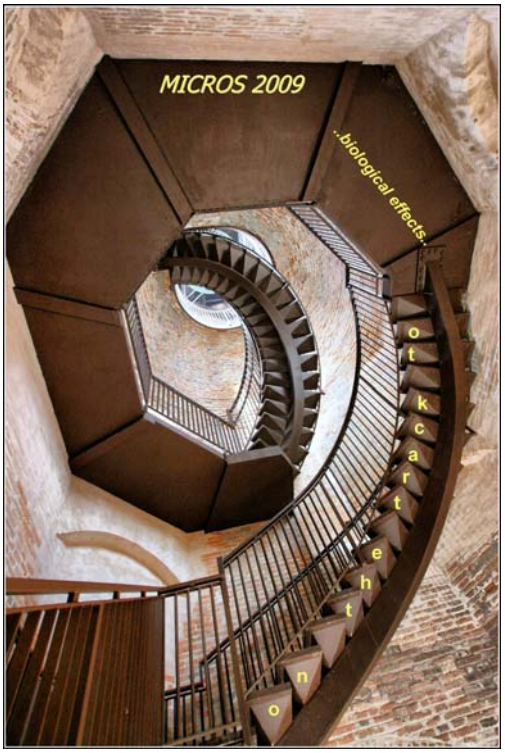
MICROS 2009
15th International Symposium on Microdosimetry

An Interdisciplinary Meeting on
Ionising Radiation Quality, Molecular Mechanisms, Cellular Effects, and Their Consequences for Low Level Risk Assessment and Radiation Therapy

October 25-30, 2009

Verona – Italy



Verona, Torre dei Lamberti-*interior stairs*

Programme and Abstracts

INFN Istituto Nazionale di Fisica Nucleare Laboratori Nazionali di Legnaro

Space Radiation NASA

NASA

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GRAY INSTITUTE FOR RADIATION ONCOLOGY & BIOLOGY

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Investigator Travel Award

ABDELRAZZAK	Abdelrazek	UK
ALLONI	Daniele	Italy
ANDREEV	Sergey	Russia
BEE	Leonardo	Italy
CUGIA	Giulia	Italy
EIDELMAN	Yuri	Russia
FABRIS	Sonia	Italy
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TALEEI	Reza	Sweden

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Sunday, October 25, 2009

15.00-18.00 **Registration at the "Congress Centre" – Hotel San Marco, Verona**

Registration Desk will remain open from Monday Oct. 26 to Friday Oct. 30 throughout the Symposium Scientific Sessions.

17.30-19.00 **Opening Cerimony**:
Opening lecture: *H.H Rossi Lecture:* **Herwig Paretzke**, Germany
Microdosimetry, Track Structures and their Impact on Radiation Risk Assessment

Introduction: Hans Menzel

19.30 ***Welcome Party*** *at the "Hotel San Marco"*

Monday, October 26, 2009

8.15 – 9.15 **Refresher Course:**

Francis A. Cucinotta, *USA*
Nuclear Interactions in Heavy Ion Transport and Event-Based Risk Models

Chair: Ritsuko Watanabe

9.15 – 9.30 **Opening Addresses**

9.30 – 10.45 **Session I - PHYSICS AND CHEMISTRY OF RADIATION TRACKS**

Chair: Peter O'Neill, Larry Toburen

Michael Dingfelder, USA *(invited)*
Heavy Ion Track Structure Simulations in Liquid Water and Bone

Ianik Plante , USA
3D Visualization of Monte-Carlo simulation's of HZE Track Structure and Initial Chemical Species

Chantal Houée Levin, France
Do oxygen free radicals exert a retro-control on the production of superoxide ions by NADPH oxidase? A radiolysis study.

10.45 Coffee-Break

11.15 – 13.15 **Session II - MODELING OF RADIATION ACTION**

Chair: Sergey Andreev, Herwig Paretzke

Werner Friedland, Germany *(invited)*
Mechanistic Simulation of Radiation Damage to DNA and Repair on the track towards Systems Radiation Biology Modelling

Carmen Villagrasa, France
Track structure calculations at molecular scale for the undestranding of initial radio-induced damages in DNA

Shaowen Hu, USA
Computational study on full-length human Ku70 with double stranded DNA: dynamics, interactions and functional implications

Tatsuhiko Sato, Japan
Analysis of cell-survival-fraction data for various heavy ion irradiations based on the microdosimetric kinetic model implemented in the PHITS code

In Memoriam: Aloke Chatterjee (1940-2009)
Mary Helen Barcellos-Hoff, USA

13.15 Lunch at the "Hotel San Marco"

14.30 – 16.00 **Session III - DNA DAMAGE RESPONSE AND RADIATION QUALITY**

Chair: Kevin Prise, Marie Davidkova

Daniele Alloni, Italy
Monte Carlo evaluation of DNA fragmentation spectra induced by different radiation qualities

Giuseppe Schettino, UK
Spatio-temporal investigations of DNA damage repair using microbeam facilities

Yoshiya Furusawa, Japan
Misrepair of DNA Double Strand Breaks causes the peak of LET-RBE relationship on cell killing

Marlis Frankenberg-Schwager, Germany
Chromosomal instability induced by 29 kV mammography X-rays in cells from mutation carriers predisposed to breast cancer

16.00 Coffee-Break

16.30 – 18.00 **Session IV - DNA DAMAGE BY AUGER ELECTRONS**

Chair: Hooshang Nikjoo, Stanizlaw Pszona

Amin I. Kassis, USA *(invited)*
Molecular and cellular radiobiological effects of Auger emitting radionuclides

Roger Howell, USA *(invited)*
Closing the gap between dose and effect for Auger electron and other internal emitters

Fang-yuh Hsu, Taiwan

Cellular dosimetry and microdosimetry for internal electron emitters

Tuesday, October 27, 2009

8.15 – 9.15 **Refresher Course:**

Peter O'Neill, *UK*
Radiation-induced DNA damage complexity and repair

Chair: Melanie Spotheim Maurizot

9.15 – 11.00 **Session V – GENOMIC INSTABILITY, GENE EXPRESSION AND SIGNALLING**

Chair: David Brenner, Marco Durante

Anna Saran, Italy *(invited)*
Long-range radiation damage to unexposed mouse brain: mechanisms and significance

Sally Amundson, USA *(invited)*
Radiation induced changes in gene expression: novel responses at low dose.

Svetlana Sorokina, Russia
Delayed effects of chronic low-dose high-LET radiation on mice in vivo

Abdelrazek Abdelrazzak, UK
The importance of the radiation track structure in the stimulation of intercellular induction of apoptosis in transformed cells following exposures of very low doses of high and low-LET radiation.

11.00

Coffee-Break

11.30 – 13.00

Session VI – Low Dose effects

Chair: Dudley Goodhead, Roger Howell

Phil Hahnfeldt, USA *(invited)*
Tissue population action in low dose cancer risk.

Marianne Sowa, USA
Lack of evidence for low-LET radiation induced bystander response in normal human fibroblasts and colon carcinoma cells

Peter Jacob, Germany
Possible expression of a bystander effect with a dose threshold in lung cancer mortality of Mayak workers

Sergey Andreev, Russia
Dose response prediction for Radiation induced chromosomal instability

13.00 Lunch at the “Hotel San Marco”

14.30 – 15.45 **Session VII – MICROBEAMS AND BIOLOGICAL APPLICATIONS**

Chair: Silvia Gerardi, Giuseppe Schettino

Kevin Prise, UK *(invited)*
Microbeams in Radiation Biology: review and critical comparison

Katsumi Kobayashi, Japan
Development of an X-ray microbeam system to irradiate cytoplasm only of mammalian cells using SR X-rays.

Guy Garty, USA
Design of a novel Flow-and Shoot (FAST) microbeam

15.45 – 16.15 Coffe-Break

16.15 – 18.15 **Session VIII - POSTER SESSION**

(Presentation of the posters with odd numbers)

Wednesday, October 28, 2009

8.15 – 9.15 **Refresher Course:**

W. Bonner, *USA*
H2AX phosphorylation in response to DNA double-strand break formation

Chair: Keiji Suzuki

9.15 – 11.00 **Session IX – RADIATION CARCINOGENESIS**

Chair: André Wambersie, Peter Jacob

Mary Helen Barcellos-Hoff, USA *(invited)*
Do Non-Targeted Effects Matter in Radiation Carcinogenesis?

David Brenner, USA *(invited)*
A new view of radiation-induced cancer

Harmen Bijwaard, Netherlands
Breast cancer risk due to mammography screening

Markus Eidemüller, Germany
Breast cancer risk among Swedish hemangioma patients and possible consequences of radiation-induced genomic instability

11.00 Coffee-Break

11.30 – 13.00 **Session X – PHYSICS AND RADIOBIOLOGY FOR SPACE RADIATION PROTECTION**

Chair: Francis Cucinotta, Tatsuhiko Sato

Marco Durante, Germany *(invited)*
Cellular effects induced by energetic heavy ions: from DNA breaks to chromosomal rearrangements

Sylvain Costes, USA *(invited)*
Evidence of DSB clustering and consequences for Radiation Induced Foci kinetic for low and high LET.

Gunther Reitz , Germany
Effective Dose Determination for Astronauts Using the MATROSHKA Experiment

13.00 Lunch at the “Hotel San Marco”

14.30 – 18.00 Social Tour

Thursday, October 29, 2009

8.15 – 9.15 **Refresher Course:**

Lennart Lindborg, *Sweden*
Microdosimetry and radiation quality determinations in medicine and radiation protection

Chair: Anthony Waker

9.15 – 10.45 **Session XI – PROGRESS IN EXPERIMENTAL MICRODOSIMETRY**

Chair: Reinhard Schulte, Bernd Grosswendt

Stefano Agosteo, Italy *(invited)*
Silicon microdosimetry

Yigal Horowitz, Israel
Thermoluminescence solid state nanodosimetry – The peak 5A/5 dosimeter

Vladimir Bashkirov, USA
Ion Time Projection Chamber for precise imaging of ionizing particle track structure

Stanislaw Pszona, Polonia
Single track nanodosimetry – from Track Ion Counter to Jet Counter

10.45 Coffee-Break

11.15 – 13.15 **Session XII –** (continuation of) **PROGRESS IN EXPERIMENTAL MICRODOSIMETRY**

Chair: Lennart Lindborg, John Dicello

Delia Perez-Nunez, USA
Replacement Tissue Equivalent Proportional Counter for the International Space Station

Shiuchi Tsuda, Japan
Microdosimetry for heavy ion beams using a Wall-Less Tissue Equivalent Proportional Counter

Katerina Brabcova, Czech Republic
Spectrometry of linear energy transfer with track etched detectors in carbon ion beams, MONO and SOBP

Sofia Rollet, Austria
Microdosimetric assessment of the biological quality of a therapeutic proton beam: comparison between numerical simulation and experimental measurements

Anthony Waker, Canada
Spectroscopic dosimetry with a Tissue Equivalent Proportional Counter for in vivo neutron activation facility

Akram Mohammadi, Japan
Influence of voxel size on specific absorbed fractions in a mouse voxel phantom for photons and electrons

13.15 Lunch at the "Hotel San Marco"

14.30 – 16.00 **Session XIII - PARTICLE RADIOTHERAPY**

Chair : Yoshiya Furusawa, Michael Scholz

André Wambersie, Belgium *(invited)*
Isoeffect-dose: A concept for biological weighting of absorbed dose in proton and heavier-ion therapy

Francesca Ballarini, Italy
From radiation-induced chromosome damage to cell death: modelling basic mechanisms and applications to Boron Neutron Capture Therapy

Thomas Friedrich, Germany
Impact of tissue type and effect level on RBE

Ivan Petrovic, Serbia
Interpretation of radiobiological results obtained after proton and carbon irradiations of melanoma cells using numerical simulations with GEANT4 code

16.00 Coffee-Break

16.30 – 18.30 **Session XIV - POSTER SESSION**

(Presentation of the posters with even numbers)

20.30 Social Dinner

Friday, October 30, 2009

8.15 – 9.15 **Refresher Course:**

Keith Baverstock, *Finland*
Can a systems approach help radiobiology?

Chair: Sylvain Costes

9.15 – 10.45 **Session XV – SYSTEMS BIOLOGY**

Chair: Keith Baverstock, Werner Friedland

William Morgan, USA *(invited)*
New Experimental Techniques for Radiation Systems Biology: The Pacific Northwest National Laboratory's Integrated Systems Biology Effort to Understand Cancer Risks from Low Doses of Ionizing Radiation

Francis A. Cucinotta, USA *(invited)*
Biophysics Model of the ATM Signal Transduction Pathway

Gastone Castellani, Italy
Systems Biology and dynamics of ionizing radiation response by multiscale analysis of gene expression measurements.

Pavel Kundrat, Germany
Modelling of intercellular induction of apoptosis in oncogenic transformed cells and radiation effects on the phenomenon

11.00 Coffee-Break

11.30 – 13.30 **Session XVI – ONGOING RESEARCH INITIATIVES AND OPEN QUESTIONS**

Chair: Mark Hill, Phil Hahnfeldt

Mary Helen Barcellos-Hoff, USA
U.S. Department of Energy Low Dose Program

Mauro Belli, Italy
MELODI – the "Multidisciplinary European LOw Dose Initiative"

Guenther Reitz, Germany
ICRP "Task Group 67" Report: Radiation Protection in Space

Andrea Ottolenghi, Italy
The risks to healthy tissues from the use of existing and emerging techniques for radiation therapy

Panel Discussion :

Do non-targeted effects impact the relation between Microdosimetry and Risk?

Chair: D.T. Goodhead
Discussants:
Mary Helen Barcellos-Hoff (USA), Dudley T. Goodhead (UK), William Morgan (USA), Peter Jacob (Germany), Herwig Paretzke (Germany)

13.30 **Symposium Closure**

Lunch at the “Hotel San Marco”

ORAL
PRESENTATIONS

THE 2009 ROSSI-LECTURE: MICRODOSIMETRY, TRACK STRUCTURES AND THEIR IMPACT ON RADIATION RISK ASSESSMENT

H. G. Paretzke

HMGU-Institute of Radiation Protection and Physics Department, Technical University of Munich

Radiation protection is concerned with the protection of man and its environments against inappropriate risk levels of negative health effects of exposures to ionising radiation. To fulfil this task, one has to be able to measure and predict radiation exposures and assess their possible effects. The great radiation physicist Harald H. Rossi (1917-2000) was working for decades on both aspects and significantly influenced many radiation physicists with his ideas of measurements and effect assessment. He introduced the concepts and instruments of microdosimetry as early as 1959 and had great influence on recommendations of ICRU and ICRP. Low pressure proportional counters, the Rossi-counter, have been proven to be excellent measurement tools in mixed fields of non-directly ionising radiation. The concepts of microdosimetry are essentially based on the determination and further use for evaluation of energy deposition frequencies in one -typically spherical- target volume of interest. This information reduction to "dose" in "one microvolume" of the full complexity of charged particle tracks has advantages and shortcomings. Some of these aspects will be discussed in this lecture. With our present, advanced knowledge of the more systemic reactions of irradiated, living objects to radiation tracks radiation risk assessment has become more complicated but closer to reality, and close also to prove the validity of Harald Rossi's late concerns about the uncritical use of a LNTH for low dose health risk estimations

NUCLEAR INTERACTIONS IN HEAVY ION TRANSPORT AND EVENT-BASED RISK MODELS

F. Cucinotta (1), I. Plante (2), A. Ponomarev (2), Myung-Hee Kim (2)

1 NASA; 2 USRA, Houston, USA

The physical description of heavy ion transport in tissue and shielding materials is of interest in radiobiology, cancer therapy, and space exploration, including a human mission to Mars. Galactic cosmic rays (GCR) consist of a large number of ion types over a wide energy range. Energy loss processes occur continuously along the path of heavy ions, and are well described by described by linear energy transfer (LET), straggling and multiple scattering algorithms. Nuclear interactions occur infrequently with mean free paths of several centimeters, however lead to much larger energy deposition than atomic-molecular collisions and alter the composition of heavy ion beams while producing secondary nuclei often in high multiplicity events. We review the main nuclear interaction processes of importance and theoretical approaches for their description. Nuclear fragmentation, elastic scattering, and knockout-cascade processes are described in quantum and Monte-Carlo approaches. Results of the quantum multiple scattering fragmentation (QMSFRG) model for the production of heavy ion fragments and light nuclei through the distinct mechanisms of nuclear abrasion and ablation, coalescence, and cluster knockout are shown to be in excellent agreement with available experimental data for nuclear fragmentation cross sections. A new computer model of the NASA Space Radiation Laboratory (NSRL) called the GCR Event Based Risk Model (GERM code), and applications to stochastic models of biological

HEAVY ION TRACK STRUCTURE SIMULATIONS IN LIQUID WATER AND BONE

M. Dingfelder, I. G. Jorjishvili, L. H. Toburen

East Carolina University, USA

Monte Carlo (MC) simulations of charged particle tracks provide detailed information on highly inhomogeneous spatial distributions of energy depositions, interaction types, and radical species produced. Heavy ions and in particular heavy charged and highly relativistic (HZE) particles are of special interest. They are considered in Medical Physics as a source of radiation for cancer treatment and they pose a potential risk to men's vision of deep space travel. MC track structure simulations rely on reliable interaction cross sections. Liquid water serves as a surrogate for soft tissue while calcium is a major component of bone. Ionization cross sections for charged particles are calculated within the framework of the (relativistic) plane-wave Born approximation (PWBA) or the (relativistic) Bethe approximation. The present model of the dielectric response function (DF) of liquid water has been modified and updated to better reflect new data from inelastic X-ray scattering experiments using synchrotron radiation. We have adopted a model for the DF of calcium. It is based on available experimental and theoretical information. We are currently on the way to calculate and update interaction cross sections for protons with calcium and liquid water and implementing them into the track structure simulation code PARTRAC.

This work is supported by the NASA Grant NNJ04HF39G.

3D VISUALIZATION OF MONTE-CARLO SIMULATION'S OF HZE TRACK STRUCTURE AND INITIAL CHEMICAL SPECIES

I. Plante (1), F. Cucinotta (2)

1 NASA/JSC (USRA) ; 2 NASA/JSC; USA

Heavy ions biophysics is important for space radiation risk assessment [1] and hadrontherapy [2]. The characteristic of heavy ions tracks include a very high energy deposition region close to the track (<20 nm) denoted as the track core, and an outer penumbra region consisting of individual secondary electrons (d-rays). A still open question is the radiobiological effects of d-rays relative to the track core. Of importance is the induction of double-strand breaks (DSB) [3] and oxidative damage to the biomolecules and the tissue matrix, considered the most important lesions for acute and long term effects of radiation. In this work, we have simulated a 56Fe26+ ion track of 1 GeV/amu with our Monte-Carlo code RITRACKS [4]. The simulation results have been used to calculate the energy depiction and initial chemical species in a "voxelized" space, which is then visualized in 3D. Several voxels with dose >1000 Gy are found in the penumbra, some located ~0.1 mm from the track core. In computational models, the DSB induction probability is calculated with radial dose [6], which may not take into account the higher RBE of electron track ends for DSB induction. Therefore, these simulations should help improve models of DSB induction and our understanding of heavy ions biophysics.

References:
[1] Nat. Rev. Cancer 8 465 (2008).
[2] New J. Phys. 10 075005 (2008).
[3] Radiat. Res. 86 185 (1981).
[4] New J. Phys. 10, 125020 (2008).
[5] Costes SV et al. PLoS Comput. Biol. 3, e155 (2007).

DO OXYGEN FREE RADICALS EXERT A RETRO-CONTROL ON THE PRODUCTION OF SUPEROXIDE IONS BY NADPH OXIDASE? A RADIOLYSIS STUDY.

