOR EARLY ORAL TONGUE CANCER -LOW DOSE RATE TO HIGH DOSE RATE-

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Purpose: To examine the compatibility of low dose rate (LDR) with high dose rate (HDR) brachytherapy.
Methods and Materials: We reviewed 399 patients with early oral tongue cancer (T1-2N0M0) treated by brachytherapy only at Osaka University Hospital between 1967 and 1999. For patients in the LDR group, treatment sources consisted of Ir-192 pin for 329 patients (1973-1996, prescribed dose was 61-85 Gy: median 70Gy), Ra-226 needle for 187 patients (1967-1986, 55-93 Gy: median 70Gy). Ra-226 and Ir-192 were combined for one patient. Ir-192 HDR (microSelectron-HDR) was used for patients in the HDR group (1991-present, 48-60 Gy median 60 Gy). LDR implantation were performed via oral and HDR via submental approach. Patients in the HDR group received radiotherapy at 6 Gy/ fraction and two fractions were administered per day (at least 6h interval).
Results: Three- and 5-year local control rates for patients in the LDR group were 84% and 80%, respectively, and those in HDR group were both 84% (n.s.). HDR brachytherapy showed the same nodal control rate as LDR brachytherapy (69% at 3 years).
Conclusions: HDR brachytherapy achieved the same locoregional result as LDR brachytherapy.
Dose rate conversion factor of 0.86 is applicable for HDR in the treatment of early oral tongue cancer.

6. Recent advancement in hadrontherapy related to space radiation effects

RESISTANCE INDUCED BY CARBON-ION IRRADIATION OF MOUSE GUT CRYPT CELLS

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Gut crypt survivals after multiple irradiations with 1 Gy of 20 keV/micrometer carbon ions were investigated. The interval time between each irradiation was 4 hr, and dose response was obtained by adding graded doses. Isoeffect doses to produce 10 crypts were unchanged when 1 Gy-per-fraction was repeated less than 5 times, but increased after 7 to 11 fractions. Isoeffect doses for 200 kVp X rays, however, linearly increased with an increase of fractions. Do values of carbon ions but not X rays increased when number of 1 Gy-per-fraction increased from 7 to 11. It is concluded that repeated irradiation with carbon ions induces radioresistance in gut.

THE CANCER TREATMENT SYSTEM AT HYOGO ION BEAM MEDICAL CENTER (HIBMC)

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Hyogo Ion Beam Medical Center is a new ion beam treatment facility which opened in April 2001. Ion Beam Treatment at this Center comprises of an ion beam treatment system, a treatment planning system and a treatment verification system. Although the treatment appears to be the result of the ion beam treatment because of the system's size, our clinical trial revealed that each component system is very important. It is important to consider the development and management of future facilities for ion beam treatment, which is based on the procedure and methods of the conventional radiotherapy.

BORON NEUTRON CAPTURE THERAPY FOR MALIGNANT TUMORS IN KYOTO UNIVERSITY

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The institute started boron neutron capture therapy study for malignant glioma and melanoma in 1990. Until 1997, thermal neutron beam with Cd ratio over 5000 was employed, and thereafter a mixed neutron beam of thermal, epithermal and fast neutrons has been used for malignant glioma. On the other hand, malignant melanoma patients have been treated by thermal neutron beam. Until end of 2000, 60 cases consisting of 17 anaplastic astrocytoma (AA) and 43 glioblastoma multiforme (GBM) were irradiated

neutrons intraoperatively by combining either of 2 kinds of boron compounds, i.e., borocaptate (BSH) and para-boronophenylalanine (BPA). Five-year survival rates are around 40% and 10% for AA and GBM, respectively. The results on GBM and AA were identical or superior to the results after standard treatment reported by Japan Neurosurgical Society, respectively. Moreover, 1/3 of GBM patients was recurrent case and received BNCT as a final treatment. Therefore, BNCT is considered to be superior to the standard treatment to achieve long term tumor control or cure. Although over radiation dose to the surrounding normal brain could not be avoided, there exist one recurrent GBM case that survived over 5 years after BNCT. Fifteen cases of malignant melanoma were treated, and 60% 5-year survival rate and over 80% local control rate were achieved. One of prominent features of BNCT for melanoma is the skin preserving high quality even after irradiation of neutrons. My institute are waiting GBM patients who will be enrolled in new postoperative BNCT protocol by epithermal neutron beams and combination of two boron compounds: BSH and BPA. Basic research related to BNCT and neutron radiobiology will be presented also in the meeting.