C. Houée Levin, M. Ostuni, M. Gelinotte, T. Bizouarn, L. Baciou

CNRS-University Paris Sud , France

The NADPH oxidase is a protein complex that catalyzes the single electron reduction of oxygen to superoxide anion in response to invasion by bacteria, viruses… and/or in oxidative stress. It consists in several protein subunits. Four of them (named p40phox, p47phox, p67phox and Rac) are cytosolic whereas two are membrane proteins (p22phox and gp91phox) and contain the redox components (two hemes and a flavin molecule) and host NADPH during functioning. Upon appropriate stimuli, rearrangements of numerous protein-protein interactions lead to the translocation of the cytoplasmic complex to the membrane, into the active form of the complex. In order to study the dynamics of interactions and the functioning of the system, we have constructed a "cell-free" system by producing the recombinant cytosolic proteins in our laboratory. The membrane subunits are isolated from bovine blood. The functional system is reconstituted in vitro in the presence of arachidonic acid acting as an activator, which mimicks the cellular activation. The amount of superoxide produced is followed by the reduction of cytochrome c. We have submitted each component of the system alone in aqueous solution to oxygen free radicals produced by gamma radiolysis, and observed that after reconstitution, the production of superoxide is always weakened. However if the complete system is irradiated during the assembly phase, which takes a few minutes, the production of superoxide is either inhibited or slightly boost

MECHANISTIC SIMULATION OF RADIATION DAMAGE TO DNA AND REPAIR ON THE TRACK TOWARDS SYSTEMS RADIATION BIOLOGY MODELLING

W. Friedland, P. Jacob, P. Kundrat

Helmholtz Zentrum München, Institute of Radiation Protection, Germany

The biophysical simulation code PARTRAC enables, by combining track structure calculations with DNA models on diverse genomic scales, to predict DNA damage yields and patterns for various radiation qualities. To improve the predictive capability for later endpoints like mutagenesis or cell survival, continuative models for repair of radiation-induced DNA damage are needed, complementing the PARTRAC code by some 12 orders of magnitude on temporal scale. For the NHEJ pathway of DSB rejoining a stochastic model has been developed; it describes step-by-step by Monte Carlo method attachment and dissociation of repair enzymes involved in this pathway and diffusion motion of DNA ends. Initial DNA lesion patterns from PARTRAC represent damage complexity; its influence on repair kinetics and outcome is implemented via cleaning steps for such DNA ends. Model parameters have been taken from measured attachment kinetics of repair enzymes and adaptation to DSB rejoining kinetics after gamma-irradiation. Four alternative scenarios have been studied, representing different hypotheses on the origin of the slow repair phase. In three scenarios, calculated dose-dependent yields of misrejoined DSB and chromosomal aberrations are in surprisingly good agreement with measurements. However, the evident overestimation of residual DSB after low-dose irradiation reveals the need of model refinements. Nevertheless, the simulation represents a promising step towards systems radiation biology modelling.

TRACK STRUCTURE CALCULATIONS AT MOLECULAR SCALE FOR THE UNDERSTANDING OF INITIAL RADIO-INDUCED DAMAGES IN DNA

C. Villagrasa (1), Z. Francis (1), S. Incerti (2)

1 IRSN/DRPH/SDE/LDRI; 2 IRSN/DRPH/SDE/LDRI; France

The ROSIRIS project aims to study the radiobiology of integrated systems for medical treatment optimisation using ionizing radiations and evaluation of the associated risk. In this frame, one of the research axes is the interpretation of the initial radio-induced damages in DNA created by ionizing radiation (and detected by pH2AX foci analysis) from the track structure of the incident particles. In order to calculate the track structure of ionizing particles at a nanometric scale we used the Geant4 Monte Carlo Code. Geant4 (OOP architecture in C++) offers a common platform, freely available for all users and a relatively easy to use extension interface. Nevertheless, the actual energy cut-off for electromagnetic processes in GEANT4 is set to 250 eV using the low energy processes. But still it is not a suitable value for nanometric applications. To minimize this cut-off value, all the needed interaction types were studied and the corresponding available cross sections were reviewed in the literature, mostly based on the plane-wave Born approximation (PWBA) for inelastic interactions and on semi-empirical models for low energies. The extensions that have been introduced in the code will be presented (Geant4-DNA processes), allowing the simulation of electron interactions (8.22 eV – 1 MeV), protons (100 eV – 100 MeV) and alpha particles (1 keV – 10 MeV) in liquid water. Simulations with photons from 250 eV can also be done using the Livermore data tables.

COMPUTATIONAL STUDY ON FULL-LENGTH HUMAN KU70 WITH DOUBLE STRANDED DNA: DYNAMICS, INTERACTIONS AND FUNCTIONAL IMPLICATIONS

S. Hu (1), H. Wang (2), J. Pluth (3), F. Cucinotta (4)

1 Universities Space Research Association, Division of Space Life Sciences; 2 Department of Radiation Oncology, Emory University School of Medicine, Atlanta, GA; 3 Lawrence Berkeley National Laboratory, Berkeley, CA; 4 NASA, Johnson Space Center, Houston, TX 77058, USA

The Ku70/80 heterodimer is the first repair protein in the initial binding of double-strand break (DSB) ends following DNA damage. In this study we construct a full-length human Ku70 structure based on its crystal structure, and perform 20 ns conventional molecular dynamic simulations on this protein and several other complexes with short DNA duplexes. The trajectories of these simulations indicate that, without the topological support of Ku80, the residues in the bridge and C-terminal arm of Ku70 are more flexible than other experimentally identified domains. We studied the two missing loops in the crystal structure and predicted that they are also very flexible. Simulations reveal that they make important contribution to the Ku70 interaction with DNA. Targeted molecular dynamic (TMD) simulation was also performed for one system with a faraway 14bp DNA duplex. The TMD trajectory and energetic analysis disclose the detailed interactions of the DNA-binding residues during the DNA dislocation and reveal a possible conformational transition for a DSB end when encountering Ku70 in solution. Free energy analysis indicates Ku70 alone is able to bind DNA with relatively high affinity, with consistent contributions from various domains of Ku70 in different systems. The functional implications of these domains in the processes of Ku heterodimerization and DNA damage recognition and repair can be characterized in detail based upon this analysis.

ANALYSIS OF CELL-SURVIVAL-FRACTION DATA FOR VARIOUS HEAVY ION IRRADIATIONS BASED ON THE MICRODOSIMETRIC-KINETIC MODEL IMPLEMENTED IN THE PHITS CODE

T. Sato (1), R. Watanabe (1), Y. Kase (2), C. Tsuruoka (2), M. Suzuki (2) Y. Furusawa (2), K. Niita (3)

1 Japan Atomic Energy Agency; 2 National Institute of Radiological Science; 3 Research Organization for Information Science and Technology

Many studies had been devoted to measure the survival fractions of cells irradiated by various kinds of HZE particles. Those data were generally expressed as a function of LET. However, it is well known that RBE for HZE particles cannot be uniquely determined from their LET, since the spatial divergence of ionization due to the production of delta-rays is not taken into account in the concept of LET. Thus, the ion-species dependences were clearly observed in the LET-RBE curves of the survival fraction data. We therefore reanalyzed the survival fraction data [1,2], using the microdosimetric-kinetic (MK) model implemented in the PHITS code. In the MK model, the cell-survival fractions can be simply expressed as a function of the saturation-corrected dose-mean lineal energy y*, which can be obtained from the probability density of lineal energy y. The probability densities of y at the cell locations in each experiment were calculated by the improved PHITS code [3], considering the contribution from secondary particles produced in the upstream apparatuses such as range shifter. It is found from the analysis that the MK model successfully accounts for the cell survival-fractions under a variety of irradiation conditions, using only y* parameter, i.e. the ion-species dependences cannot be observed in the y*-RBE curves.

[1] Y. Furusawa et al, Radiat. Res. 154, 485 (2000)
[2] C. Tsuruoka et al, Radiat. Res. 163, 494 (2005)
[3] T. Sato et al, Radiat. Res. 171, 107 (2009)

IN MEMORIAM: ALOKE CHATTERJEE (1940-2009)

M. H. Barcellos-Hoff

New York University, NY, USA

Aloke Chatterjee, an internationally known radiation biophysicist, former senior scientist and deputy director of the Life Sciences Division of Lawrence Berkeley National Lab, passed away peacefully, surrounded by loved ones, on Saturday, June 20, 2009 at his home in Clayton, CA at the age of 68. The cause was heart failure. Aloke was born November 29, 1940 in Kolkata, India and came to the United States in 1966. In 1970 - the same year he married his wife, Cathy – he came to Berkeley Lab after getting his Ph.D. in chemical physics from Notre Dame University. His bachelor's and master's degrees in physics were obtained from St Stephen's College at the University of Delhi. At Berkeley Lab his research centered on radiation track structure. He was specifically interested in identifying the molecular mechanisms associated with damage to DNA, which are considered critical to radiation effects. From 1989 to 2001, Aloke served as the deputy director of the Life Sciences Division. During much of this period, he also served as department head for that division's Radiobiology group. Aloke Chatterjee also served on numerous review panels for DOE and NIH. His expertise in low-dose ionizing radiation led him to become the first director of NASA's Specialized Center of Research and Training (NSCORT), which, among other things, looked at the effects of radiation in space on biological functions at the cellular and molecular level. He served two consecutive five-year terms as NSCORT's director

MONTE CARLO EVALUATION OF DNA FRAGMENTATION SPECTRA INDUCED BY DIFFERENT RADIATION QUALITIES

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We have investigated DNA fragment spectra induced in human fibroblasts by irradiation with nitrogen and iron ions of different energies and doses with the Monte Carlo code PARTRAC. The simulations data for both types of ions were analyzed in terms of DNA mass distribution as a function of fragment size, to have a direct comparison with the available experimental data. A relevant result obtained from the simulations is the large production of very small fragments in the size range lower than 1 kbp, usually not accessible experimentally. In particular, the simulations with nitrogen ions were compared with the experimental results published by Höglund and Stenerlöw (Radiat. Res. 155, 818 (2001)). The agreement between the PARTRAC and the experimental DNA mass distributions is very good in all cases. In the analysis of the experimental data the fragment number distribution is obtained from the mass distribution using the mean fragment size of each size range. This unavoidable approximation is good for intermediate and large fragment sizes, but it introduces large errors for the smallest fragments. In fact, the PARTRAC and the experimental fragment number distributions are in excellent agreement except for the point at the smallest size range, which is greatly underestimated by the experimental evaluation. Thus, experimentally the total DSB yield is heavily underestimated, and so is the RBE for DSB production, since gamma rays do not produce a large number of very small fragments.

SPATIO-TEMPORAL INVESTIGATIONS OF DNA DAMAGE REPAIR USING MICROBEAM FACILITIES

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Cellular response to radiation damage is made by a complex network of pathways and feedback loops whose spatiotemporal organization is still unclear despite its decisive role in determining the fate of the damaged cell. Revealing the dynamic sequence of the repair proteins is therefore critical in understanding how the DNA repair mechanisms work. There are also still open questions regarding the possible movement of damaged chromatin domains and its role as trigger for lesion recognition and signalling in the DNA repair context. The single-cell approach and the high spatial resolution offered by microbeams provide the perfect tool to study and quantify the dynamic processes associated with the induction and repair of DNA damage. We have followed the development of radiation induced foci for three DNA damage markers (i.e., gamma-H2AX, 53BP1 and hSSB1) using normal fibroblasts (AG01522), human breast adenocarcinoma cells (MCF7) and human fibrosarcoma cells (HT1080) stably transfected with GFP fusion proteins following irradiation with the QUB X-ray microbeam (carbon X-rays <2 µm spot). The size and intensity of the foci has been analysed as a function of dose and time post irradiation to investigate the dynamics of the above mentioned DNA repair processes and monitor the remodelling of chromatin structure that the cell undergoes to deal with DNA damage.

MISREPAIR OF DNA DOUBLE STRAND BREAKS CAUSES THE PEAK OF LET-RBE RELATIONSHIP ON CELL KILLING

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Repair of DNA double strand break plays very important roles in radiobiological effects, rather than induction of initial breaks. However the detail of the repair system and cell killing at high LET beams is still not well known. We studied the LET dependence of sensitivity on Chicken DT-40 cell lines; ku70^{-} (NHEJ deficient), rad54^{-} (HRR deficient), ku70^{-} rad54^{-} (double deficient), and wild cells using ion-beams from the Heavy Ion Medical Accelerator in Chiba at NIRS. The double deficient strain showed the steepest survival curve, HRR deficient strain follows, and wild strain was the third. The NHEJ deficient strain showed a double phased survival curve. The initial part of the curve was extremely same to that of the double deficient strain. The final part of the curve was much more resistant compare with that of wild strain. The RBEs for repairable strains showed a typical LET dependence, i.e., RBE increase with LET, show a peak at around 200 keV/µm, and then decrease. However, that for irreparable strains does not showed a peak of RBE, and simply decreased with LET above 100 keV/µm, as well as initial yield of DNA dsb in cells. We can conclude that the repair causes the peak of LET-RBE from the difference in LET-RBE spectrum between cell strains that have different repair system but the same genetic background.

CHROMOSOMAL INSTABILITY INDUCED BY 29 KV MAMMOGRAPHY X-RAYS IN CELLS FROM MUTATION CARRIERS PREDISPOSED TO BREAST CANCER

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Women who are carriers of a BRCA mutation have a high risk to develop breast cancer and are advised to undergo early and frequent mammography screening. BRCA1/2 proteins are partners in a complex required for the error-free repair of radiation-induced DNA double-strand breaks by homologous recombination. Since an un- or misrepaired double-strand break may lead to genomic instability and finally to cancer, we asked the question whether mammography is a suitable screening method for familial predisposed women. We have used fibroblasts of three BRCA1, three BRCA2 mutation carriers, one Fanconi anaemia patient with a biallelic mutation (BRCA2-/-) and three controls. BRCA1+/- cell lines have protein truncations increasing from 27.6% (C 2860) to 62.5% (C 2899) to 76.7% (C 2852). BRCA2+/- cell lines (C 2902, C 2845, C 2851) carry the same mutation, allowing to study the influence of the genetic background of carriers. Confluent cells were irradiated with 29 kV mammography X-rays and chromosomal anomalies (Giemsa and chromosome X, 1, 9, 13 and 17-specific FISH) were scored at 1.mitosis and at several population doublings post-irradiation. Aneuploidy with great variation of chromosome numbers as typical for cancer cells was observed for three mutated cell lines (C 2860 (BRCA1+/-), C 2902 (BRCA2+/-) and FA 145 (BRCA2-/-)) several population doublings after exposure to only the lowest dose applied (0.5 Gy). The yield of dicentrics was enhanced 70-fold (FA 145) to 1790-fold (C 286)

MOLECULAR AND CELLULAR RADIOBIOLOGICAL EFFECTS OF AUGER EMITTING RADIONUCLIDES

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Although the general radiobiologic principles underlying external beam therapy and radionuclide therapy are similar, significant differences in the biophysical and radiobiologic effects from the two types of radiation continue to accumulate. In this talk, I will address the unique features that distinguish the molecular and cellular radiobiological effects of Auger electron emitting radionuclides consequent to (i) the physical characteristics of the decaying atom and its subcellular localization, (ii) DNA topology, and (iii) the bystander effect. Based on these experimental findings, it is postulated that the ability of track structure simulations as primary tools in modeling DNA damage and cellular survival at the molecular level would be greatly enhanced when these contributions are factored in.

CLOSING THE GAP BETWEEN DOSE AND EFFECT FOR AUGER ELECTRON AND OTHER INTERNAL EMITTERS

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Unlike most external beams of radiation, radionuclides produce complex radiation fields within the body when they are internalized. While these radiation fields often seem intractable, the unique patterns of energy deposition produced by different classes of radionuclides provide experimental opportunities to explore radiobiology at a spatial level of detail not readily achievable with most other sources of radiation. This presentation will examine microdosimetry aspects of the extreme radiotoxicity of Auger electrons and their exquisite capacity to irradiate specific sites. Auger electron emitters will be compared and contrasted to their alpha and beta particle emitting counterparts. Additionally, the implications of recent discoveries in atomic and molecular physics on the interpretation of the Auger effect will also be addressed. Finally, a glimpse of the potential of radionuclides to contribute to future progress in radiobiology and a variety of fields of study will be offered.

CELLULAR DOSIMETRY AND MICRODOSIMETRY FOR INTERNAL ELECTRON EMITTERS

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Cellular dosimetry and microdosimetry of internal sources are important for applications in the targeted radionuclide therapy such as radioimmunotherapy, the intracellularly localized radinuclide including organically bound tritium, and the boron neutron capture therapy. For these applications, the mean absorbed dose to the target per emission from the source, or the cellular S-value, has been calculated for different subcellular source-target configurations. The single-event lineal energy has also been calculated for similar configurations. In radiobiological applications, the cell nucleus was generally taken as the target for dosimetric and microdosimetric calculations. On a cellular level, the question is how many radioactive atoms are required in a cell in order to apply the cellular S-value. With very few atoms per cell, the stochastic quantity of specific energy should instead be applied. In the present work, Monte Carlo simulations were performed to deal with this question assuming different electron energies and cell dimensions. Another question is what parameter should be used to characterize the target size in defining the energy deposition per unit length. For the energy deposition from crossers, the parameter of mean chord length seemed appropriate. However, this parameter is inappropriate for insiders, starters and stoppers due to the lack of definition of the chord length. Here Monte Carlo simulations were also performed to calculate the specific energy deposition

RADIATION-INDUCED DNA DAMAGE COMPLEXITY AND REPAIR

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The various biological effects of ionising radiation arise in part as a consequence of both the spatial distribution of lesions defined by the radiation track and chemical modifications to DNA. Ionising radiation appears to be uniquely responsible for the production of clustered DNA damage sites, in which two or more elemental lesions are formed within one or two helical turns of the DNA through passage of a single radiation track. A percentage of DNA double strand breaks (DSB) are characterised by the presence of base lesions, abasic (AP) sites or SSB close to the break ends. Predictions from biophysical models indicate that significant levels of DNA lesions are formed in clusters and that their complexity increases with increasing LET of the radiation. As a consequence, it has been hypothesised that they pose problems for the DNA repair machinery. Low LET experiments have verified that the yield of bistranded non-DSB clusters is about four to eight times that of prompt DSB in mammalian cells. Recently, significant advances have been made in the study of the reparability of clustered DNA damage induced by ionising radiation. Drawing on examples from the literature, I will discuss reduced reparability of clustered DNA damage and the consequences of inefficient repair in terms of enhance mutability and latent DSB formation. The consequences of inefficient repair of complex DNA damage will be discussed in the context of low dose radiation-induced carcinogenesis

LONG-RANGE RADIATION DAMAGE TO UNEXPOSED MOUSE BRAIN: MECHANISMS AND SIGNIFICANCE

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Radiation-induced bystander effects have been shown in single-cell systems and in more complex three-dimensional human tissue systems in vitro for an array of biological endpoints having implications in cancer development. However, the carcinogenic potential of such responses has only recently been shown in the mouse. The mechanisms behind long-range radiation effects in vivo remain largely unknown. We have investigated some of the factors in radiation bystander signaling in mouse central nervous system CNS, namely, how soon after irradiation the bystander effects can be initiated and how far the bystander signal can be propagated once it is triggered in vivo, the dependence on radiation dose, whether the same signal can produce different responses in different genotypes. A main focus of our investigation has been on the role of gap-junction intercellular communication (GJIC) in propagating radiation stress signals in vivo through the CNS. We show that GJIC is critical for transmission of long-range bystander damage in mouse CNS. Our data provide a novel hypothesis for transduction of distant bystander effects and suggest that the highly branched nervous system, similar to the vascular network, may play an important role.

RADIATION INDUCED CHANGES IN GENE EXPRESSION: NOVEL RESPONSES AT LOW DOSE.