EARLY EFFECT OF BRAIN IRRADIATION WITH LOW DODE OF CARBON-BEAMS ON MEMORY FUNCTION IN THE MICE

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Cerebral dysfunction is one of the major concerns associated with radiotherapy of brain tumors. However, little is known about the neurochemical basis of brain dysfunction induced by carbon-beams irradiation. We investigated early and delayed consequences of brain damages caused by carbon ions. Brain of ddy male mice was locally irradiated with 290 MeV/u carbon ions. A Spread-Out-Bragg-Peak of 5-mm width was used to locally irradiate brain. At 36 hr after irradiation, impairment of the long-term memory was not observed in the irradiated mice compared to control. But, mice irradiated with 1~30 Gy showed marked deficits in water maze working memory task compared with age-matched controls. Furthermore, mice receiving 1~30 Gy irradiation not showed degeneration of hipocampal at 36 hr after irradiation. 30 Gy irradiated mice showed marked deficits in water maze place learning at 16 weeks after irradiation, particularly neuronal degeneration was observed in the hippocampus. The findings further suggest that although 30 Gy irradiation-induced hippocampal degeneration is substantial impairment, cognitive deficits may be detected after a low dose and early effect, not associated with the histrogical damage.

HEAVY ION RADIOTHERAPY FOR PANCREAS CANCER AND RECURRENT OF RECTAL CANCER

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There have been international interests in the use of charged particles in cancer radiotherapy. In June 1994 clinical research was begun using carbon ions at our institute.Charged particle offer theoretical advantages in treating pancreas and rectal cancer. Excellent localization of energy into a tumor can be obtained using carbon ions. Increased effectiveness against the relatively hypoxic pancreas cancer and recurrent rectal cancer cells is anticipated because of the high relative biologic effectiveness (RBE). This present discusses the experience in using carbon charged particles in treating 6 patients with pancreas carcinoma as preoperative radiation therapy and 8 patients with pelvic recurrence of rectal cancer at NIRS between 1999 and 2001.Our results clearly suggests the usefulness of heavy ion radiotherapy in the treatment of pancreas carcinoma and rectal cancer compeered to conventional photon radiotherapy.

7. The ISS as a platform for human space exploration

ASTRONAUT EVA EXPOSURE ESTIMATES USING CAD MODEL SPACESUIT GEOMETRY

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On-going assembly and maintenance activities at the International Space Station (ISS) require considerably more extra-vehicular activity (EVA) than did the earlier U. S. Space Shuttle missions. It is thus desirable to determine and analyze radiation exposures to those involved as accurately as possible in order for risks to be minimized and established exposure limits not to be exceeded. A detailed CAD model of the U. S. Spacesuit, formulated at NASA Langley Research Center (LaRC), is used to represent directional shielding of the astronaut. The CAD model includes detailed helmet and backpack structure, as well as hard upper torso and multi-layer spacesuit fabric material. The NASA Computerized Anatomical Male and Female (CAM and CAF) models are used in conjunction with the spacesuit CAD model. The ISS trapped proton and electron environments are taken from the orbit-averaged NASA AP8 and AE8 models at solar cycle maxima and minima. Transport and interaction of the energetic particles that propagate through the various spacesuit materials and body tissue are calculated using the NASA LaRC HZETRN code and a recently developed deterministic electron transport code. The doses within the CAM and CAF models are determined from energy deposition at given target points along 968 directional rays convergent upon the point. Doses are evaluated for skin, eye, and blood-forming organ points, as well as for other selected internal organ locations. The shielding effectiveness of the helmet, hard upper torso section, and backpack unit are individually addressed. Dosimetric quantities include contributions from primary protons, light ions, and electrons, as well as secondary brehmsstrahlung and target fragments. Directional dose patterns are displayed on spherical surfaces using a gray-scale intensity representation.