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The radiation bystander effect is an established aspect of low dose response, but the regulatory mechanisms have not been well elucidated. Global gene expression profiling of exposed or bystander primary human lung fibroblasts showed bystander cells mount a full NFkB response, but a muted p53 response. While common p53-regulated radiation response genes like CDKN1A were expressed at elevated levels in the directly exposed cultures, they showed little or no change in the bystanders. In contrast, genes regulated by NFkappaB, such as PTGS2, IL8 and BCL2A1, responded identically in bystander and irradiated cells. This altered balance of signaling is likely to lead to different outcomes in irradiated cells and their bystanders, perhaps leading to greater survival of bystanders and potentially increasing the risk from any long-term damage they have sustained. Extending our studies to a 3D human skin model, we found structural alterations consistent with measured global gene expression alterations after high or low dose exposures, and in bystander tissue. A disturbance of cell cycle dominates in the high dose exposed tissues, followed by a shift toward terminal differentiation at 24 hours. Tissues exposed to low doses appear to mount a more protective response, and return to a state closer to that of the un-irradiated controls. Network analysis revealed TP53 as the major hub involved in response to high dose exposure, and a new potential regulator of low dose response, HNF4A.

DELAYED EFFECTS OF CHRONIC LOW-DOSE HIGH-LET RADIATION ON MICE IN VIVO

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The delayed effects of chronic high-LET radiation in the dose range of 0.5-16 cGy (0.43 cGy/day) in the radiation field behind the concrete shield of the accelerator of 70 GeV protons (Protvino) on SHK mice have been investigated. The dose dependence, adaptive response (AR), and genetic instability in F1 and F2 generations from males irradiated with a dose of 0.5 cGy and males exposured to combination of irradiation with a dose of 16 cGy and the immunomodulator bendazole hydrochloride (BH) were examined in bone marrow cells using the micronucleus (MN) test. It was found that: 1) irradiation of mice with these doses leads to an increase in the level of cytogenetic damage compared with the level of spontaneous lesions and induces no AR in polychromatic erythrocytes (PCE); 2) the levels of spontaneous PCE with MN in F1 and F2 from males irradiated with doses of 0.5 and 16 cGy and in unirradiated mice are the same; 3) in F1 and F2 from males irradiated with a dose of 0.5 cGy, the sensitivity to irradiation (1.5 Gy of X-rays) does not differ from that of the descendants of unirradiated males; in F1 that was irradiated by the scheme of AR, AR is absent, whereas in F2 generation AR is induced; 4) in F1 and F2 from males irradiated with a dose of 16 cGy, the radiosensitivity increases and AR does not occur; 5) the combined exposure to (BH) and 16 cGy induces no AR in F0 but induces AR in F1 and F2. The magnitude of the AR was equal to that of the descendants of unirradiated males.

THE IMPORTANCE OF THE RADIATION TRACK STRUCTURE IN THE STIMULATION OF INTERCELLULAR INDUCTION OF APOPTOSIS IN TRANSFORMED CELLS FOLLOWING EXPOSURES OF VERY LOW DOSES OF HIGH AND LOW-LET RADIATION

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Ionising radiation (IR) is recognized as a major risk factor for cancer induction in living cells. Ionising radiation not only induces effects in irradiated cells but also initiates stress-inducible signals which may also influence non-irradiated cells. Our previous studies have shown that low doses of radiation to normal non-transformed cells can stimulate apoptosis and selectively eliminate transformed cells from co-culture via cytokine and ROS/RNS signalling. The aim of the study was to identify the importance of the radiation track in stimulating these cellular signalling processes. We have irradiated non-transformed 208F cells with either densely ionizing alpha-particles, sparsely ionizing gamma-rays or ultrasoft X-rays and determined the levels of apoptosis in co-cultured non-irradiated transformed 208Fsrc3 cells. We have shown that low doses of any of these radiations to non-transformed 208F cells lead to an increase in the level of apoptosis in co-cultured, non-irradiated transformed 208Fsrc3 cells as a result of signalling through ROS/RNS and TGFbeta. Using ultrasoft x-rays enabled us not only to vary the dose to the cells but also the percentage off cells irradiated. Although no difference was observed in the IIA response of transformed cells between different radiation qualities at medium to high doses, radiation quality is important at low doses. The results indicate that the stimulation of IIA by IR require both sufficient energy deposition within irradiated cells and fraction of cells irradiated. In conclusion, radiation-induced apoptosis may represent a natural anticancer mechanism, stimulated by extremely low doses of IR, selectively removing transformed cells, but not non-transformed cells.

TISSUE POPULATION ACTION IN LOW DOSE CANCER RISK

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One factor limiting tumor cell proliferation is local shortage of space to grow, a condition that may be alleviated by cell migration, and, paradoxically, reduced cell proliferation capacity and increased cell death within the mass. We developed an agent-based computer model of the interaction of cancer stem cells and their non-stem progeny to study early tumor dynamics. Simulations show that three basic components of tumor growth -- cell proliferation, migration, and death -- combine in unexpected ways to control tumor progression and thus, clinical cancer risk. Increased proliferation capacity in non-stem cells and limited cell migration are shown to lead to space constraints that inhibit stem cell proliferation and tumor growth. By contrast, even slight increases in cell death e.g. from low-dose radiation, lead to a paradoxically accelerated long-term growth owing to the liberation of cancer stem cells and formation of self-metastases. Accelerated growth can be explained by the proliferation of quiescent tumor cells, most notably stem cells, into space made available by cell attrition. Importantly, the process favors the creation of stem cells via the symmetric division of previously-quiescent stem cells, as cancer stem cells tend to be more resistant. This study reveals an unexpected population-level contribution to carcinogenesis risk following radiation exposure, while at the same time informing the stem cell debate in favor of a minority presence of such cells.

LACK OF EVIDENCE FOR LOW-LET RADIATION INDUCED BYSTANDER RESPONSE IN NORMAL HUMAN FIBROBLASTS AND COLON CARCINOMA CELLS

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Purpose: To investigate radiation induced bystander responses and to determine the role of gap junction intercellular communication and the radiation environment in propagating this response. Materials and Methods: We use medium transfer and targeted irradiation to examine radiation induced bystander effects in primary human fibroblast (AG1522) and human colon carcinoma (RKO36) cells. We examined the effect of variables such as gap junction intercellular communication, linear energy transfer (LET), and the role of the radiation environment in non-targeted responses. Endpoints included clonogenic survival, micronucleus formation and foci formation at histone 2AX over doses ranging from 10 to 100 cGy. Results: The results show no evidence of a low-LET radiation induced bystander response for the endpoints of clonogenic survival and induction of DNA damage. Nor do we see evidence of a high-LET, Fe ion radiation (1 GeV/n) induced bystander effect. However, direct comparison for 3.2 MeV a-particle exposures showed a statistically significant medium transfer bystander effect for this high-LET radiation. Conclusions: From our results, it is evident that there are many confounding factors influencing bystander responses as reported in the literature. Our observations reflect the inherent variability in biological systems and the difficulties in extrapolating from in vitro models to radiation risks in humans.

POSSIBLE EXPRESSION OF A BYSTANDER EFFECT WITH A DOSE THRESHOLD IN LUNG CANCER MORTALITY OF MAYAK WORKERS

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Lung cancer mortality data for male workers hired at the Mayak Production Association before 1973 have been analyzed. The two-step clonal expansion (TSCE) model of carcinogenesis was found to describe the data significantly better than empirical models. Smoking, alcohol consumption, lung dose rate from a-radiation due to incorporation of plutonium, and lung dose rate from external radiation were found to influence significantly the TSCE model parameters. In the preferred TSCE model, the dependence of the initiation rate on lung dose rate from a-radiation is a bystander-type dose response with a threshold at about 10 mGy/a. The same threshold value was found for the hyperplastic growth rate. In the empirical models, the dependence of the excess relative risk on lung dose from a-radiation contains a threshold in the order of (100-200) mGy. Although there is no evidence for an effect of the a-radiation in the low dose-rate range, an alternative TSCE model indicates a small effect that could be revealed by a data set with more statistical power. According to these results, models without a threshold generally overestimate strongly average risks in cohorts with low exposures to plutonium. In the preferred TSCE model, effects of external radiation on the hyperplastic growth rate were best described by a linear dependence in the low and moderate dose-rate range without a threshold. Accordingly, the ERR in the preferred empirical model depends linearly on external dose.

DOSE RESPONSE PREDICTION FOR RADIATION INDUCED CHROMOSOMAL INSTABILITY

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Ionising radiation induces chromosome aberrations (CA) in first post-irradiation cell cycle and delayed aberrations observed in descendants of irradiated cells. The latter are believed to be a manifestation of chromosomal instability phenotype (CIN). One of the basic questions is to explain why unstable CA can be observed after many cell generations. To predict dose response for CIN a mechanistic model is elaborated. It focuses on relationship between radiation induced DNA double strand breaks (dsb), CA in first mitosis and lesion transmission through the cell cycle. CA in later mitoses are assumed to be formed owing to dsb generation de novo in each cell cycle and CA transmission from previous cycle. Monte Carlo simulation of processes underlying CIN (dsb induction, repair, first mitosis CA formation, cell cycle kinetics, chromosome lesions transmission) is performed to quantify dose response for CIN triggered by low LET radiation. Variation of CIN dose response with time of cell proliferation is predicted. This finding implies that proliferating cells population has some kind of “memory” about initial DNA damage, or dose, manifested in the form of dose dependence of delayed CA. This occurs despite dose independence for dsb generation rate and elimination of cells with unstable CA. Dose dependence turns into dose independence at times when steady state between CA formation and elimination is established.

MICROBEAMS IN RADIATION BIOLOGY: REVIEW AND CRITICAL COMPARISON

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Microbeams have undergone a renaissance since their introduction and early use in the mid 60s. Recent advances in imaging, software and beam delivery have allowed rapid technological developments in microbeams for use in a range of experimental studies. Microbeams allow the effects of single radiation tracks to be determined in a highly quantified way. More importantly, they allow radiation to be targeted to specific regions within a cell to probe subcellular radiosensitivity. They are also playing an important role in our understanding of bystander responses, where cells not directly irradiated can respond to irradiated neighbours. Although these processes have been studied using a range of experimental approaches, microbeams offer a unique route by which bystander responses can be elucidated. Without exception, all of the microbeams currently active have studied bystander responses in a range of cell and tissue models. Together these studies have considerably advanced our knowledge of the underpinning mechanisms. Much of this has come from charged particle microbeam studies, but increasingly, X-ray and electron microbeams are starting to contribute quantitative and mechanistic information on bystander effects. A recent development has been the move from studies with 2-D cell culture models to more complex 3-D systems where the possibilities of utilizing the unique characteristics of microbeams in terms of their spatial and temporal delivery will make a major impact.

DEVELOPMENT OF AN X-RAY MICROBEAM SYSTEM TO IRRADIATE CYTOPLASM ONLY OF MAMMALIAN CELLS USING SR X-RAYS.

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We already reported our microbeam irradiation system using synchrotron monochromatic X-rays. Our system adopted a precise slit system to make an X-ray microbeam, which enables us to change the beam size arbitrarily larger than 5 micron square. Using this advantage of our system, we have measured dose-survival relationships of V79 cell with two different beam sizes, namely, 10-micron square beam aiming at nucleus only and 50-micron square aiming at whole cell. This work revealed that hypersensitivity in low dose region is more enhanced in nucleus-irradiated cells than in whole-cell irradiated cells. These results suggest that intracellular communication between nucleus and cytoplasm plays an important role in determining the cell death in low dose region. For further investigation, we have developed a method to irradiate cytoplasm only without irradiating cell nucleus. In order to shield the nucleus in the uniform irradiation field, we made a gold mask, 15 micron in diameter and 20 micron thick, on a very thin (200 nm thick) SiN film. The thickness of the gold was determined to decrease the intensity of 5.35 keV X-rays to less than one-thousandth. It was mounted on a small X-Y stage and set in the system between the slit system and the sample stage. Using a scintillater dish, we adjusted the position of the mask and the size of the beam, and irradiated V79 cells, leaving the nuclei unirradiated. Survival curve of cytoplasm-irradiated cells will be presented.

DESIGN OF A NOVEL FLOW-AND SHOOT (FAST) MICROBEAM

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RARAF - Columbia University, NY, USA

Current microbeam systems typically irradiate cells adhered to a thin membrane. The cells are mechanically moved to the location of the microbeam where they are individually targeted, either by a precision mechanical stage or by deflecting the beam slightly to hit individual cells (Point & Shoot). There are two drawbacks to this procedure. First, it only allows irradiation of adherent cells, which can be made to adhere to the membrane. Second, the positioning of the cells limits irradiation throughputs to under 10,000 cells/hour, limiting the possibility to probe rare endpoints such as mutagenesis and oncogenesis. We describe here a completely novel miocrobeam technology, under development at RARAF – the Flow and Shoot (FAST) microbeam. In this system, cells undergo controlled flow through a microfluidic channel intersecting the microbeam path. They are imaged and tracked in real time, using a high-speed camera and dynamically targeted, using a magnetic Point & Shoot system. With the proposed FAST system, we expect to reach a throughput of 100,000 cells per hour, which will allow experiments with much higher statistical power. The implementation of FAST will also allow irradiation of non-adherent cells (e.g. lymphocytes) which are of great interest to many of our users. We present here the design of the FAST microbeam and results of first tests of cell imaging and tracking as well as a discussion of the achievable throughput.

H2AX PHOSPHORYLATION IN RESPONSE TO DNA DOUBLE-STRAND BREAK FORMATION

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Within 10 min of DNA double-strand break (DSB) formation, hundreds to thousands of H2AX molecules in the chromatin flanking the break site are phosphorylated on serine residue 139 (in mammals). Because of this amplified response, virtually every DSB site in a nucleus can be visualized within 10 min of its formation using an antibody to phosphorylated H2AX (?-H2AX). This large amount of biological amplification makes this assay unsurpassed in its sensitivity for the DSB. While H2AX phosphorylation has helped our understanding of DNA DSB recognition and repair, the sensitivity of the assay has also facilitated studies of the involvement of DNA double-strand damage in other biological contexts. One example is the increasing numbers of DNA double-strand lesions in senescing cells and aging animals, including humans and mice. Another is the early involvement of DNA double-strand damage in non-target effects of ionizing radiation and other damaging agents. Phosphorylated H2AX detection may have considerable clinical utility as an almost immediate measure of the effects of biological agents. In cancer treatment, chemotherapeutic agents are used to target replicating tumor cells, often by inducing replication-linked DSBs. H2AX phosphorylation may potentially provide a quantitative measure of the efficacy of these agents to induce DSB damage in individual patients by taking into account their differential sensitivities to particular agents.

DO NON-TARGETED EFFECTS MATTER IN RADIATION CARCINOGENESIS?

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Many studies have shown that irradiated cells and tissues exhibit large scale alterations in gene expression and that the progeny of irradiated cells exhibit altered signaling and phenotypes. Although targeted effects of ionizing radiation like DNA damage are considered to be paramount to its action as a carcinogen so-called non-targeted radiation effects are postulated to impact radiation carcinogenesis. Our prior studies showed that high dose (4 Gy) radiation promotes malignant progression of unirradiated orthotopically transplanted mammary cells. Similarly, a recent report shows that a high radiation dose (3 Gy) increases tumor development in shielded brain of Ptch mutant mice. These in vivo studies support the contention that non-targeted radiation effects may be potent mediators of radiation carcinogenesis but both are high doses, while most occupational radiation exposures of concern to public health are unlikely to be greater than 0.1 Gy. Thus, despite the importance of these processes in carcinogenesis and a better understanding of underlying molecular mechanisms of non-targeted effects in cells, the absence of a direct demonstration that signaling induced low dose radiation modifies carcinogenesis has precluded consideration of its contribution to health effects. Recent experimental studies provide further evidence that non-targeted radiation effects could be a significant component of human health risks following radiation exposure.

A NEW VIEW OF RADIATION-INDUCED CANCER

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Biophysical models of radiation carcinogenesis are important for understanding mechanisms and for interpreting or extrapolating radiation risk. There are two classes of such models: 1) long-term formalisms that track premalignant cell numbers throughout an entire lifetime but treat initial radiation dose–response simplistically, and 2) short-term formalisms that provide a detailed initial dose– response even for complicated radiation protocols, but address its modulation during the subsequent cancer latency period only indirectly. We argue that integration of short- and long-term models is needed. As an example of this approach, we integrate a stochastic short-term initiation / inactivation / repopulation model with a deterministic two-stage long-term model. We assume that radiation can act as an initiator of cancer, by inducing pre-malignant stem cells in stem-cell niches, but also as a promoter of pre-malignant damage, by increasing the average number of pre-existing pre-malignant stem cells per niche, which in turn is subject to post-exposure homeostatic regulation. We show that such an approach is useful at high radiation doses, providing some insight into the mechanisms of radiotherapy-induced second cancers, and also at low radiation doses, shedding some light into the prima facie puzzling patterns of lifetime radiation risk as a function of age at exposure.

BREAST CANCER RISK DUE TO MAMMOGRAPHY SCREENING

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Western populations show a very high incidence of breast cancer and in many countries mammography screening programs have been set up for the early detection of these cancers. Through these programs large numbers of women (900,000 per year in the Netherlands) are exposed to low but not insignificant X-ray doses. ICRP based risk estimates indicate that the mammography screening program in the Netherlands may induce 200 fatal breast cancers. The number of lives saved is estimated to be much higher, but for an accurate calculation of the benefits of screening a better estimate of these risks is indispensable. Here it is attempted to better quantify the radiological risks of mammography screening. A biologically based two-mutation model is applied to breast cancer incidence data obtained from the National Institutes of Health in the U.S. These data concern female TB patients who received high X-ray breast doses in the period 1930-1950 through frequent fluoroscopy of their lungs. The derived accurate model fit allows for a more sophisticated extrapolation of risks to the low exposures and to the higher ages that are involved in mammography screening. It predicts that the Excess Relative Risk doubles when screening starts at age 40 instead of 50, but remains below 1% for current screening practises. These results have implications for the frequency of screening, the number of mammograms taken at each screening, and the minimum and maximum ages for screening.

BREAST CANCER RISK AMONG SWEDISH HEMANGIOMA PATIENTS AND POSSIBLE CONSEQUENCES OF RADIATION-INDUCED GENOMIC INSTABILITY

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Breast cancer incidence among 17,158 female Swedish hemangioma patients was analyzed with empirical excess relative risk models and with a biologically based model of carcinogenesis. The patients were treated in infancy mainly by external application of radium-226. The mean and median absorbed doses to the breast were 0.29 and 0.04 Gy, and a total of 678 breast cancer cases have been observed. Both models agree very well in the risk estimates with an excess relative risk and excess absolute risk at the age of 50 years, about the mean age of breast cancer incidence, of 0.25 Gy^{-1} (95% CI 0.14; 0.37) and 30.7 $(10^5 \text{ BYR Gy})^{-1}$ (95% CI 16.9; 42.8), respectively. Models incorporating effects of radiation-induced genomic instability were developed and applied to the hemangioma cohort. The description of the radiation risk was significantly improved with a model of genomic instability at an early stage of carcinogenesis.

CELLULAR EFFECTS INDUCED BY ENERGETIC HEAVY IONS: FROM DNA BREAKS TO CHROMOSOMAL REARRANGEMENTS

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Risk from exposure to energetic heavy ions is considered one of the main problems for human space exploration. Late stochastic risk estimates, particularly cancer, are affected by large uncertainties. Basic cell biology studies to elucidate the mechanisms involved in genetic damage are necessary reduce the uncertainty and eventually design effective countermeasures. DNA damage is normally considered the primary cellular event leading to late effects, but it is the damage processing that makes the difference between sparsely- and densely-ionizing radiation. Beamline live cell microscopy analysis is a useful tool to visualize and monitor the evolution to cell damage. This damage is then translated into chromosomal aberrations. Our recent experiments in human cells show that the movement of damaged DNA sites is short-range, and the relative position of interphase chromosome domains and particle tracks play an important role in the formation of chromosomal rearrangements.

EVIDENCE OF DSB CLUSTERING AND CONSEQUENCES FOR RADIATION INDUCED FOCI KINETIC FOR LOW AND HIGH LET

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High Z energy ions (HZE) deposit their energy by two main mechanisms, direct ionization due to dense energy deposition along track (high-LET component) and sparsed energy deposition resulting from secondary electrons moving away from the track (delta-rays, low-LET component). In this work, high content image analysis was performed to characterize Radiation Induced Foci (RIF: phosphorylated variant histone H2AX - yH2AX and p53 binding protein 1 - 53BP1), as a function of time and dose following exposure to X-rays and HZE. The imaging approach used could separate the high and low-LET RIF within the same cell exposed to HZE. Doing so, we could unambiguously show that RIF formation is faster along the track as the maximum RIF frequency is reached within 5 min pos-IR, but that their resolution is slower (5-10 hrs half life). In contrast, RIF from delta-rays has a delayed formation kinetic with maximum frequencies reached 30 min post-IR. Live cell imaging of 53BP1-GFP exposed to HZE confirmed these results. Similarly, computing the kinetic response following exposure to X-ray, we show that RIF kinetic and RIF yield are dose dependent, with doses higher than 1 Gy eliciting faster RIF formation but lower RIF yield and slower resolution. Finally, studying various ions, we noticed that RIF frequencies reach a maximum value of ~1 RIF/ µm along the track when LET is greater than 150 keV/µm. Taken together, these data suggest the clustering of DSB within units which are ~1 µm.

EFFECTIVE DOSE DETERMINATION FOR ASTRONAUTS USING THE MATROSHKA EXPERIMENT

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For assessment of the astronaut's radiation exposure, the effective dose can be determined by using radiation transport codes with anatomical models or by applying tissue-equivalent phantoms with dedicated radiation detectors placed at positions of radiation relevant organs. MATROSHKA is an ESA multi-user experiment unit developed and manufactured under ESA contract by DLR for studies of depth dose distribution of the different components of the orbital radiation field at different sites of the organs, occurring in astronauts being exposed during an EVA or inside the International Space Station (ISS). The facility comprises an anthropomorphic phantom to simulate the human body, active and passive detectors for space radiation dosimetry, data acquisition and processing electronics. MATROSHKA was launched with PROGRESS on January 29, 2004 and until now used for one outside and two inside exposures. The MATROSHKA experiment delivered a unique set of data from the evaluation of numerous detectors. This paper concentrates on the results of passive detector systems. A short overview of the MATROSHKA facility and its instrumentation is followed by the results on skin and organ dose measurements and the calculation of effective dose. The data received serve as baseline for further verification and benchmarking of current radiation transport codes and in combination with the codes as requisite for an improved risk assessment for future long term missions.

MICRODOSIMETRY AND RADIATION QUALITY DETERMINATIONS IN MEDICINE AND RADIATION PROTECTION

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Different radiation beams may for the same absorbed dose give different results for a specific biological end point. This is often referred to as a difference in radiation quality. The observed difference may need to be corrected for. In radiation therapy a change of total absorbed dose may be needed, while different radiation quality factors may be applied in radiation protection. Differences in radiation quality are thus important to identify in many practical situations either by measurements or a combination of measurements and calculations. The lecture will discuss some of the more commonly used quantities in particular, LET, and lineal energy, y, their distributions and averages. The numerical values of those quantities are dependent on whether focus is on targets in the micrometer range (chromosomes, cell nucleus etc) or in the nanometer range (DNA structures). Some examples on how microdosimetric results have been used in medical applications and radiation protection situations will be given.

SILICON MICRODOSIMETRY

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Silicon detectors are being studied as microdosimeters since they can provide sensitive volumes of micrometric dimensions. They can be applied for assessing single event effects in electronic instrumentation exposed to complex fields around high-energy accelerators or in space missions. When coupled to tissue-equivalent converters, they can be used for measuring the quality of radiation therapy beams or for dosimetry. The use of micrometric volumes avoids the contribution of wall effects to the measured spectra. Further advantages of such detectors are their compactness, cheapness, transportability and a low sensitivity to vibrations. Anyway, the following problems should be solved when a silicon device for microdosimetry: i) the sensitive volume has to be confined in a region of well-known dimensions; ii) the electric noise limits the minimum detectable energy; iii) corrections for tissue-equivalency should be made; iv) corrections for shape equivalency should be made when referring to a spherical simulated site of tissue; v) the angular response should be evaluated carefully; vi) the efficiency of a single detector of micrometric dimensions is very poor and detector arrays should be considered. Several devices are being proposed as silicon microdosimeters, based on different technologies (telescope detectors, silicon on insulator detectors and arrays of cylindrical p-n junctions with internal amplifications), in order to satisfy the issues mentioned above.

THERMOLUMINESCENCE SOLID STATE NANODOSIMETRY - THE PEAK 5A/5 DOSIMETER

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It has been demonstrated that peak 5a (a low temperature component of peak 5 arises from recombination between a locally trapped e-h in a trapping center/luminescent center complex of ~20Å dimensions (a "2-hit" process) [1]. Peak 5 arises from delocalized recombination arising from a singly-trapped electron (a "1-hit" process). The intensity ratio of peak 5a to peak 5 thus represents a measure of ionization density in a nm volume correlatable with radiation damage in biological systems. Accurate use of this "solid-state nanodosimeter" has been hampered by the low intensity of peak 5a relative to peak 5 of ~ 0.05 following low-ionization density irradiation in samples which are naturally cooled following the 400ºC pre-irradiation anneal. This led to precision of ~ 50 % (1 SD) in the measurement of the 5a/5 ratio. Recently we have demonstrated the development of a new material which improves the precision of measurement [2]. In this paper we report on measurements of the peak 5a/5 ratio for a large variety of radiation fields increasing from 0.11 ± 0.02 following 90Sr/90Y irradiation to 0.43 ± 0.016 for 1.3 MeV protons to 0.80 ± 0.04 for 20.7 MeV I ions.

1. Horowitz, Y.S., Oster, L., Biderman, S. and Einav, Y., (2003) "Localized transitions in the thermoluminescence of LiF:Mg,Ti:Potential for nanoscale dosimetry" J. Phys. D. Appl. Phys., 36, 446-459.
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ION TIME PROJECTION CHAMBER FOR PRECISE IMAGING OF IONIZING PARTICLE TRACK STRUCTURE

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A new instrument for precise imaging of the track structure of ionizing radiation is described. The new instrument utilizes the concept of single-ion registration in low-pressure gas models of condensed matter. The use of gaseous media permits expanding condensed matter dimensions up to a million times, and positive ion registration grants an unprecedented fine resolution in space and ionization quantity. The instrument operates as an ion time projection chamber (TPC): positive ions induced by ionizing radiation in a gas volume are collected under an electric field onto a planar ion detector; drift time measurements and 2D detector readout provide a full 3D track structure reconstruction. This required development of a novel two-dimensional ion detector able to operate in various multi -atomic gases with single-ion sensitivity. First track structure 3D images in propane, air, and water vapor obtained with the prototype of this novel TPC are presented. Further plans to improve the performance of the instrument are discussed.

SINGLE TRACK NANODOSIMETRY – FROM TRACK ION COUNTER TO JET COUNTER

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In a view of the fact, that the DNA molecule (nm size) is main target of biological effects of ionizing radiation. So, at nanometre level the single particle interaction is responsible for the initiations of radiation damage to biologically important molecules. Therefore the single track structure of an interacting particle at nanometre segments has to be taken into account. The first operated set up for single track nanodosimetry studies was described at Fifth Symposium on Microdosimetry in 1975. This set up was called Track Ion Counter, TIC, and was the results of works done at Radiological Research Laboratory, Columbia University in 1972-1973 . The idea of TIC is based on single ion counting of ions created at gas volume of nanometre size when irradiated by single charged particle. After almost 30 years the idea of TIC was successfully developed by a group from Weizmann Institute of Science as an . The device of this type are now operated at PTB and at Loma Linda Univerasity. Another line of development of an experimental nanodosimetry was based on modified idea of differential pumping in order to get the higher sizes of nanosites up to 30 nm (in unit density scale) known as Jet Counter. One of pecularities of this device is an ability to study the low energy electrons interaction with the nanosites. The recent experiment with Jet is motivated by target radio therapy and application of Auger emitters (low energy electrons) I-125. The details will be presented.

REPLACEMENT TISSUE EQUIVALENT PROPORTIONAL COUNTER FOR THE INTERNATIONAL SPACE STATION

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The Tissue Equivalent Proportional Counter (TEPC) used on the International Space Station (ISS) have exceeded their planned useful lives, and are scheduled to be replace with the new units taking advantage of improved technology. Requirements for the new detectors include resolution and vibration resistance equivalent to the old detectors, lower electronic noise, isotropic response reduced weight, and a total wall of 0.5 gm/cm2. The new detector produces the resolution and vibration resistance of the cylindrical detector with the isotropic response and compact size of a spherical detector. The cathode structure consists of A-150 conductive tissue equivalent plastic layers separated by thin polyethylene insulating layers perpendicular to the anode. Each conductive layer is held at the electrical potential needed to produce uniform electric field strength along the anode wire. The new design contains the whole preamplifier inside the vacuum chamber to reduce electronic noise. Also the vacuum chamber uses a novel design with a 0.020 inch aluminum wall in order to achieve the total thickness of 0.5 g/cm2 that is the typical shielding provided by the thinner parts of a space suit. The vacuum chamber has a new bayonet clamping system that reduces the total detector weight to less than half of the old TEPC. These detectors will be used with an advanced electronic system being developed at Johnson Space Center and will replace the TEPC systems currently in use on the space station.

MICRODOSIMETRY FOR HEAVY ION BEAMS USING A WALL-LESS TISSUE EQUIVALENT PROPORTIONAL COUNTER

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Deposit energy distribution is basic information for understanding of biological effects of energetic heavy ion beams. To estimate relative biological effectiveness, RBE, lineal energy, y, can be an appropriate physical index because it can treat each energy deposition by a single event and delta-rays. In the present work, a wall-less tissue equivalent proportional counter, wall-less TEPC, has been designed and used for the measurement of the y distributions for heavy ions in order to verify a biological dose calculation model incorporated in the PHITS code. The wall-less TEPC has a cylindrical detection volume whose height and diameter are both 1 mm. The simulated site diameter was equivalent to a thickness of 0.72 µm tissue. A lineal energy distribution was obtained in the wall-less TEPC irradiated by 500 MeV/u argon broad beam in the y form 2 to 200 keV/µm. It is found that the dose-mean value of y obtained by the wall-less TEPC is 50-60 % of the LET of the argon ions in water, since the delta-rays with relatively low y can be measured. On the other hand, the dose-mean value of y measured by a general TEPC with a tissue equivalent plastic wall is almost equal to the LET. The result indicates that the practical energy deposit in a micrometer-size site would be overestimated in the case of the LET-based estimation. The measurements using the wall-less TEPC will enable us to investigate the lineal energy distributions by kinds of heavy ions with different Z and LET.

SPECTROMETRY OF LINEAR ENERGY TRANSFER WITH TRACK ETCHED DETECTORS IN CARBON ION BEAMS, MONO AND SOBP

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Track etched detectors (TED) were exposed in carbon beam with energy 290 MeV/nucleon at HIMAC-BIO facility. Configuration of beam was either mono energetic (MONO), or spread-out-Bragg-peak (SOBP). For both arrangements, sets of TED were exposed behind increasing thickness of filters from the entrance up to the depths behind Bragg peak. We tested five different types of TED; they all are polyallyl diglycol carbonates, however, according to different production condition and additives, they differ in detector abilities. TED are able to classify particles according to their linear energy transfer in range from 10 to 400 keV.um-1 approximately, thus we are able to compile relevant LET spectra, or even to count other radiation quantities. Employed method enabled detail description of therapeutic beams as well as depth-dose distribution in tissue. The paper will also discuss the possibilities of combination of several TED to achieve the best goal.

MICRODOSIMETRIC ASSESSMENT OF THE BIOLOGICAL QUALITY OF A THERAPEUTIC PROTON BEAM: COMPARISON BETWEEN NUMERICAL SIMULATION AND EXPERIMENTAL MEASUREMENTS

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To preserve the vision using protons treatment for ocular melanoma (especially for posterior pole tumors) and to minimize the damage to healthy tissue, the radiation quality must be precisely assessed. The physical quality of a therapeutic proton beam at the Centre Antoine Lacassagne in Nice (France) has been previously measured using microdosimetric techniques. The measurements were performed with a mini-TEPC (Tissue Equivalent Proportional Counter) with a sensitive volume of less than 1 mm3. The chamber was filled with a tissue-equivalent gas mixture at low pressure in order to simulate a tissue site size with a diameter of 1 µm. The counter was inserted in an eye-phantom and placed at the treatment position in front of the therapeutic beam. Several lucite layers with different thicknesses were inserted into the beam to simulate measurements within different depths of compensator in front of the eye that shapes the beam. Experimental data showed a significant increase of the beam quality in the distal edge of the Spread Out Bragg Peak (SBOP). In this paper, the numerical simulation of this experimental set-up are done with the FLUKA Monte Carlo radiation transport code and with a recently developed particle-track MC code. The simulated microdosimetric spectra are compared with the measured ones at different depth in tissue for a monoenergetic proton beam (E=61.5 MeV) and for a modulated SBOP.

SPECTROSCOPIC DOSIMETRY WITH A TISSUE EQUIVALENT PROPORTIONAL COUNTER FOR AN IN VIVO NEUTRON ACTIVATION FACILITY

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Introduction: The accelerator based in vivo neutron activation facility at McMaster University has been used successfully for the measurement of several minor and trace elements in human hand bones due to their importance to health. Materials and Methods: In this study we present the results of the investigation of spectroscopic dosimetry measurements conducted with a TEPC at the position of hand irradiation in the facility. The lineal energy measurements were conducted in the proton beam energy (Ep) range of 1.884 to 2.5 MeV to study the quality factor (QICRP60), microdosimetric averages, absorbed dose and dose equivalent of neutron fields generated via the 7Li(p, n)7Be reaction. Results and Conclusions: We have observed a continuously increasing trend in absorbed dose with increase in Ep mainly due to an increase in neutron yield and mean neutron energy. However, microdosimetric averages and QICRP60 demonstrated an interesting trend such that maximum values were observed at Ep=1.884 MeV (En=33±16 keV) and then continued to decline with increasing Ep until achieving a minimum value at Ep=2.02 MeV. Following this minimum the microdosimetic quantities started increasing with further increases in Ep. The series of measurements conducted with thermal and fast neutron fields demonstrates that the 14N(n, p)13C produced 580 keV protons in the detector play an important role in the response of the counter under 2.02 MeV proton energy (En = 250 keV).

INFLUENCE OF VOXEL SIZE ON SPECIFIC ABSORBED FRACTIONS IN A MOUSE VOXEL PHANTOM FOR PHOTONS AND ELECTRONS

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Photon and electron specific absorbed fractions (SAFs) are evaluated in mouse organs using the voxel based mouse phantom. In the study, for a mouse voxel phantom two different voxel sizes are considered for evaluation of voxel size effect on SAFs for self and cross-irradiation. For this purpose two voxel phantoms were constructed, both with cubic voxels, one with 0.1 mm sides and the other with 0.4 mm sides. A comparison of their organ masses shows that changing the voxel size from 0.1 mm cube to 0.4 mm cube does not have an appreciable effect on the masses of organs. For instance, the difference between two voxel phantom masses for the eyes is highest (about 8.7%) and for the kidneys is lowest (about 0.01%). The sources are considered to be mono-energetic in the energy range of 10 keV to 4 MeV and the radiation transport was simulated using the Monte Carlo method. The SAFs depend on organ mass for self-irradiation and on geometry effect, i.e source and target shape, and distance between them, for cross-irradiation. In voxel phantom it is important to choose the voxel size carefully since it affects on accuracy of results. Clearly, the smaller size reconstructs more realistic anatomy. Thus comparison of SAFs for self and cross-irradiation in organs of the phantoms with 0.1 mm and 0.4 mm voxel size would show how the values of SAFs depend on voxel size. Also the SAFs in organs of two phantoms would help us to find relation between the parameters which affect on the SAFs.

ISOEFFECT-DOSE: A CONCEPT FOR BIOLOGICAL WEIGHTING OF ABSORBED DOSE IN PROTON AND HEAVIER-ION THERAPY

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When reporting radiation therapy procedures, ICRU recommends to specify absorbed dose at all clinically relevant points. However, the medical outcome does not only depend on absorbed dose but also on a number of other factors such as dose per fraction and radiation quality (RBE). Therefore, weighting factors have to be applied to absorbed dose when different types of treatments are to be compared or to be combined. This has led to the concept of "isoeffect absorbed dose" proposed by ICRU and IAEA. The isoeffect absorbed dose DIsoE is the absorbed dose of a treatment with a reference irradiation that would produce the same effect on the target volume as the actual treatment. It is the product of the absorbed dose (in Gy) used in the treatment and a weighting factor WIsoE (dimensionless). DIsoE = D x WIsoE In fractionated photon-beam therapy, the dose per fraction is one of the main parameters that the radiation oncologist has the freedom to adjust. The weighting factor for an alteration of the dose per fraction is evaluated using the linear-quadratic (a/ß) model. For therapy with protons and heavier ions, radiation quality has to be taken into account. A "generitc proton RBE" of 1.1 is recommended in a joint ICRU-IAEA Report for clinical applications. For heavier ions (e.g., carbon-ion beams), the situation is more complex as the RBE varies markedly with particle type and energy and depth in tissue.

FROM RADIATION-INDUCED CHROMOSOME DAMAGE TO CELL DEATH: MODELLING BASIC MECHANISMS AND APPLICATIONS TO BORON NEUTRON CAPTURE THERAPY

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Cell death is a crucial endpoint in radiation-induced biological damage, since any cancer therapy aims to kill tumour cells and cell death is a reference endpoint to characterize the radiation action in biological targets. Starting from Lea's target theory, many models have been proposed to interpret radiation-induced cell killing. After discussing the main models of cell survival, in this paper we will present a theoretical approach based on the experimentally observed link between chromosome aberrations and cell death [1]. A mechanistic model and a Monte Carlo code originally developed for chromosome aberrations were extended to simulate radiation-induced cell death adopting a one-to-one relationship between the average number of "lethal aberrations" (dicentrics, rings and deletions) per cell and –lnS, being S the fraction of surviving cells. Although the observation by Cornforth and Bedford was related to normal fibroblasts exposed to X rays, in the present work the approach was applied also to intermediate- and high-LET radiation. The good agreement between simulation outcomes and literature data provided a model validation for normal cells exposed to different radiation types. The same approach was then successfully applied to simulate the survival of cells enriched with Boron and irradiated with thermal neutrons at the Triga Mark II reactor in Pavia, to mimic a typical BNCT treatment.

1. M. Cornforth and J. Bedford (1987), Radiat. Res. 111, 385-405

IMPACT OF TISSUE TYPE AND EFFECT LEVEL ON RBE

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The relative biological effectiveness (RBE) quantifies the enhanced effect of ions compared to that of photons. Both experiments and model calculations suggest that RBE depends on the resistance of a cell or tissue type against photon radiation and thus on the ratio of the parameters a and ß of the linear quadratic model. Based on clonogenic cell survival experiments reported in the literature we demonstrate that the correlation between RBE and the ß/a-ratio for different cell lines can be empirically described by a linear relationship within the uncertainty limits of the experimental data. This picture is confirmed by simulations with the Local Effect Model (LEM) which is used to predict the increased RBE of ions for treatment planning in the GSI pilot project in carbon ion therapy and in several future clinical carbon ion facilities. The correlation between RBE and the ß/a-ratio is most prominent for low doses and thus small effect levels, whereas it decreases and finally vanishes with increasing dose. We discuss possible implications of these findings for RBE modelling and treatment planning, also taking into account the variability of involved quantities, reflected by associated error limits.