INTERNATIONAL SPACE STATION SHIELDING MODEL DEVELOPMENT

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The Aerospace Safety Advisory Panel, in their report to the NASA Administrator, has criticized the projected radiation levels within the International Space Station (ISS). Methods for optimal

reconfiguration of ISS equipment and optimal augmentation of the ISS shielding to reduce these radiation levels to acceptable levels are now being developed. Computational models of the ISS modules and equipment are being developed in conjunction with computational procedures that model the highly anisotropic ISS radiation environment, to be used with both parametric and organizational optimization procedures. Current analyses are focusing on the crew quarters where the astronauts sleep and the exterior of the station where the astronauts will receive protection from the surrounding ISS modules and their spacesuits. The ISS models developed allow for reconfiguration, to accurately reflect various and subsequent ISS assembly configurations. Currently, users may also interactively change the locations of equipment racks within ISS modules and immediately evaluate the impact of the changes on the internal radiation environment. These tools have been designed to exploit numerical optimization procedures capable of analytically determining configurations that will result in the lowest crew radiation exposures. Additionally, software is being developed which will analytically fit optimally sized panels of lightweight shielding materials to areas like the crew quarters to augment the shielding provided by the surrounding structure and equipment. These tools will allow the mass of the shield augmentation to be minimized while reducing predicted crew exposures to required levels. The optimization process is being integrated into the NASA Langley Research Center's Immersive Design and Simulation Laboratory and will rely on High Performance Computing and Communication (HPCC) for rapid evaluation of shield parameters and their gradients.

HISTORY OF THE NASDA'S LIFE SCIENCE EXPERIMENT EQUIPMENTS IN SPACE.

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Taking a general view of the past ten years of NASDA's Life science experiment in Space. Describe history of the experiment H/W development including typical results from the Space shuttle and Space lab projects.
On the 1992, NASDA had performed the first life science research in Space using the Space lab. The mission is called as the FMPT project. Since then four Space lab projects (FMPT, IML-2, Neulo-lab and STS-95) and several other projects using Space HAB have done. For these projects NASDA had developed Cell biology experiment equipments, Aquatic animal experiment equipments, Radiation monitoring equipments, protein crystallization experiment tools and other support tools for the life science experiment in space. Interesting results are obtained. Introduce the result of early phase developmental of vertebrate animals in the micro-gravity using aquatic animals or chicken embryos as typical space experiment.

GROUND RESEARCH ANNOUNCEMENT FOR SPACE UTILIZATION

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The orbital assembly works of the International Space Station have started in Nov. 1999, marking a new era for human space utilization on a full scale.
Outer space offers an arena where we are able to conduct experiments under many peculiar environmental conditions, such as microgravity and high vacuum, which cannot be obtained on the Earth.
Japan is committed to participating in the International Space Station Program with its on-orbit laboratory, viz., Japan Experiment Module "Kibo". When the space station is constructed, opportunities for human space utilization will certainly increase by leaps and bounds.

Hence, there is a need to accumulate achievement of space-related ground research activities before space experiments are actually proposed in the coming new era of full-scale space utilization. Because we have to efficiently incorporate a wide variety of ongoing research activities into space experiments. Based upon such a need, this Announcement of Research Opportunity aims not only at providing researchers with excellent opportunities to carry out a wide variety of studies, but also at promoting space-related ground research activities as a preparatory step for space utilization using mainly the “Kibo” facilities.

APPROACH TO THE PUBLIC OFFERING OF SPACE LIFE SCIENCE EXPERIMENTS

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Although the assembly schedule of International Space Station (ISS) is running slow, Japanese experiment module "Kibo" will be launched in 2004. After "Kibo" launching, Japanese astronauts would be ready to stay in ISS and Japanese space experiments in ISS would be started as soon as "Kibo" is operated. However, before full-scale operation of ISS and/or for the short duration experiments, we will take advantage of the opportunity of Space Shuttle missions or other resource such as free flier Bion and participate in biospecimen sharing program (BSP) of rodent used for space experiment. The space life science experiments including BSP are selected by the international public offering that purpose is the efficient implementation of space experiments. The international space life science working group (ISLSWG) consisting of seven space agencies in the world (U.S.A., Europe, Canada, Germany, France, Ukraine, and Japan) is leading and stirring this offering. Four times public offering have already been done by now (Japan has participated from the second time).
On the other hand, in Japan, we have also the public offering system of ground-based researches in the life science field (space medicine, biomedical and biological sciences) supporting the experiments aimed to utilize the space environment. This system has been started from 1997.

KIBO (JEM) EXPOSED FACILITY UTILIZATION PLAN

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Kibo (JEM: Japanese Experiment Module) Exposed Facility is a part of Kibo, which is being developed by NASDA (National Space Development Agency of Japan). Kibo will be launched around 2004,5 and attached to the International Space Station (ISS). Kibo Exposed Facility is a facility, which can provide unique environments for experiments, such as microgravity, high-energy cosmic rays, high-vacuum, and wide observability. Now, NASDA is developing following four experiments as initial phase Kibo Exposed Facility utilization.

1. SEDAAP: Space Environment Data Acquisition equipment-Attached Payload
2. MAXI: Monitor of All-sky X-ray Image
3. LCDE: Laser Communications Demonstration Equipment
4. SMILES: Superconducting Submillimeter-Wave Limb-Emission Sounder

THE DEVELOPMENTS OF CENTRIFUGE ROTOR (CR), CENTRIFUGE ACCOMMODATION

MODULE (CAM) AND LIFE SCIENCES GLOVEBOX (LSG) BY NASDA

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The Centrifuge Facility (CF) is a laboratory for space biology research on the International Space Station (ISS), to investigate the fundamental role of gravity in biological systems. NASA and Japan agreed on September 1997 that NASDA provides the following items to NASA as part of the offset of NASA's Shuttle launch services for the Japanese Experiment Module (JEM). Since then, the developments of centrifuge rotor (CR), centrifuge accommodation module (CAM) and life sciences glovebox (LSG) are under way by NASDA. The CAM accommodates 5 active payloads (CR, LSG, Freezer, Hbitat-Holding Racks 1 and 2). The LSG provides enclosed work-space, called "work volume", where biological experiment procedures are conducted, and the CR provides simulated gravity environment (selectable acceleration from 0.01*g* to 2.00*g*) for biological specimen. Although the CF is essential for performing the most promising ISS "world class" biological research, because of budget and technical issues the centrifuge delivery has been delayed until Calendar Year 08.

THE DEVELOPMENTS OF LIFE SCIENCE EXPERIMENT EQUIPMENTS FOR KIBO(JEM*)*

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NASDA has been developing various experiment equipments to conduct space biology researches in KIBO (JEM). The Cell Biology Experiment Facility (CBEF) is a CO_2 incubator to provide a controlled environment (temperature, humidity, and CO_2 concentration), in which a rotating table is equipped to make variable gravity (0-2g) for reference experiments. The containers called "Canisters" can be used to install the Biological Experiment Unit (BEU) in the CBEF. The developments of the first two BEUs are in progress. Engineering models of the Plant / Cell Experiment Units have been accomplished. Other BEUs will be designed to meet each science requirement of experiments using cells, tissues, plants, small animals, or microorganisms. The Clean Bench (CB) provides a closed aseptic work-space for experiment operations. The CB has an air lock (Disinfection Chamber) to prevent contamination, and HEPA filters to make class-100-equivalent clean air inside the work-space chamber. Alcohol swabs and built-in UV lamps are used to sterilize equipments and insides of the CB. A phase contrast / fluorescent microscope is equipped in the CB to support experiments. Flight models of the CBEF and the CB are scheduled for completion in 2002.