INTERPRETATION OF RADIOBIOLOGICAL RESULTS OBTAINED AFTER PROTON AND CARBON IRRADIATIONS OF MELANOMA CELLS USING NUMERICAL SIMULATIONS WITH GEANT4 CODE

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Effects of gamma-rays, protons and 12C ions on the HTB 140 human melanoma cells have been extensively studied in the dose range from 2 to 24 Gy. Irradiations were performed at INFN-LNS with the 62 MeV/u protons - at full energy Bragg peak and along spread out Bragg peak (SOBP), and 12C ions - along Bragg curve, including their distal declining edges. Although surviving fractions at 2 Gy were large in all cases, rather high values of relative biological effectiveness were obtained with respect to gamma-rays, showing better effectiveness of 12C than protons. Significant cell inactivation on the distal declining end of the Bragg curve was higher for 12C than for protons. Proliferation capacity was lower for protons than for 12C. This is due to the different quality of damage produced in the irradiated cells. The ratio of irreparable to reparable damages is bigger for 12C than for protons, enabling greater number of cells to maintain active proliferation instead of undergoing repair. As radiation dose is proportional to particle fluence and linear energy transfer (LET) variations of these parameters were examined, particularly for the distal Bragg curve fall off. Detailed numerical simulations of dose, particle energy, fluence and LET distributions as functions of depth were carried out with the GEANT4 code. The role of secondary particles produced by 12C was investigated as well. These simulations enabled better insight and understanding of the measured radiobiological parameters.

CAN A SYSTEMS APPROACH HELP RADIOBIOLOGY?

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The term “systems biology” has many interpretations, some trivial. At the other end of the spectrum of meanings is the “systems approach” based on the early work of Bertalanffy on “General System Theory”. A system can be described as any “ensemble of things that belong together”. A “systems approach” treats the ensemble as a whole from the outset rather than studying its individual components in isolation and then reassembling the whole. In the context of biology a systems approach involves a re-framing of the subject away from traditional molecular pathways in favour of studying the “state” of the system: phenotypic transitions are seen as transitions between system states. I will review the theoretical basis for this approach with an emphasis on the cell as the system, although the principles apply equally to tissues, organisms and populations. Particular attention will be paid to the terminology of systems, such as “complexity”, “emergence”, “non-linearity” etc. and the concepts or “tools” entailed, e.g., state space, attractors, etc.. Radiobiology is the biology that ensues when a system has been perturbed by exposure to radiation. As such it must be securely based in biology which in turn has its foundations in physics. An important impediment to “systems thinking” is the inapplicability of the Newtonian-Cartesian paradigm to complex systems, resulting in complex phenomena sometimes being counter-intuitive.

NEW EXPERIMENTAL TECHNIQUES FOR RADIATION SYSTEMS BIOLOGY: THE PACIFIC NORTHWEST NATIONAL LABORATORY’S INTEGRATED SYSTEMS BIOLOGY EFFORT TO UNDERSTAND CANCER RISKS FROM LOW DOSES OF IONIZING RADIATION

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Improving risk prediction, especially for low doses of ionizing radiation, can be made by linking mechanisms of cellular and molecular processing of radiation damage to macroscopic processes at the tissue, organ and organism levels. Traditionally however, radiation research has been a qualitative science in which parts of the process are studied individually by individual investigators. Systems biology is enabling a transition from this qualitative science to a quantitative and ultimately predictive science. This transition is possible by advances in technology that have created a wealth of new information revealing the enormous complexity underlying biological processes. In higher organisms cells operate in networks to form tissues and organs. Cells regulate their internal functions through networks of interacting proteins. The Pacific Northwest National Laboratory’s (PNNL’s) systems radiation biology program focuses on understanding cellular networks responding to low doses of ionizing radiation. The program takes advantage of PNNL’s expertise in this area and the laboratories traditional strengths in mass spectrometry, high-performance computers, and imaging technologies. It brings together biologists, mathematicians, computational scientists, chemists, physicists and investigators with expertise in instrumentation and applied technologies. This presentation will describe the program, its goals and the research strategy proposed to attain these goals.

BIOPHYSICS MODEL OF THE ATM SIGNAL TRANSDUCTION PATHWAY

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The ATM signal transduction pathway plays a central role in the response of cells to radiation. Because the ATM pathway has been well studied by experiment, it a good candidate for the development of detailed biophysics models of radiation effects that include initial DNA and oxidative damage, protein regulation and cellular responses. The ataxia telangiectasia (AT) disorder is a rate recessive disease where both copies of the ATM gene are mutated, however AT heterozygotes occur more frequently representing 2 to 5% of the general population. DNA damage responses do not differ dramatically between wild type and cells deficient in on copy of the AT gene, however recent studies have shown that AT heterozygotes display altered transcription responses compared to wild-type cells. We have developed a mathematical model of the DNA damage response including ATM signal transduction and the phosphorylated form of the histone variant H2AX, denoted as gammaH2AX, and downstream events including regulation of transcription. We describe a mathematical approache to integrate DNA damage responses with cellular functions following high and low dose irradiation, and to investigate gene dosage effects on responses to ionizing radiation. Differences between deterministic and stochastic models are discussed.

SYSTEMS BIOLOGY AND DYNAMICS OF IONIZING RADIATION RESPONSE BY MULTISCALE ANALYSIS OF GENE EXPRESSION MEASUREMENTS

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We selected, from public databases (Gene Expression Omnibus (GEO), ArrayExpress (EBI) and Stanford Microarray Database (SMD)) sets of gene expression measurements derived from experiments of response to ionizing radiations. Among various experimental designs, we mainly selected those with a time series design in order to identify dynamical responses of selected genes and reconstruct gene networks by a correlation based method. This method, jointly with statistical analysis (Analysis of Variance with false discovery rate correction for repeated measurements (FDR)) allows to identify global variations in large gene expression datasets at different scales and is indicative of co-regulation changes. To reduce the dimensionality of the problem and introduce a-priori biological knowledge, the correlation method has been extended by mapping the array onto gene pathways and ontologies. Multiscale correlation shows that the changes in correlation profiles is not only founded at several scales (whole array, gene family and pathways) but it also informative of significant changes induced by ionizing radiation response and allows pathways synthesis into single funtional forms. This methodology allowed to observe co-regulation between and within several pathways with precise biological functions. One of the principal results of our study is the identification of a common set of genes influenced by ionizing radiation exposure belonging to the family of ion channels.

MODELLING OF INTERCELLULAR INDUCTION OF APOPTOSIS IN ONCOGENIC TRANSFORMED CELLS AND RADIATION EFFECTS ON THE PHENOMENON

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The removal of transformed cells via induction of apoptosis through intercellular signalling by surrounding cells is supposed to represent an important control mechanism limiting carcinogenesis (Bauer 2007 Int J Radiat Biol 83: 873). Low doses of radiation influence the efficiency of this anti-carcinogenesis process (Portess et al 2007 Cancer Res 67: 1246), indicating possible beneficial effects of low doses of radiation mediated by intercellular communication ('non-targeted effects'). Multi-scale modelling studies have been started with the aim to quantitatively understand the signalling system involved and the effects of radiation, and to enable extrapolations from in vivo experiments to physiologically relevant conditions. The model takes into account (i) triggering of effector function in cells in the vicinity of transformed cells, (ii) intercellular signalling between effector and transformed cells, modelled using a chemical kinetics approach and considering cellular release of superoxide, nitric oxide and peroxidase, followed by a complex cascade of chemical reactions leading to the formation of apoptosis-inducing signals, and (iii) execution of apoptosis in attacked cells. The model will be reviewed and its results discussed. Conditions for radiation effects on intercellular induction of apoptosis to be beneficial will be presented. Relevance to physiological conditions will be discussed.

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U.S. DEPARTMENT OF ENERGY LOW DOSE PROGRAM

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DOE Low Dose Program supports research to expand current understanding of normal tissue responses to low doses of radiation and the development of new mechanistic models that incorporate the radiation biology from cellular and molecular actions within tissues to the evolution of cancer as a multi-cellular disease. Since its inception in 1999, Low Dose Program projects have generated more than 600 peer-reviewed publications, 100 of which were published in the last year. The current focus, which is coordinated with NASA's program in space radiation, emphasizes experimental research on radio-adaptive responses, systems genetics of inter-individual variation and low dose and/or low dose-rate effects on epigenetics, proteomics, the immune system, and molecular and cellular hallmarks of aging. Ongoing research in the Low Dose Program promote systems biology approaches that hold promise in providing a modeling framework to facilitate moving new biological paradigms into the regulatory process.

MELODI – THE "MULTIDISCIPLINARY EUROPEAN LOW DOSE INITIATIVE"

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Although there is a wide consensus on the current international radiation protection system, a number of questions still remain in risk assessment of low and protracted exposures. The importance of research to reduce uncertainties in these risks is now recognised globally. In Europe a new initiative, called “Multidisciplinary European LOw Dose Initiative” (MELODI), has been proposed by a "European High Level and Expert Group on low dose risk research" (www.hleg.de), aimed at integrating national and EC (Euratom) efforts. Five national organisations: BfS (DE), CEA (FR), IRSN (FR), ISS (IT), STUK (FI), with the support of the EC, have initiated the creation of MELODI by signing a Letter of Intent (LoI). In the forthcoming years MELODI will integrate in a step by step approach EU institutions with significant programmes in the field and will be open to other scientific organizations and stakeholders. A key role of MELODI is to develop and maintain over time a strategic research agenda (SRA) and a roadmap of scientific priorities within a multidisciplinary approach, and to transfer the results for the radiation protection system. Under the co-ordination of STUK a network have been proposed in the 2009 Euratom Programme, called DoReMi (Low Dose Research towards Mutidisciplinary Integration), that can help the integration process within the MELODI platform. DoReMi and the First MELODI Open Workshop, organized by BfS in September 2009, are now important inputs for the European SRA.

ICRP "TASK GROUP 67" REPORT: RADITION PROTECTION IN SPACE

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A task group, "Task Group 67", of the International Committee on Radiological Protection (ICRP) dealing with radiation protection in space is preparing a report on the "Assessment of radiation exposure of astronauts in space".
Information will be given on the main aims of that report and on the topics which will be included in.

THE RISKS TO HEALTHY TISSUES FROM THE USE OF EXISTING AND EMERGING TECHNIQUES FOR RADIATION THERAPY

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The ALLEGRO consortium (www.allegroproject.eu) on “Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy” is a 2 year project started in February 2009 funded by the European Commission (EURATOM) to address the many aspects of damage to normal healthy tissues that are not yet well understood in both conventional treatment techniques and emerging techniques such as protons and heavy ions. The project includes measurement of radiation doses outside the treatment volume and investigation of the accuracy of methods of dose calculation in this region. The extensive existing databases of radiation treatments and outcomes are used to investigate models of normal tissue damage and second primary cancer. The measurements and data analysis are supported by theoretical modelling and surveys to develop the link between radiobiological mechanisms and empirical normal tissue complication probability (NTCP) models, and to extend conventional models to apply to the emerging techniques. Particular attention is given to the risk of second cancers. Indeed criteria and strategies to quantify (and model) risks for cancer induction by radiotherapy and to optimise treatment plans in radiotherapy to minimise the risk of second cancers, still need to be established. An overview of the consortium strategy and of the ongoing activities will be presented, together with the results achieved during the first part of the project.

POSTER
PRESENTATIONS

A 1

MICRODOSIMETRIC CHARACTERISTICS OF PROTON BEAMS FROM 10KEV TO 200MEV

J. Chen

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Proton beams are of growing interest for radiation therapy due to their special physical and radiobiological properties. Many radiobiological studies have shown that protons have somewhat increased relative biological effectiveness compared to electrons and photons. The radiation quality depends on the kinetic energy and the linear energy transfer of protons. This study focuses on the microdosimetric characteristics of monoenergetic protons from 10 keV to 200 MeV. Monte-Carlo techniques are used to simulate track-segments of protons in water. Within a simulated track segment, a proton of constant kinetic energy undergoes various interactions and deposits energies along its track. Microdosimetric quantities are calculated for track-segments of various initial energies, and for the two components of a track-segment, i.e. the track-core formed by energy deposition of protons and the extended region around the track-core produced by energy deposition of secondary electrons. For radiation therapy applications, the isoeffective dose was introduced. The isoeffective dose is the product of the absorbed dose and a weighting factor which takes into account all factors influencing the clinic effects. Radiation quality is one of those factors, Therefore, the results provided in this study can be used to describe proton beams at various depths with changing kinetic energy and microdosimetric characteristics, and applicable to accurate dose planning in proton therapy.

A 2

A MODEL OF CARBON ION INTERACTIONS IN WATER USING THE CLASSICAL TRAJECTORY MONTE CARLO METHOD

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We present a model calculation for the interactions of carbon ions of energies 1 keV/u to 1 MeV/u in water as a surrogate for tissues. Detailed description of energy deposition of carbon ions in tissue-like medium is of particular interest for describing its biological effectiveness in irradiated cells in biophysical modeling, microdosimetry, and heavy-ion therapy. From a practical point of view, the most interesting impact energy region covers the ion energy at which energy loss per unit path length exhibits a maximum, the so-called Bragg peak. At this energy region, not only ionization, but also charge transfer contributes significantly to the energy-loss processes, giving rise to the complexity of physical interactions. The model calculation is based on the Classical Trajectory Monte Carlo (CTMC) method, for which interactions of three collision partners (projectile ion, target core and active electron) are taken into account. We calculate the cross sections for ionization and electron capture by C6+ ions in water. Interactions of electron and projectile with the target core are simplified using the model potential of screened nucleus. The total cross sections for the target ionization and electron capture, and the energy and angular distribution of secondary electrons in an ionization process are presented. The results from the calculations will be used for implementing a Monte Carlo track structure code for the simulation of carbon-ion tracks of 1keV/u – 1MeV/u.

A 3

FREQUENCY DISTRIBUTIONS OF ENERGY IMPARTED IN NANOMETRE SIZE TARGETS BY ELECTRONS AND IONS

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Linear energy transfer (LET) is an average quantity which cannot display the stochastic of the interactions of radiation tracks in the target volume. For this reason, microdosimetric distributions have been defined to overcome the LET shortcomings. In this paper we report model calculations of frequency distributions for energy depositions in nanometre size targets, diameters 1nm to 100nm, for electrons and ions. Frequency distributions for energy depositions in small size targets with dimensions similar to those of biological molecules are useful for modelling and calculations of DNA damage. Monte Carlo track structure codes KURBUC and PITS99 were used to generate tracks of primary electrons 10eV to 1MeV, and ions 1keV/u to 300MeV/u energies. Delta electrons were followed down to 1eV. Distribution of absolute frequencies of energy depositions in volumes with diameters 1–100 nm randomly positioned in unit density water irradiated with 1Gy of the given radiation were obtained. Data are presented for frequency of energy depositions and microdosimetry quantities including mean lineal energy, dose mean lineal energy, and frequency mean specific energy, dose mean specific energy, and radial dose distributions. Calculated data are compared with other model calculations and published experimental data. The modelling and calculations presented in this work are useful for characterization of the quality of radiation beam in biophysical studies and in radiation therapy.

A 4

CHO-K1 OVERKILL EFFECT AT HIGH LET OF ^{12}C AND ^{20}NE IONS

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The decrease of relative biological effectiveness (RBE) with increasing linear energy transfer (LET) from 438 keV/µm to 1616 keV/µm was estimated using formulas related to the existing theories that explain the effect in terms of cellular and molecular overkill.
For this purpose CHO-K1 cells were irradiated with carbon ions (LET: 438, 576, 832 keV/µm) and neon ions (LET: 1017, 1245, 1616 keV/µm) ions as well as gamma-rays from cobalt source and survival fractions (SF) were estimated. The performed calculations show that:
- the average number of lethal damage events per unit dose (NLD/Gy) decreases with increasing LET values indicating an increase in the level of damage which is in accordance with the theory of Barendsen (Barendsen et al. Rad. Res. 18, 1963),
- the non hit fraction of cells (NHF) increases with increasing LET confirming the theory of Goodhead (Goodhead et al. Int. J. Rad. Biol. 37, 1980),
- the ratio of lnNHF/lnSF is greater than 1.0 and increases with decreasing LET confirming the theory of Kiefer (Kiefer Int. J. Rad. Biol. 48, 1985).
Thus, our results confirm that these theories are different points of view on the dependence of RBE-LET relationship and that they do not contradict but rather complement each other.

A 5

MICRODOSIMETRIC EVALUATION OF NEUTRON FIELD FOR BNCT AT KYOTO UNIVERSITY REACTOR BY USING THE PHITS CODE

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Monte Carlo Particle and Heavy Ion Transport cord System (PHITS) developed recently by Niita et el. enable to find microscopic radiation behavior, since that can calculate all information of the correlation at each nuclear reaction (e.g. kinetic momentum of residual nucleus and two particle correlation). In this study, the results of PHITS calculation, which simulated energy deposition at size of 1μm in boron-neutron capture therapeutic field, were compared with experimental data. Geometry for PHITS calculations based on experimental condition measured by onizuka et el. which is inserted two types of tissue equivalent proportional counters (TEPC) with A-150 wall and 50 ppm boron containing wall into the PMMA phantom at neutron field of Kyoto University reactor (KUR). This field was two irradiation types measured by Sakurai el. (the epithermal neutron mode and the thermal neutron mode). The size of TEPC was the inside diameter of 1.27 cm and the wall thickness of 1.27 mm, and the inside of the wall is filled with low-pressured methane-based tissue equivalent gas. We evaluated alteration of radiation quality with depth by changing insert position of TEPC in PMMA phantom.

A 6

EDDIX - A DATABASE OF IONIZATION DOUBLE DIFFERENTIAL CROSS-SECTIONS

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Use of Monte Carlo track structure is a choice method in biophysical modeling and calculations. To precisely model 3D and 4D tracks the cross-section for the ionization by an incoming ion, double differential in the outgoing electron energy and angle, is required. However, the double differential cross-section cannot be theoretically modeled over the full range of parameters. To address this issue, a database of all available experimental data has been constructed. Currently, the Experimental Double Differential Ionization Cross-sections Database (EDDIX) contains over 1200 digitalized datasets from the 1960's to present date, covering all available ion species (hydrogen to uranium) and all available target species. Double differential cross sections are presented by the aid of an 8 parameters functions fitted to the cross sections. The parameters include projectile species and charge, target nuclear charge and atomic mass, projectile atomic mass and energy, electron energy, and deflection angle. We plan to freely distribute EDDIX and make it available to the radiation research community for use in the analytical and numerical modeling of track structure.

A 7

A MONTE CARLO ANALYSIS OF POSSIBLE CELL DOSE ENHANCEMENT EFFECTS BY URANIUM MICROPARTICLES IN PHOTON FIELDS

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There has been recent speculation regarding micro/nano- sized particles containing heavy elements causing hazardous dose depositions via photon interactions. Specifically, fears have arisen concerning particles of U-238 embedded in living tissue. The claim has been that, when exposed to background radiation, the large photoelectric cross-section, and the cascade that results, might lead to elevated local dose deposition.

To investigate this, MCNP5 was used to model schematic representations consisting of concentric spheres of microparticle and surrounding cells, exposed to the natural background photon distribution. The material of the cells was defined as ICRU 4-element tissue, considering a proximate layer (1μm radius), a 'cell' layer (10μm radius), and surrounding tissue (10mm radius). The energies deposited in the various layers were tallied. The radius of the microparticle was varied (50nm to 1.25μm), and its material defined either as U-238 or tissue; when the results from the two cases were compared, any enhancement could thus be estimated.

It was found that, for a 1μm diameter microparticle, the dose deposited in the inner layer was raised by a factor of ~3.8, and by ~1.1 in the cell layer. For a typical background fluence rate, this corresponds to increased energy depositions of ~100 eV/year in the cell layer, and a few 10s of eV/year in the inner layer. However, any biological effects would likely be dwarfed by those caused by radiation from the U-238 decay-chain.