AQUATIC ANIMAL EXPERIMENT FACILITY FOR SPACE UTILIZATION RESEARCH

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National Space Development Agency of Japan (NASDA) has developed aquatic animal experiment facilities for NASA Space Shuttle use and has conducted many experiments in space with various aquatic animals. Aquatic animals, especially small fish such as medaka and zebrafish, are useful models for genetics and embryology because of their high productivity, external embryonic development, short generation time, and so on. Also, the previous experiment results with medaka suggested that the small fish have a high possibility of the multi-generational experiment in space. Currently, we are studying the next-generation aquatic animal experiment facility or the Aquatic Habitat (AQH) for both of Space Shuttle and Space Station use. The AQH will have the capabilities for 90-day experiment, that is, life-support function, multi-generational breeding function (for medaka and zebrafish), specimen monitoring capability, specimen sampling capability, and so on. We will introduce the characteristics and advantages of aquatic animals as space utilization research model, the concept of AQH, and the results of multi-generational breeding test of medaka with AQH prototype model.

8. International collaboration on space radiation research and cancer therapy

GEANT4 - A TOOLKIT FOR THE SIMULATION OF THE PASSAGE OF PARTICLES THROUGH MATTER

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On behalf of Geant4 Collaboration

Geant4 is a general-purpose simulation toolkit for elementary particles interacting with matter. Its usage ranges from high energy cosmic or accelerated particle physics, nuclear physics, the assessment of radiation shielding and satellites, and is expanding into medical physics studies. Geant4 provides a comprehensive set of tools for all domains of simulation in these fields: geometry, tracking, detector response, run, event and track management, visualization and user interface. An abundant set of physics models handles the diverse interactions of particles with matter across a wide energy range. The first version of Geant4 was released in 1998. Since then, the production services, user supports and further developments are continuously provided by a world-wide collaboration of more than 100 scientists participating in more than 10 large high energy physics experiments, space science missions and medical science studies. The Geant4 object-oriented design allows the user to understand, customize or extend the toolkit in all domains. In this presentation, capabilities of Geant4 will be outlined putting emphasis on its application to space radiation research and radiotherapy.

A METHOD TO ESTIMATE RADIOBIOLOGICAL EFFECTIVENESS AT A VERY LOW SURVIVING LEVEL OF CELLS

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An estimation method of radiobiological effectiveness at very low-survival (or high-dose) region on a malignant melanoma cells was investigated, for a treatment planning of eye melanoma at HIMAC, where high-dose exposure per each fractionation is required. Survival fractions were obtained using X-rays and heavy-ions at LET values among 13 - 300 keV/μm by colony formation methods for single-cells (low-dose region) and multicellular spheroids (high-dose region) of HMV-I cells. The linear-quadratic (LQ) equation and the multi-target single-hit (MS) equation together with a combined (LMS) equation, $S = \exp(-\square D)[1-\{1-\exp(-D/Do)\}^n]$, obtained from the linear part of the LQ equation and the MS equation were used for survival data fitting. Survival data obtained from single-cells and spheroids were combined each other. The LQ equation fits well for the combined survival data at lower dose region or single-cells survival data. The MS equation fits well combined survival data at higher dose region of spheroid data. The LMS equation fits well for the combined survival data for all dose region tested. We estimated the RBE values of the ion-beams from low to high dose regions by using the combined survival data with LMS equation. The RBE values at very high survival level (> 50 %) were ~3.7 at 300 keV/□m or ~1.8 at 13 keV/□m, decreased with survival level quickly at higher (~ 10 %) survival level and converged at very low survival level to be ~1.5 for ion-beams at LET value 13 - 300 keV/μ□.