A 8

ANALYSIS ON THE YIELD AND THE LEVEL OF CLUSTERING OF RADIATION-INDUCED DNA STRAND BREAKS IN HYDRATED PLASMIDS

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Although it is widely accepted that the spatial distribution of strand breaks is highly relevant to the biological consequences of ionizing radiation, to what extent strand breaks are clustered is not usually demonstrated directly from experimental data. To evaluate the spatial distribution of radiation-induced strand breaks, we have developed a simple analytical model based on several assumptions for the generation of strand breaks in plasmid DNA after irradiation. The model assumes that 1) a radiation track "hits" a plasmid with a probability following a Poisson distribution, 2) the "hit" randomly generates strand break(s) with its number following a Poisson distribution within a single, relatively short DNA segment, and 3) a double strand break is formed when each strand has at least one strand break in the segment hit by the track. To find out whether the model is valid, we compared the calculated values to experimental data obtained by the plasmid DNA assay. Taking into account the inherent bias of the plasmid assay, the model described well the experimental results of hydrated plasmids exposed to radiation with low linear energy transfer (LET). Our analysis led to the finding that the yield of strand breaks in hydrated plasmids increases with increasing LET. We suggest that both the pattern of initial energy deposition and the pathway leading to DNA lesions are quite different between low and high LET radiations.

A 9

A NOVEL TECHNIQUE USING DNA DENATUREATION TO DETECT MULTIPLLY INDUCED SINGLE-STRAND BREAKS IN A HYDRATED PLASMID DNA MOLECULE BY X-RAY AND HE ION IRRADIATION

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Many studies on damaged DNA reported on yields of single-(SSB) and double-strand breaks (DSB) in plasmid DNA as a simple model molecule based on the conformational change from a closed-circular to open-circular or linear-form. However, these studies do have some limitations when revealing clustered DNA damage sites. For instance, clustered damage sites induced by high LET radiation are predicted to contain more SSBs with base lesions. These complex SSBs would be underestimated since these multiple SSBs will not cause additional conformational changes if they are on the same strand or on the opposite strand but separated each other sufficiently (>6 bp) so as not to induce a DSB. In order to observe these invisible multiple SSBs, we have developed a novel technique using DNA denaturation by which irradiated DNA is analyzed as single strand DNA (SS-DNA). The multiple SSBs which arise in both strands of DNA, but do not induce a DSB, are measured as molecular size distribution of SS-DNA using agarose gel electrophoresis. We have applied this method to the X- and He2+ ion irradiated sample of hydrated pUC18 plasmid DNA. Obtained dose-response curve of the remaining SS-DNA fraction shows a half of SS-DNA population remains as an intact molecular weight within the experimental resolution (<140 bases) for both irradiations. Contrary to our initial expectation, these results indicate that SSBs are not multiply induced over 140 bp even by high-LET irradiation.

A 10

SIMULATION OF SECONDARY ELECTRON YIELDS FROM THIN METAL FOILS AFTER PROTON IMPACT

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Electron emission spectra from thin metal foils (e.g., Al, Cu, Au and those covered by thin layers of frozen gases, like frozen water) provide valuable information on low-energy electron transport properties in condensed phase materials and can be used to validate or update Monte Carlo (MC) track-structure codes. These codes require reliable interaction cross sections of protons and electrons with the material under consideration as input data. We have recently simulated electron emission yields from liquid water. A comparison with preliminary experimental results showed a good agreement for electron emission energies of 100 eV and higher, but revealed large discrepancies at lower energies. In order to test the accuracy and applicability of our theoretical model assumptions used in the transport of charged particles in liquid water we have calculated total and energy differential inelastic cross sections for Al, Cu and Au using the same plane wave Born formalism. These calculations are based on optical oscillator strengths available in the literature and the d-oscillator dispersion model from Ashley. Elastic electron scattering cross sections are taken from the ICRU report 77. We have implemented a transport model for Cu into the track-structure code PARTRAC and simulated secondary electron emission from thin Cu foils. Preliminary results show similar trends as obtained for liquid/amorphous solid water. This work is susupported in part by the NIH Grant No. 2R01CA093351-04A1.

A 11

DIELECTRIC AND OPTICAL PROPERTIES AND INTERACTION CROSS SECTIONS OF CALCIUM WITH HZE PARTICLES

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Heavy, high energy and highly charged (HZE) particles are a major concern for deep space travel. Little is known about their interaction with biological materials, especially bone and bone marrow. Calcium is a major component of bone and serves as a surrogate for trabecular bone.
Monte Carlo (MC) track structure simulations require reliable interaction cross sections with the material under consideration. Ionization and excitation cross sections for charged particles are calculated within the framework of the (relativistic) plane-wave Born approximation (PWBA) or the (relativistic) Bethe approximation. We have derived and adopted a model for the dielectric response function (DF) of calcium. It is based on available experimental and theoretical information and constraints and uses a modified delta-oscillator extension algorithm. The calculated mean excitation energy is I =172 eV, which is around 10 % smaller than the ICRU recommended value of 191 ± 8 eV. We are currently on the way to calculate interaction cross sections for protons and electrons with calcium and implementing them into the track structure simulation code PARTRAC.
This work is supported by the NASA Grant NNJ04HF39G.

A 12

TOTAL, ELASTIC AND INELASTIC ELECTRON SCATTERING CROSS SECTIONS OF TETRAHYDROFURAN IN THE ENERGY RANGE BETWEEN 20 EV AND 1.0 KEV

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Electron scattering cross sections of biomolecules are of great interest because electrons are produced in a large number as secondary particles by ionizing radiation penetrating tissues and therefore responsible for the great part of radiation damages that are primarily initiated by lesions in DNA. To understand the physical processes leading to DNA damages such as double strand breaks, a comprehensive data base for the electron scattering cross sections of molecules composing DNA are required. In view of this fact, total, differential elastic and doubly differential inelastic electron scattering cross sections were measured for THF (tetrahydrofuran) which serves as the model molecule for the deoxyribose, a main component of a DNA backbone. The cross sections were determined absolutely for primary electron energies T from 20 eV to 1.0 keV, at scattering angles from 5° to 135°. The energy of secondary electrons ranges from 4 eV to (T-I)/2, where I is the ionization potential of THF. The comparison of the present results for elastic scattering to the theoretical values calculated using modified independent atomic model shows a good agreement in the energy range between 60 eV and 1 keV. To our knowledge, there are no other experimental data for doubly differential ionization cross sections of THF for electrons. Singly differential ionization cross sections that are obtained by the integration of the experimental doubly differential cross sections over the scattering angle are compared to computations using the binary encounter-dipole(BED) model.

A 13

SIMULATION OF INTRA-TRACK SPATIAL DISTRIBUTION OF SIMPLE AND COMPLEX DNA DAMAGE INDUCED BY HEAVY IONS

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It is well known that heavy-ion induced biological effect is different depending on the types of ions even if the LET values are the same. The difference is thought to be caused by the difference of radial energy deposition distribution, which should affect on the DNA damage spectrum and also on the spatial distribution of DNA damage along the tracks. In this study, we focus on the intra-track spatial distribution of DNA damage based on the detailed Monte Carlo track structure simulation.
The simulation was performed using a Monte Carlo code TRACION for event-by event track structure of ions and the code system DBREAK for simulation of DNA damage induction process by both of direct and indirect actions. Radial energy deposition distribution, the DNA damage spectrum and the radial distribution of single and complex damages were calculated for C and Ne ions with similar LET values around 440 keV/micron. As the results, the DNA damage spectrum for C ions is estimated to be more complex rather than that for Ne ions. Also, it has been found that DSB or non-DSB type clustered damage are likely formed in the central area while the isolated damages as SSB and base lesions are spread in the larger area. This tendency is significant for Ne ions than for C ions. This result shows good agreement with the previously obtained experimental observation at the TIARA, which indicates that the radial distribution of SSB and DSB is clearly different around C and Ne ions in cell nuclei.

A 14

CALCULATION OF RELATIVE BIOLOGICAL EFFECTIVENESS OF XOFT LOW-ENERGY X-RAYS AND IR-192 FOR MAMMOSITE HDR BRACHYTHERAPY

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An important consideration for the choice of brachytherapy sources is their relative biological effectiveness (RBE). Microdosimetry is a useful tool for comparing the RBEs among different brachytherapy sources . The generalized formulation of the theory of dual radiation action (TDRA) provides an expression for the ratio of alpha/beta in terms of two fundamental functions: t(x) is the probability distribution function of distances between pairs of sublesions; and gamma(x) is the probability that two sublesions at a distance x aprt results in a lesion. The MammoSite® radiotherapy system is for patients with early-stage breast cancer. The device (balloon) is placed inside the breast surgical cavity and inflated with a combination of saline and radiographic contrast to completely fill the cavity. The treatment schedule for the MammoSite is 34 Gy delivered in 10 fractions at 1.0 cm from the balloon surface. In this study, we calulated the RBEs at 3 cm from the MammoSite HDR sources: Ir-192 and Xoft 50kVp x-rays. The composite proximity function t(x) for each source (Xoft, Ir-192, and Co-60) was calculated based on the electron spectrum generated from GEANT Monte carlo simulation. The biological function gamma(x) was combined with t(x) to estimate the biological effectiveness of Xoft and Ir-192, using Co-60 as the reference. Based on Brenner and Zaider, the low-dose RBEs obtained from the above calculations were then modified to high-dose RBEs: Xoft 1.1; Ir-192:1.0

A 15

ELECTRON TRANSPORT IN CONDENSED PHASE MATERIAL

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Monte Carlo track simulation has become an important tool in radiobiology. Monte Carlo transport codes commonly rely on elastic and inelastic electron scattering cross sections determined using theoretical methods supplemented with gas phase data; experimental condensed phase data are often unavailable or infeasible. The largest uncertainties exist for low-energy electrons, important in simulating electron track ends. To test these codes we have measured yields of low-energy secondary electrons ejected from thin foils following passage of fast protons and heavy ions. Fast ions, where interaction cross sections are well known, provide the initial spectrum of low-energy electrons that subsequently scatter in the material before reaching the foil surface and being detected. These data, measured as a function of the energy and angle of the emerging electrons, provide stringent tests of the physics of electron transport. Initial measurement from amorphous solid water frozen to a copper substrate indicated substantial disagreement with MC simulation, although questions remain because of target charging. More recent studies, using different freezing techniques, do not exhibit charging, but confirm the disagreement seen earlier between theory and experiment. We now have additional data on the differential electron yields from copper, aluminum, and gold, as well as for thin films of frozen hydrocarbons. These data will be presented and compared with recent calculations.

A 16

INVESTIGATION OF DIFFERENT CROSS SECTIONS EFFECT ON VARIOUS TRACK PARAMETERS

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Monte Carlo track-structure analysis requires accurate cross sections in order to reach reliable results. The aim of the present work is to investigate the effect of different models for elastic and inelastic cross sections on several track parameters with help of an in-house developed track structure code. The code is tested by computing various probability distributions, such as the radially most distant transfer point of the primary particle (R), the projection on to the z-axis of the deepest primary interaction point (Zmax), the projection on the z-axis of the final primary transfer point (Zabs), the position of the final primary transfer point (T) and the most distant energy transfer point (V). The present calculations agree fairly well with the results obtained by Wilson et al. However, below 500 eV small differences is seen, probably due to the different cross section incorporated in the codes. To highlight the effects on track calculations caused by differences in the ionization cross sections at low energies (below 500 eV), two of the track parameters, R and Zmax, are compared. It is clear that differences in the stopping power at low energies will affect the distributions and consequently the R and Zmax distribution will be shifted toward shorter penetration depth when the stopping power is larger. The difference in ionization cross section will also influence the angular distribution since the branching ratio will be slightly altered.

A 17

CHROMOSOME ABERRATION INDUCTION IS DEPENDENT ON THE SPATIAL DISTRIBUTION OF ENERGY DEPOSITION THROUGH A CELL NUCLEUS

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A novel irradiation system is described which enables a comparison of the biological response of mammalian cells following uniform or non-uniform exposures of low-LET 1.5 keV ultrasoft x-rays. The non-uniform exposures were achieved using a thin copper irradiation mask in contact with the thin Mylar base on which the cells are grown. The mask contained Poissonly distributed micron sized holes. In addition to being highly attenuated by the copper, the ultrasoft x-rays essentially produce no scatter as they predominately interact via the photoelectric effect and the resulting electrons have a very short range (~0.05 μm). The importance of the spatial distribution of energy through the nucleus in determining the resulting chromosomal rearrangements was investigated using fluorescent In-situ hybridization (FISH) techniques in HF19 human fibroblast cells following either a uniform or non-uniform exposure of low-LET ultrasoft x-rays. The results obtained with for cells irradiated with ultrasoft x-rays through the Poissonly distributed holes were also compared to aberration formation following exposure to Poissonly distributed a-particles. For the same radiation quality, the spatial distribution of energy deposition within the nucleus was found to be important in determining the ultimate biological response. Comparisons between low-LET ultrasoft x-rays and high-LET a-particles shows that the sub-micron clustering of damage along the a–particle track may be more important than just

A 18

R&D FOR CO-WORKING TRANSPORT METHODS IN GEANT4

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Geant4 is nowadays a mature Monte Carlo system, widely used in a variety of applications. Since its first release, new functionality has been added; nevertheless, the architectural design and fundamental concepts defining Geant4 application domain have remained substantially unchanged. New experimental requirements have emerged in the recent years, which challenge general-purpose Monte Carlo transport codes like Geant4 in domains like microdosimetry, nanotechnology-based detectors, radiation effects on components, plasma physics etc. A R&D project has been launched in 2009 to address fundamental methods in radiation transport simulation and revisit Geant4 design to cope with new experimental requirements. The project focuses on simulation at different scales in the same experimental environment: this set of problems requires new methods across the boundaries of condensed-random-walk and discrete transport schemes. The first phase has been devoted to the evaluation of software technology capable of supporting the concept of mutability and adaptation to the environment in physics processes. Effort has been invested in issues arising in the simulation of intrinsically discrete processes, like PIXE, in association with condensed schemes handling ionization. All these topics are especially relevant to Monte Carlo simulation for microdosimetry applications. An overview of this Geant4-related R&D is presented, together with the developments in progress and the first results.

A 20

MEGA-VOLTAGE VS. KILO-VOLTAGE CT USED IN IMAGE-GUIDED RADIATION THERAPY: COMPARATIVE STUDY OF MICRODOSIMETRIC PROPERTIES

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Background: Mega-voltage CT (MVCT) and kilo-voltage Cone Beam CT (CBCT) are routinely used in Image-Guided Radiation Therapy (IGRT). MVCT and CBCT may be acquired prior to each fraction of a treatment with dose ranging from 1 to 10 cGy depending on tumor location and scan settings. In current practice, doses from MVCT and CBCT are reported with no correction for radiation quality. In this study we compared microdosimetric properties for MVCT and CBCT. Methods: BEAMnrc was used to simulate MV photon spectra representative of Varian and Tomotherapy MVCT beams and a CBCT 125kVp photon beam. . DOSXYZnrc was used to simulate primary electron spectra for CT sets of several patients previously treated with radiation therapy. Primary electron information was sent to NOREC, a Monte Carlo code to simulate electron tracks in liquid water. C++ code was developed to compute lineal energy in a sphere of 1 micrometer diameter by homogenously distributing these electron tracks in a cube of the dimension of the largest electron range. Doses to organs and dose-mean lineal energy-based quality factors were calculated for both in-field and out-of-field locations. Results: Calculated dose-mean lineal energy for CBCT of a pelvic patient inside the field ranged from 3.6 to 4keV/micron, at depths 2 to 10cm. The estimated quality factor for CBCT is up to a factor of up to 1.3 times that of MV beams. Conclusion: The beam quality of CBCT should be accounted for when discussing risk analysis in IGRT.

B 1

COMPLEX INTERCHCHANGES AS A COMPLEX FUNCTION OF CHROMOSOME ORGANISATION

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The authors developed a Monte Carlo technique for biophysical modelling of dynamic organisation of 46 chromosomes within human lymphocyte interphase nucleus. The technique takes into account: different levels of chromatin organisation; excluded volume interactions between chromosome subunits; nonrandom localisation of particular chromosomes; nucleolar chromosome association. This technique is quite comprehensive to avoid internal limitations of other modelling approaches. A pattern of dynamic intra/ interchromosomal contacts is simulated to predict radiation-induced CA. Distance dependence of interaction probability is calculated directly for the first time with taking chromosome dynamics and DNA breaks repair into account. Cell cycle progression is simulated to reproduce conditions of first mitosis CA measurement in real experiment. Dose response for simple and complex CA is calculated to analyse mFISH data for human lymphocytes. Simple CA frequencies fit the data; unexpectedly, complex aberrations are underpredicted despite big number of interchromosomal contacts. To study sensitivity of dose response prediction to uncertainty of chromosome organisation knowledge, CA are recalculated for several alternative concepts of nucleus organisation and chromosome lesion interactions. Underprediction remains. To explain this modelling finding lesions movement from different chromosomes to common repair factories is proposed as an additional mechanism of complex CA formation.

B 2

INDUCTION OF DNA DSB AND ITS REJOINING IN THE CLAMPED AND NON-CLAMPED TUMORS AFTER CARBON ION BEAMS COMPARED WITH X RAYS

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We studied DSB induction and rejoining in the clamped and non-clamped tumors after low- and high-LET radiations. SCCVII cells were transplanted into the right hind legs of C3H male mice. Conditioning irradiation with either 80 keV/μm carbon ions or 200 kVp X rays was delivered to the tumors at 5 mm diameter. Hypoxic cells were produced by clamping tumor-bearing mice 15min before irradiation in situ. Immediately after and 1 hr after irradiation, tumors were excised and rapidly cooled on ice. DSB in the tumors was analyzed by a static-field gel electrophoresis, and assayed for DSB induction and rejoining. The DSB immediately after X rays under normoxic condition was higher than under hypoxic condition. These damages in both tumor conditions were rejoined 60 to 70% within 1 hr in situ. The OER of DSB after X rays was 1.68 ± 0.31, and this value was not changed by 1 hr rejoining incubation (1.40 ± 0.26). On the other hand, no difference between X rays and carbon ions was found for the induction and rejoining of DSB. The rejoined fraction and the OER of DSB after carbon ions were similar to that after X rays. Additionally, the RBE of DSB immediately after and 1 hr after irradiation, these values were 0.9 to 1.3, and were not dependent on gases conditions. The yields of DSB induced by X rays in vivo might be similar to that after carbon ions, because the OER and RBE were not found a major difference.

B 3

TELOMERE ALTERATIONS AND GENOMIC INSTABILITY IN LONG TERM CULTURES OF NORMAL HUMAN FIBROBLASTS IRRADIATED WITH X-RAYS AND PROTONS

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Telomeres are heterochromatin regions at the end of linear chromosomes, responsible of chromosome stability and cell viability. Functional telomeres are constituted by short, tandem DNA repeats of the 5'-(TTAGGG)n-3'sequence ad a multitude of associated proteins. A dysfunctional telomere is detected as damaged DNA and results in activation of the DNA-damage checkpoint and increased chromosome instability. We have used human primary fibroblasts (HFFF2) to study whether exposure to 4 Gy of X-rays or low-energy protons (0.8 MeV which corresponds to 28.5 keV/um; LNL, INFN) alter the telomere length as evaluated by means of Q-FISH technique. We have performed the analysis at two different harvesting times (24 hrs and 15 days) in order to ascertain a possible delayed telomere dysfunction. Results from cells irradiated with X-rays indicated a delayed telomere lengthening 15 days after the treatment whereas protons were able to induce a significant increase in average telomere fluorescence shortly from irradiation as well as longer harvesting times. To test the relation between delayed telomere lengthening and chromosome instability, chromosome painting for chromosome 1,2 and 4 will be performed in mass culture cells harvested 15 days after irradiation. Work partially supported by INFN-CSN5 (Experiment SHEILA/EXCALIBUR)

B 4

ATM-DEPENDENT CELLULAR RESPONSE TO DNA DOUBLE STRAND BREAKS PLAYS A PIVOTAL ROLE IN THE MAINTENANCE OF THE INTEGRITY OF THE GENOME

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ATM-dependent cellular response to DNA double strand breaks plays a pivotal role in the maintenance of the integrity of the genome. Upon irradiation, autophosphorylation and monomerization of ATM proteins are taken place, and activated ATM phosphorylates various downstream mediators and effectors, such as histone H2AX, MDC1, 53BP1 and NBS1. Recently, we have shown that activated ATM creates discrete foci within the nuclei, which are detectable under fluorescence microscopes. The number of foci increases linearly as increasing the dose between 10 mGy and 1000 mGy. Interestingly, the size of the foci is also increasing as increasing the time after irradiation. Particularly, when the other foci are disappeared by DNA repair, the residual foci form large foci, whose sizes reach to approximately 2 micrometer in diameter. This indicates that the "foci growth" is a mechanism of amplifying DNA damage signals. We confirmed DNA damage checkpoint factors including histone H2AX, MDC1, NBS1 were essential for the foci growth. Thus, a proper DNA damage response of cells exposed to especially low dose of ionizing radiation requires amplification of the ATM-dependent damage signal by recruiting the DNA damage checkpoint factors to the site of chromatin.