RADIOPROTECTIVE EFFECT OF HATAKESHIMEJI *(LYOPHYLLUM DECASTES)* ON THE ORGANOGENESIS STAGE OF EMBRYOS IN ICR MICE

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The organogenesis stage of embryos in ICR mice is most sensitive for radiation. We paid attention to the radioprotective effect of a Hatakeshimeji *(Lyophyllum decastes)* on the radiation induced malformation at the organogenese stage, embryonic death and the effects of Hatakeshimeji *(Lyophyllum decastes)* on the *In vivo* level of the fetuses.[Materials and Methods]: ICR mouse from Japan National Institute of Health was used for the experiment. One or two female mice and one male mouse of same age range were mated for only three hours from 8:00 to 11:00. The pregnant mice were placed in plastic cages for radiation exposure, and were treated with a single whole-body X -radiation at 1 Gy with a dose rate of 35 cGy/min on 8 days after the conception. 100 mg/kg of Hatakeshimeji *(Lyophyllum decastes)* (isotonic sodium chloride solution: 0.2 ml) was injected by i.p.route to the pregnant mice. The embryonic death, external malformations, fetal body weight, sex ratio and embryonic death were observed in these experiments.

[Results]: **Radioprotective effects of Hatakeshimeji *(Lyophyllum decastes)***

	Control	Sham control	1Gy	Hatakeshimeji+1Gy
Preimplantation Deaths(%)	3.0	3.6	1.9	2.48
Embryonic Deaths(%)	3.3	2.2	20	13
Fetal Deaths(%)	0.8	2.17	6.8	6.5
External Malformatations(%)	0.4	1.6	18	13.2
Fetal Body Weights(♂)	1.29	1.44	1.31	1.50
Fetal Body Weights(♀)	1.25	1.37	1.24	1.44

BNL ACCELERATOR-BASED RADIOBIOLOGY FACILITIES.*

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For the past several years, the Alternating Gradient Synchrotron (AGS) at Brookhaven National Laboratory (USA) has provided ions of iron, silicon and gold, at energies from 600 MeV/nucleon to 10 GeV/nucleon, for the US National Aeronautics and Space Administration (NASA) radiobiology research program. NASA has funded the construction of a new dedicated ion facility, the Booster Applications Facility (BAF). BAF construction is scheduled for completion in the winter of 2002. The first beams for research will be available in 2003. The Booster synchrotron will supply ion beams ranging from protons to gold, in an energy range from 40-3000 MeV/nucleon with maximum beam intensities of 10^{10} to 10^{11} ions per second (0.5 second beam spill every second). The BAF Project will be described and the future AGS and BAF operation plans will be presented.

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SECOND CANCER FOLLOWING RADIATION THERAPY FOR UTERINE CERVICAL CARCINOMA.

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Purpose: To examine the incidence of second cancer following radiation therapy and clinical feature.
Materials and methods: Between 1961and 1990, 1877 patients with uterine cervical squamous cell carcinoma were treated radically with radiation therapy alone at NIRS. Patients were followed up intensively and follow up rate at the 10 years after radiation therapy was more than 90%. We diagnosed a radiation-associated second cancer using the following criteria: (1) difference of histologic type from the primary cancer (except for vagina), (2) latency period of at least 2 years after radiation therapy, and (3) the development site in the irradiated field.
Results: Twenty-nine of 1877 (1.54%) patients developed second cancer. The sites of second cancer were rectum in 8 patients, bladder in 3, uterus in 6, ovary in 5, vagina in 2, and bone and soft tissue in 5, respectively. Patient age at diagnosis of cervical carcinoma was 40 to 75 years, with a median of 58 years and at diagnosis of second cancer was 49 to 95 years, with a median of 72 years. Latency period from RT to the development of second cancer ranged from 3 to 27years, with a median of 16 years. Treatment of second cancer consisted of surgery in 12 patients (41%), RT in 4 (14%), chemotherapy in 1 (3%). Median survival from the diagnosis of second cancer was 7 months.
Conclusion: Radiation therapy for cervical carcinoma results in large numbers of long term survivors who can develop second cancers very late in life. The advantage of radiation therapy is considered large enough to compensate the risk of radiation-associated cancer