B 5

GENETIC AND BIOCHEMICAL ANALYSIS OF BASE EXCISION REPAIR COMPLEXES

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The project aims to understand how vertebrate cells cope with oxidative DNA damage induced by radiation. The work is of relevance for humans exposed to various forms and levels of radiation and for many forms of human disease related to defects in DNA damage repair pathways.

Using the homologous recombination proficient DT40 cell line, we shall inactivate genes encoding key repair factors. The marker that we have specifically developed for this purpose is a positive (green fluorescent protein-GFP)/negative (nitroreductase-NTR) dual selection system. Cells harbouring a viable NTR gene will break down the pro-drug metronidazole into a cytotoxic substance thereby killing the cell. In contrast, cells harbouring mutations in the NTR gene can be selected for and the mutations can be sequenced. This marker can easily be inserted into the genome of DT40 and functions as a site-specific DNA damage trap allowing us to isolate even extremely rare events leading to inactivation of gene function.

The mutant clones will then be analyzed for damage induced by ionizing radiation with respect to i) genetic analysis of damage leading to inactivation of the negative selection marker, ii) protein/DNA repair complex formation, and iii) phenotypic and morphological alterations.

The project should give insight in how vertebrate cells repair ROS (reactive oxygen species) induced DNA damage and which repair factors are recruited to deal with various types of radiation.

B 6

BOOSTING INACTIVATION CAPACITY OF A MELANOMA CELL LINE BY COMBINED TREATMENTS WITH ANTICANCER DRUGS AND PROTONS

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Human HTB140 melanoma cells were exposed to different chemotherapeutic drugs (fotemustine – FM, dacarbazine – DTIC) and several radiation qualities (gamma-rays, protons). The cells expressed high radioresistance and poor response to these anticancer drugs. To boost inactivation capacity, the cells underwent treatments combining FM and protons. Irradiations were carried out in the middle of the 62 MeV proton SOBP using therapeutic doses. Drug concentrations were close to those producing 50% of growth inhibition. Cell viability was assessed 48h after irradiation. Results did not show significant changes of viability when compared to single treatments. The level of apoptosis increased after combined treatments and apoptotic indexes ranged from 1.11 – 6.43. Induction of apoptosis was associated with p53 and Bax up regulation and Bcl-2 down regulation. Further improvement of cell inactivation was tested by introducing the antiangiogenic antibody bevacizumab to FM and proton treatments. Triple treatments reduced cell viability and proliferation, provoked G1 or G2 arrest and stimulated apoptosis. Still the combination of FM and proton was somewhat better. The effects of combined treatments of FM and protons, including changes in their administration order, were also estimated 7 days after irradiation. Better effects on cell inactivation were revealed when FM was applied prior to proton irradiation, implying that FM improved the level of radiosensitivity of HTB140 cells.

B 7

EFFECT OF TAMOXIFEN ON THE STABILITY OF DNA-PROTEIN COMPLEX BETWEEN THE ESTROGEN RESPONSE ELEMENT AND THE ESTROGEN RECEPTOR UNDER IRRADIATION.

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The estrogen receptor protein (ER) is a ligand-activated transcription factor that regulates expression of genes controlled by estrogens, female sex hormones. Their signaling is mediated through their binding to the estrogen receptor, followed by the formation of a specific complex between ER and a DNA sequence, called estrogen response element (ERE). Estrogens are risk factors in development of several cancers. One of the widely used treatment options is hormone therapy. Its principle is based on blocking the estrogen signal transduction by their competitive inhibitors, anti-estrogens.

We have been interested in the effect of ionizing radiation on hormone action at molecular level. We have studied in vitro the radiosensitivity of the complex between ERalpha, subtype of estrogen receptor, and a DNA fragment bearing ERE and the influence of an anti-estrogen tamoxifen, used in breast cancer treatment, on the stability of this complex under irradiation. We observe that the complex is destabilized upon irradiation with gama rays in aerated aqueous solution. The analysis of the decrease of binding abilities of the two partners shows that destabilization is mainly due to the damage to the protein. The destabilization is reduced when irradiating in presence of tamoxifen. The mechanism that can account for our results is related to structural changes of the ER DNA-binding domains, which can differently affect ER-ERE interaction.

B 8

MUTAGENIC POTENTIAL OF CLUSTERED DNA DAMAGE CONTAINING A SINGLE STRAND BREAK AND 8-OXOGS

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It is proposed that a single track of ionizing radiation induces clustered DNA damage sites and that their complexity increases with increasing LET. Non-DSB clustered damage is thought to contribute to the biological effects of radiation such as mutation. In this study, we have investigated the mutagenicity of clustered DNA damage containing SSB and base damage.
We have used a plasmid based assay with Escherichia coli to measure the mutation frequency induced by bistranded clustered damage. As a model of clustered damage, we have synthesized oligonucleotides containing a SSB and/or 8-oxo-7,8-dihydroguanines (8-oxoGs) within the recognition site of the restriction enzyme (Alw26I). Plasmid constructs containing damaged DNA was transfected into wild-type or glycosylase-deficient strains and propagated in cells. The mutation frequency was assessed by the inability of Alw26I to cut the oligonucleotide sequence.
The mutation frequency of bistranded clusters containing an 8-oxoG opposite to a second 8-oxoG 2bp apart was the highest of all the types of clusters tested in the present study. When a SSB was included in clusters containing bistranded 8-oxoGs, the mutation frequency is lower in all E. coli strains tested. These results suggest that a SSB located on the same strand to one of the 8-oxoG reduces the mutagenic potential of 8-oxoG. Our studies demonstrate that the mutagenic potential of clusters containing 8-oxoG is modified if a SSB is present within the cluster.

B 9

SIGNALLING AND REPAIRING OF DOUBLE STRAND BREAKS IN HUMAN FIBROBLASTS IN DIFFERENT PHASES OF CELL CYCLE

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High linear energy transfer (LET) radiation are biologically more effective than low LET radiation because of the complex nature of radiation-induced damage. Ionizing radiation (IR) induces DNA double strand breaks (DSBs), which represent the most severe damage for genome integrity. In our work we analysed the progression of DSBs repair in human lung fibroblasts after irradiation with low-energy protons and gamma rays, by following formation and disappearance of ionizing radiation-induced foci (IRIF), constituted by gamma-H2AX and 53BP1 proteins. In order to distinguish DSBs repair ability throughout cell cycle we analyzed IRIF kinetics in relation with the expression of CENP-F, a protein marker of late S, G2 and M phases. We observed a cell cycle delay on G2 phase, both after gamma-rays and protons. With 5 Gy of gamma-rays this effect is pronounced at 6 hours and persists up to 24 hours. With 5 Gy of protons G2 delay is mild at 6 hours and very marked at 24 hours. The kinetics of DSB rejoining after gamma-irradiation is very similar in CENP-F positive and negative cells with a faster IRIF disassembly in late S-G2 cells, in which the repair is almost complete at 6 hours after irradiation. After irradiation with low-energy protons, a higher percentage of IRIF is still present at 6 hours, showing that a slower repair takes place in fibroblasts irradiated with protons compared with those gamma irradiated.

B 10

EFFECTS OF MODELED MICROGRAVITY ON HUMAN FIBROBLASTS CULTURE IRRADIATED WITH GAMMA RAYS

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Space missions expose humans to both radiation and gravity environment that profoundly differ from those experienced on Earth. We investigated the possibility that microgravity could affect the DNA double-strand breaks (DSBs) repair ability, increasing the risk of carcinogenesis. Through the use of Cytodex®-3 microcarriers we finalized a way to grow normal human lung fibroblasts, CCD-34Lu, in modeled microgravity (MMG) by using the Rotating Wall Vessel (RWV) bioreactor with fairly good recovery of vital cells over the evaluated times. Fibroblasts grown on microcarriers were exposed to high dose of &gamma-rays (5 Gy) and incubated in stirrer-flasks (1 g) and in RWV (MMG). We studied the DSBs repair kinetic monitoring formation and disappearance of the ionizing radiation induced foci (IRIF) of 53BP1 protein as DSBs marker. Our preliminary results show that at 6 and 24 h after irradiation the mean number of foci per nucleus is significantly higher in fibroblasts incubated in MMG (13-6) than 1 g (11-4). At 24 h about 33% of irradiated cells presented 5-9 foci/nucleus when incubated in MMG compared to 15% in 1 g; moreover 50% of cells incubated in 1 g completed the DSBs repair in contrast to 20% of cells maintained in MMG. Our data showed that analyzing the cell cycle we found also that, after 24 h of incubation in the two gravity conditions, the percentage of cells replicating the DNA is smaller for fibroblasts grown in MMG, suggesting that MMG could alter cell cycle progression.

B 11

TELOMERE MAINTENANCE AND DNA REPAIR PROTEINS: ROLE IN CANCER PROGRESSION AND RADIATION-INDUCED TUMOURS

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Carcinogenesis is a complex process, characterized by the stepwise accumulation of genetic and molecular abnormalities. Telomere length (TL) abnormality seems also to be one of the most prevalent genetic alterations acquired. Telomere loss is an efficient mechanism for generating many of the types of chromosome rearrangements commonly associated with human cancer including allelic imbalances. A single break at the telomere has dramatic consequences on the genome stability (Murnane and Sabatier,Bioessay 2004, Sabatier, Mol Cancer Res 2005). Here we explored TL and its link with a DNA damage response (DDR) pathway in colorectal carcinoma. A DDR activation is observed including H2AX, Chk2 and ATM phosphorylations, appears somewhere between normal and low grade dysplasia with a maximum in high grade dysplasia. In contrast, in fully invasive cells, only week signs of DDR were found. Our data confirms that DDR is a dynamic process (Raynaud, AnnOncol 2008). We propose that the major impact of the loss of telomere integrity might occur in the long term. Following radiation exposure, telomeres instability would act as an amplificator event unmasking in one single step recessive radiation-induced mutations among thousands of genes and providing cellular proliferative advantage.

C 1

A KINETIC MODEL OF SINGLE STRAND ANNEALING (SAA) FOR THE REPAIR OF DOUBLE STRAND BREAKS

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Ionizing radiation induces different types of DNA damage including single strand break (SSB), double strand break (DSB), and base damage. DSBs are considered to be the most critical lesion to be repaired. The three main competitive pathways in repair of DSBs are Non-homologous end joining (NHEJ), homologous recombination (HR), and single strand annealing (SSA). SSA is a nonconservative repair pathway requiring direct repeat sequence for the repair process. In this work we present a biochemical kinetic model to describe the SSA repair pathway. The model consists of a system of nonlinear ordinary differential equations describing the repair processes. The reaction rates were estimated by comparing the model results with the experimental data for DT40 cells irradiated by 20 Gy X-ray (Wang et al 2001). The model successfully predicts repair of the DT40 cells with the reaction rates driven from the 20 Gy X-ray experiment. The experimental data and the kinetic model show fast and slow DSB repair components. The half time and fractions of the slow and the fast components of the repair were compared for the model and the experiments. Mathematical and computational modelling in biology has played an important role in predicting biological mechanisms and stimulating future experimentation. The present model of SSA adds to the modeling of NHEJ, and HR to provide a more complete description of DSB repair pathways, which can be used for radiation risk assessment and other applications.

C 2

GROWTH CURVE ANALYSIS OF TUMORIGENESIS USING CELLULAR LEVEL CANCER MODEL

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Biological effects of low-dose radiation are studied by computational methods. Recent years, risk assessments of radiation induced cancer are getting worth for the public health view points because of an increase of various low dose exposures, including medical exposures, and for the radiation protection view points. In general, we know that carcinogenesis by low dose radiation will start from DNA damage by ionizing radiation. After the long time period, these very small effects will appear on a cellular scale by accumulation of various intracellular biological responses and finally grow to the tumor with clonal expansion of cancer cell.
Thus, the biological radiation effects are phenomena with a very wide scale from DNA damage(10^-9 m, 10^-6 s) to the tumor (10^-3 m, 10^5 s), so the risk estimation of low dose radiation is difficult to study by the experiments. To overcome these difficult situations at low dose radiation effects problem, it is good to study process of carcinogenesis using biologically based mathematical model.
In this presentation, we will introduce our cellular scale mathematical model of tumorigenesis and show some results of statistical calculations about tumor growth curve. We will show not only the population dynamics of cancer but also morphological aspects of carcinogenesis, even in a uniform cell culture system or in a tissue environment.

C 3

APPLICATION OF THE MICRODOSIMETRIC KINETIC MODEL TO EVALUATE THE DOSE-EFFECT RELATION FOR HEAD AND NECK SQUAMOUS CARCINOMA CELLS EXPOSED TO HIGH-LET IONS

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Several models have been proposed to predict the biological effects of high-LET particles, based on the microdosimetric concepts and quantities. One of the new microdosimetric models is the "Microdosimetric Kinetic Model" proposed by R.B Hawkin (1996). Recently, Kase et al (2008) have published a comparative study of the MK model and the Local Effect Model (LEM) in the calculation of the biological dose for treatment planning in Hadrontherapy. In their study, an amorphous track structure model was used to calculate the energy deposition for both models. In this work, we apply the MK model to calculate the survival probabilities of head and neck squamous carcinoma cells (SCC61 and SQ20B Cells) exposed to high-LET ions. Unlike Kase et al, we use the Monte Carlo method to simulate the initial energy distribution in the cells and practically consider the Geant4 simulation toolkit. Previous analyses of the dose-effect relation of SCC61 and SQ20B cells with the LEM were reported by Beuve et al (2008). The first part of the presentation will be devoted to the analysis of the Geant4 simulation toolkit. The microdosimetric concept of the proximity function is used to perform this analysis. Finally, the results obtained with the MK model will be analyzed and the model parameters of the two cell lines will be compared in term of radiosensitivity to high-LET ions.

C 4

THE APPLICATION OF AMORPHOUS TRACK MODELS TO STUDY CELL SURVIVAL IN PROTON AND CARBON BEAMS

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Amorphous track models are considered to provide the most suitable description of cell survival under ion irradiation. The aim of this paper is to compare predictions from different approaches: the phenomenological model by Katz and co-workers and a Monte-Carlo-based approach as implemented in the Local Effect Model by Scholz et al, including application of the Kellerer algorithm to fold energy deposition distributions.

A suitable software library embracing the mentioned models including numerous submodels with respect to delta-electron range, radial dose distribution (RDD) and gamma response models was developed. This software was applied for numerical comparison between the models, submodels and experimental data. Model predictions were compared with survival data concerning normal human cell fibroblasts irradiated in vitro with ion beams, published by Tsuruoka et al.

Preliminary results show that with the unique set of four parameters and a large set of experimental; data it is possible for clinical doses to obtain agreement within 10% between model predictions and the experimental data. When investigating the influence of RDDs on inactivation cross section in the Katz model we found that one of the most important factors is the normalization of the energy distribution around the particle tracks to the actual LET value. The effect of the shape of the RDD on the value of the kappa parameter was studied for different ion species at different energies.

C 5

TRACK STRUCTURE CALCULATIONS ON HYPOTHETICAL SUBCELLULAR TARGETS FOR THE RELEASE OF CELL KILLING SIGNALS IN BYSTANDER EXPERIMENTS WITH MEDIUM TRANSFER

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To investigate the possibility of revealing, from the response on dose and other conditions, the information on initiating targets and mechanisms of bystander effects mediated by signals released into culture medium, track structure studies using PARTRAC have been performed. Dose-dependent probabilities have been assessed of given energy deposits in a number of subcellular targets (spheres and spherical shells) mimicking mitochondria and cellular membranes as hypothetical targets for the release of signals. Results of simulations agree with target theory, and yield the dependence of characteristic dose on target topology and size. The results can only partially explain the dose-dependence of bystander response in medium transfer experiments, where a dose threshold around 2 mGy and saturation above 0.1 Gy have been observed for reduced survival of unirradiated HPV-G cells cultured with medium from gamma-irradiated cells (Liu et al 2006 Radiat Res 166:19). The threshold could be explained using multiple-hit theory, and the gradual dose dependence towards threshold related to variations in cellular characteristics among the irradiated and/or reporter cells. The results indicate that not only the release of but also the response to bystander signals may be highly non-linear and have to be considered in modelling bystander effects. Refined concepts considering data on medium dilution (Ryan et al 2008 Radiat Res 169:188) are under development.
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C 6

COMPARING NATIVE AND IRRADIATED E. COLI LACTOSE REPRESSOR-OPERATOR COMPLEX BY MOLECULAR DYNAMICS SIMULATION

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The function of the E. Coli lactose operon requires the binding of a protein, the tetrameric repressor (a dimer of identical dimers) to a specific DNA sequence, the operator. The formation of this DNA-protein complex involves the interaction of at least one dimer of the tetramer with the operator sequence. This occurs via the DNA-binding domains (called headpieces) of the two constitutive monomers. We have previously shown that upon irradiation with gamma rays the complex is destabilised mainly because the repressor losses its DNA binding ability. By mass spectrometry combined with RADACK model calculations we have identified some of the radiation-induced lesions that may be responsible for this deleterious effect: all Tyr residues of the headpieces are oxidized into 3,4-dihydroxyphenylalanine (DOPA). In order to unravel the mechanisms leading to the observed destabilization of the complex, we compare by molecular dynamics simulation: 1. the native complex formed by two headpieces and a fragment of DNA with the operator sequence and 2. the damaged complex in which all Tyr residues of the headpieces are replaced by DOPA. Based on a NMR-based structure of the native complex from PDB databank (1CJG), 20 ns trajectories were simulated for the two complexes. The analysis of these results shows that the damages of the headpieces trigger an increased flexibility of the complex, an increased bending of DNA, a change in the network of H-bonds, a decrease of the positive potential at

C 7

REGIONAL BLOOD FLOW IS AN ESSENTIAL FACTOR FOR FUNCTIONAL DIAGNOSIS OF GUT TO CARBON-ION IRRADIATION

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Radiation-induced gut injuries are most potent threat to radiotherapy for abdominal cancer.
We determined that radiotracer of 2-14C-thymidine is useful for detecting radiation-induced gut injuries, in term of crypt repopulation and early diagnosis of cell death.
We examined the 2-14C-thymidine accumulation in gut after irradiated with carbon-ion until 84 hrs. Mice were given whole body irradiation with carbon-ion (290MeV/u, 6cm-SOBP, 20keV/μm). 2-14C-thymidine accumulation in gut significantly decreased 4 hrs after irradiated with 9 Gy. At 12 hrs after irradiation, accumulation of 2-14C-thymidine decreased with an increase of carbon-ion doses (1-9 Gy). On the other hand, 2-14C-thymidine accumulation not showed dose dependence at 84 hrs after irradiation. However, the dose dependence was obtained when 2-14C-thymidine accumulation was corrected by blood flow. The regional blood flow marker 14C-labeled N-isopropyl-p-iodoamphetamine (IMP) in gut markedly increased after 9-18 Gy irradiation. The results of the present study are first demonstration that the 2-14C-thymidine uptake in vivo could be an appropriate marker for early gut response to irradiation and correction by blood flow is essential for the evaluation by 2-14C-thymidine.

D 1

STUDY OF A SOLID STATE MICRODOSIMETER BASED ON A MONOLITHIC SILICON TELESCOPE: IRRADIATIONS WITH LOW-ENERGY NEUTRONS AND DIRECT COMPARISON WITH A CYLINDRICAL TEPC

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A monolithic silicon telescope coupled to a tissue-equivalent plastic was proposed and investigated for solid state microdosimetry. The device is constituted by a DeltaE stage geometrically segmented in a matrix of micrometric diodes and a residual-energy measurement stage E, about 2 um and 500 um in thickness, respectively. Each thin diode has a cylindrical sensitive volume 9 um in nominal diameter, similar to that of a cylindrical Tissue Equivalent Proportional Counter (TEPC). Irradiations with quasi mono-energetic neutron fields were performed in order to compare systematically the microdosimetric spectra from the silicon device with those acquired with a cylindrical TEPC. Both detection systems were irradiated with neutrons between 0.64 MeV and 2.7 MeV at the INFN-Laboratori Nazionali di Legnaro (LNL, Legnaro, Italy), in the same experimental conditions. The TEPC was set in order to simulate a tissue site about 2 um in diameter. The spectra of the energy imparted to the DeltaE stage of the silicon telescope were corrected for tissue-equivalence through an optimized procedure that exploits the information from the residual energy measurement E-stage. A geometrical correction based on parametric criteria for shape-equivalence was also applied. The agreement between the dose distributions of lineal energy and the corresponding mean values is satisfactory at each neutron energy considered. The analysis of the results will be presented and discussed in details.

D 2

TRACK NANODOSIMETRY OF PROTONS

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Many radiobiological data point out that radiation quality depends only on ionisation event statistical properties in a "biological significant" site of nanometric size. In turn, such statistical properties depend on primary particle kind, velocity, site size and its distance from the primary particle track. The STARTRACK experimental set up, mounted on the +50° beam line of the Tandem-Alpi particle accelerator of Legnaro National Laboratories, has been conceived to give experimental basis to nanodosimetric calculations. STARTRACK is a detection system able to perform track nanodosimetry. That is ionisation cluster distribution measurements in 20nm propane sites placed at different distances from the primary particle track (different impact parameter). Measurements have 1 ionisation event resolution. Previous measurements, performed with 244Cm alpha particle, had pointed out that the track quality, namely some statistical properties used as definition of quality in microdosimetry, is invariant with the impact parameter. One of STARTRACK aims is verifying if the same invariance holds for light ions of therapeutic interest, namely protons, lithium and carbon ions. Proton track nanodosimetry data will be presented, discussed and compared with Monte Carlo calculations

D 3

NOVEL POLYSILOXANES BASED SCINTILLATORS FOR NEUTRON DETECTION

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Polysiloxane based scintillators proved to be promising for the employment in harsh environments, owing to their outstanding radiation resistance and thermal properties over the traditional plastics (PVT and PS).In this work, cross-linked polydimethyl-co-diphenylsiloxane scintillators(PMPS) with different molar percentages of phenyl units have been synthesized. As dopants, 2,5-diphenyl oxazole (PPO) and Lumogen Violet (BASF) were employed as primary and secondary fluors, respectively. Scintillation yield measurements made by exciting with an 241Am alpha source (3 kBq, 5.484 MeV) on samples with different concentrations of phenyl pendant groups and dye molecules allowed to find the best set of synthesis parameters to obtain a PMPS with a light yield comparable with NE102. Fast neutrons were produced by irradiating with a 4.0 MeV proton beam a LiF target, owing to the reaction 7Li(p,n)7Be. From the thickness of the target an energy of about 2.2 MeV was evaluated for the produced neutrons. The scintillator pulses related to the impinging particles were selected by means of time of flight (TOF) measurements.From the integrated counts, the particle flux and the solid angle, an estimation of the efficiency were evaluated. A similar test was performed with a BaF2 scintillator for comparison. Measurements with thermal neutrons, on B and Gd doped samples, were obtained by shielding the scintillator with lead and polyethylene bricks.

D 4

MICRO-AND-MACRO DOSE ESTIMATIONS OF THE MEDICAL LINEAR ACCELERATOR

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The medical linear accelerator (Linac) is the main equipment used in modern radiotherapy. Two types of radiation, photons and electrons, are produced by the medical Linac. As the energy of photons is beyond 10 MeV, probability of photonuclear reaction is increased; secondary particles such as high LET photoneutrons may be following emitted. In microdosimetry, the dose distributions in micro-cell targets present extremely asymmetric for high LET radiations. In this work, a tissue equivalent proportional counter was used to assess the radiation quality of the medical Linac, by means of analyzing the lineal energy distributions contributed by photons and photoneutrons. Besides, the paired-dosimeter (dual ion chambers and dual TLD 600/700 chips) systems were also used to distinguish the photon and neutron doses. The microdosimeter and the paired-dosimeters were placed in different depths inside the self-made Snyder ellipsoidal head phantom and irradiated by different energies of photon and electron beams produced by the medical Linac, separately. Dose contributions from different radiations measured by the micro- and macro dosimeters were analyzed and compared. Effective relative biological effectiveness (RBE) values for radiotherapy using the medical Linac (in different operating conditions) were also estimated in the results.

D 5

NANODOSIMETRY OF AUGER-ELECTRON EMITTERS

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Because of the potential importance of Auger-electron emitters for future clinical applications, the formation of ionization cluster size caused in a nanometre sized target volume of nitrogen by low energy electrons emitted from an 125I Auger-electron source was determined experimentally and by Monte Carlo simulation. Additionally, the ionization clusters size formation due to mono-energetic electrons in the energy range between 100 eV and 2 keV was studied. The nanometre sized targets were produced in a device called Jet-Counter. The latter consists of a pulse-operated valve which injects an expanding jet of nitrogen into an interaction chamber where a gaseous sensitive volume of cylindrical shape is created. The cluster size spectra for the sensitive volume (0.2 $\mu g/cm^2$ in diameter) irradiated by electrons emitted from the 125I source as well as by mono-energetic electrons were collected and analysed. Afterwards, the first moments of the cluster-size distributions as well as the cumulative distribution functions of cluster size greater than or equal to 2 were derived and compared with the corresponding results of a Monte Carlo simulation of the Jet Counter measurements. In the end, the new nanodosimetric descriptors of radiation quality of mono-energetic low-energy electrons and of the electrons emitted from an 125I Auger-electron source, in particular, are discussed.

D 6

BAYESIAN ANALYSIS OF NANODOSIMETRIC IONIZATION DISTRIBUTIONS DUE TO ALPHA PARTICLES AND PROTONS

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Track-nanodosimetry has the objective to investigate the stochastic aspect of ionization events in particle tracks, by evaluating the probability distribution of the number of ionizations produced in a nanometric target volume of size D positioned at distance d from a particle track. Such kind of measurements makes use of electron (or ion) gas detectors, having detecting efficiency non-uniformly distributed inside the target volume. As ionizations are not produced independently each other, the measured ionization distributions are generally not equivalent to the distributions that would be measured in a volume characterized by a uniform detection efficiency. This fact makes not trivial the reconstruction of true ionization distributions which correspond to an ideal efficiency of 100%. Bayesian data analysis is particularly suited for this type of inverse problems. Bayesian unfolding has been applied to ionisation distributions produced by 5.4 MeV alpha-particles and 20 MeV protons in cylindrical volumes of propane (at 300 Pa of pressure), 3.7 mm in diameter and height (corresponding to 20.6 nm in a material of density 1.0 gcm-3) positioned at different impact parameters with respect to the primary beam. It will be shown that a Bayesian analysis performed by subdividing the target volume in sub-regions of different detection efficiencies is able to provide a good reconstruction of the true nanodosimetric ionization distributions.

D 7

DESIGN CONCEPT FOR A SQUID BASED MICRODOSIMETER

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The interest in proton and ion beam therapy has increased substantially in recent years. Contrary to the situation with conventional x-ray treatments, one of the problems of proton and ion beam therapy is that the biological effect is not proportional to the quantity absorbed dose but depends on other factors which are mainly related to microdosimetric phenomena. For these types of radiation, the BIPM has recommended the definition of a new quantity that accounts for the biological effect of ionising radiation used in radiotherapy. In response to this recommendation, this work pertains to the design of a new microdosimeter capable of detecting energy deposited in single events by photons, hadrons or ions whilst being comparable in size to a cell, a cell nucleus or other site of interest. Until now the standard tool for measuring microdosimetric spectra has been to use gas-filled tissue equivalent proportional counters. Whilst these detectors rely on the assumed proportionality between the number of charges in an avalanche and the deposited energy, the proposed detector measures directly the energy deposited by way of the change in inductance caused by heating. The work presented here describes progress made so far towards the design of this detector as well as the future work to be carried out before the new quantity is realised.

D 8

SECONDARY PARTICLE PRODUCTIONS AND TARGET FRAGMENTATIONS IN P 160 MEV BEAM AND VARIOUS MATERIALS

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Protons are widely used in radiotherapy; they also compose significant part of cosmic radiation. The knowledge of proton interactions is therefore important. Protons passing through the material interact with nuclei; created secondary particles and target fragments can have higher linear energy transfer (LET) than primary protons. Even the number of such particles is relatively low, they represent radiation risk due to high radiobiological effectiveness. To study production of secondary particles in proton beam, we used plastic nuclear track detectors (PNTD). The detection threshold is about 5 keV/um, so PNTD can not detect primary protons; only short-range, high-LET particles are detected. The detectors were irradiated at HIMAC accelerator (NIRS, Japan) by 160 MeV protons, behind PE (polyethylene) and Al targets of various thicknesses. After the irradiation the detectors were evaluated using different etching times; the short etching time (removed layer 6-10 um) is used to determine contribution mainly from short-range high-LET particles, long-etching time (20-30 um) to measure particles with lower LET. The LET spectra for different etching times and behind various PE and Al targets will be presented. From the LET spectra, dosimetric characteristics due to registered secondary particles are calculated; their dependence on the depth in the materials or on protons' energy will be analyzed. The experimental results are also compared with calculations using the code PHITS.

D 9

DESIGN OF A MULTIELEMENT TEPC FOR NEUTRON MONITORING

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Tissue equivalent proportional counters (TEPC) have long been considered suitable candidate instruments for more accurate neutron monitors and that further efforts should be directed towards the production of a truly light-weight device. This paper deals with the construction of a multielement TEPC designed to have the sensitivity of a 12.7 cm (5 inch) diameter TEPC, but with approximately one tenth its volume. The use of a multielement device to increase the sensitivity of a TEPC without a concomitant increase in physical size is not new and was first demonstrated by the Columbia University group of Harald Rossi two decades ago; however, development of such devices has been hampered by the need to maintain uniform electric field conditions in each counting element and the resulting complexity of design and construction to achieve this condition. The device reported in this work achieves uniform electric field conditions and simplicity of construction by machining 61 elongated cylindrical cavities in a single block of A-150 TE plastic and employing a novel design for the support of the anode wire at each end of each cylinder. Comparative measurements carried out in neutron fields with mean energies ranging from 33 keV to 600 keV between the METEPC and a 5 inch TEPC demonstrate that the sensitivity of the TEPC is matched by the METEPC and that lineal energy spectra measured with both counters have the same features and show the same changes with neutron radiation quality.

D 10

NANOENHANCED TECHNOLOGY FOR INTRACELLULAR DETECTION OF RADIATION-INDUCED METABOLIC PROCESSES

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The objective of this research is to design a novel nanotechnology for an intracellular detection of metabolic processes that includes identification and quantification of metabolites without destroying the viability of the interrogated cells. This new approach utilizes surface plasmon resonance to enhance interaction between photon-absorbing metabolites and metal nanoparticles in contact with cells growing in living body or tissue culture. Photon absorption within the metal nanoparticles create plasmon fields that enhance intrinsic fluorescence of interacting cellular metabolites thereby: substantially increasing absorption and emission rates, creating new spectral emission bands, shortening fluorescence lifetime, becoming more photo-stable and increasing fluorescence resonance energy transfer efficiency. The presented technique leads to new noninvasive photonic multi-parametric imaging tools that do not destroy the viability of the cells tested while allowing the identification of unique signatures of metabolites too weak to detect with conventional methods. Because the cells remain viable, they may be interrogated prior to and after irradiation, thereby establishing a new robust technology for automated analyses of intracellular metabolites and their dynamic pathways. The design of the instrument will be presented and compared with those of existing methods for the detection of metabolic processes.

D 11

MICRODOSIMETER INSTRUMENT (MIDN-II) FOR PERSONNEL DOSIMETRY

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The objective of this project is to develop a prototypic instrument that measures in real time the regulatory risk to personnel in a time-varying radiation field. The MIcrodosimeter-Dosimeter Nucleon (MIDN) instrument is for use in a spacesuit, spacecraft, remote rover, or other applications. The measurements provide absorbed dose, dose rate, and dose equivalent in real time so that appropriate action can be taken to reduce exposure. The instrument is based on a MIDN-MidSTAR microdosimeter launched on the MidSTAR spacecraft in 2007, the only solid-state microdosimeter flown in space. The system is characterized by its ruggedness, portability, low power, low mass, low voltage, and real-time remote programmability.The research has two elements: 1) improvements in solid-state microdosimetric sensors, 2) development of systems suitable for spaceflight, and 3) performance assessments at the Naval Academy, the NASA Space Radiation Laboratory at Brookhaven National Laboratory. This project has been approved by both the Navy and DoD Space Experiments Review Boards for a flight opportunity in space. The space system will be described and results of the ground-based studies will be presented, discussed, and compared with predictions obtained with transport codes.
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E 1

ONLINE IMAGING OF INITIAL DNA DAMAGES AT THE PTB MICROBEAM

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Low dose risk research requires new efforts in order to better quantify the risk from exposure to low doses of natural radiation and medical use of radiation. Micro- or nanodosimetric modelling of natural or targeted radiation exposures will also benefit from benchmark studies with precise and selective irradiation techniques. Our goal is to generate and use new and highly reliable cell systems for studying the initial steps of DNA-damage response and repair kinetics after microbeam irradiation with high- and low-LET particles.

In an inter-disciplinary collaboration of PTB, DSMZ and HHU, live cell imaging has been established at the charged-particle microbeam facility of PTB. Stable expression of candidate genes representing major DNA repair pathways was achieved in HT-1080 fibroblasts. PARP1, MRE11, PCNA and p53BP1 have been fused to fluorescent proteins.

Using alpha particles, we were able to observe online the fast accumulation of GFP-labelled p53BP1, creating foci along the particle tracks. Furthermore, co-localization of gamma-H2AX foci could confirm the functional indication of DNA/chromatin damage by p53BP1. In order to relate the initial damage and response to relevant biological endpoints, we also measured survival curves for corresponding wild-type and transfected cells. Significant differences were observed. These have to be further investigated in order to determine if results and conclusions obtained with GFP-tagged clones are applicable to wild-type cells.

E 2

WAVELET-SVM CLASSIFICATION AND AUTOMATIC RECOGNITION OF UNSTAINED VIABLE CELLS IN PHASE-CONTRAST MICROSCOPY

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Irradiation of individual cultured mammalian cells with a pre-selected number of ions, down to one-ion per single-cell, is a useful experimental approach to investigate the low-dose ionizing radiation exposure effects and to contribute to a more realistic human cancer risk assessment. One of the crucial tasks of all the microbeam apparatuses is the visualization, recognition and positioning of every individual cell of the cell culture to be irradiated. Before irradiations, mammalian cells (specifically, Chinese hamster V79 cells) are seeded and grown as a monolayer on a mylar surface used as bottom of the special designed holder, having as cover another mylar foil and allowing the cell culture to be in wet and sterile conditions. Manual recognition of unstained cells in bright-field is a time consuming procedure, therefore a parallel algorithm has been conceived and developed in order to speed-up this irradiation protocol step. Many technical problems have been faced to overcome the complexity of the images to be analyzed: cell discrimination in an inhomogeneous background, among many disturbing bodies mainly due to the mylar surface roughness and culture medium bodies; cell shapes, depending on how they attach on the surface, which phase of the cell cycle they are in and on cell density. Preliminary results of the recognition and classification based on novel method of wavelet kernels for the SVM classifier will be presented.

E 4

THE REQUIREMENTS OF BEAM COLLIMATION FOR MICROBEAM RADIATION THERAPY

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The efficiency of the beam collimators currently employed in Microbeam Radiation Therapy (MRT) studies has been estimated by Monte Carlo simulation. The beam collimator is characterized by the size of beam opening, the center-to-center distance of the neighboring beam openings and its thickness. The beam opening was fixed to be either 25 (micro)m × 4 mm or 50 (micro)m × 4 mm. The center-to-center distance of adjacent beam openings was assumed to be 50 mm, 150 mm or 175 mm. Two values of 5 mm and 1 cm were assigned to the collimator thickness. The photon energy was considered to range from 50 keV to 400 keV, which meets the suggestions made in the earlier studies. The radiation dose was estimated for the targets of tissue-equivalent material at different depths. The value at the target volume under the collimator opening is defined as the "peak dose" whereas the one under the collimator structure (shield) as the "valley dose". The efficiency of a collimator was evaluated by the corresponding "Peak-to-Valley Dose Ratio (PVDR)". The change in dose profiles by the non-parallel beam coming onto the beam collimator has been also assessed.

F 1

CELL DEATH EVALUATION OF FROZEN PHERIPHERAL BLOOD MONONUCLEAR CELLS IRRADIATED BY GAMMA RAYS

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Cell preservation is obtained by cell freezing and storing in liquid nitrogen. However, ionizing radiation (IR) background can affect cryopreserved cells. It is known that IR can induce apoptotic cell death of living cells. Few information on the response of cryopreserved cells to IR are available. To this aim, we have investigate the effect of relatively low (0.1, 0.3 and 0.9 Gy), intermediate (3.0 Gy) and high (18.6 Gy) doses of gamma rays (662 KeV del 137Cs) on peripheral blood mononuclear cells (PBMCs) immersed in liquid nitrogen. Cell death has been evaluated by flow cytometry after thawing and incubation for 0, 24, 48, 72 and 96 hours at 37°C and 5% CO_2. Cell death gradually increased both with dose radiation and incubation time. Interestingly, no significative cell death was detectable below 0,3 Gy dose radiation, and hypersensitivity at low dose radiation, typical of fresh cells, was not observable in frozen PBMCs. We propose that both impaired functionality of apoptotic signalling after thawing and reduced free radical formation at low temperature might be responsible for loss of low dose radiation hypersensitivity and low percentages of cell death after irradiation.

F 2

ADAPTIVE RESPONSE: MODELLING AND EXPERIMENTAL STUDIES

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Adaptive response (AR) is a term that describes the ability of a low "priming" radiation dose to decrease the cell response to a subsequent higher "challenging" dose. The main proposed mechanisms to explain AR are: increased efficiency of DNA repair, induction of anti-oxidant enzymes, alteration of cell cycle progression, changes in chromatin conformation. We propose a model that considers a modulation of the efficiency of DNA repair activity and of the level of anti-oxidant enzymes, starting from the framework of lethal-potentially lethal (LPL) model (Curtis S.,1986). Such model was extended with the inclusion of the dynamical variables representing the efficiency of repair, the levels of radiation induced radicals and of anti-oxidant enzymes. Our model is able to describe the protective effect of a priming dose. Moreover, in agreement with the literature data, the simulations show that the AR happens in a given priming dose and priming dose rate ranges only, and requires at least 4 hours to develop. In order to get more insights on the influence of radiation quality as well as on the role of cell-cell communication as factors affecting the AR, experimental studies were planned using sparse or confluent AG1522 cell monolayer. The results until now obtained after gamma-irradiation suggest that cell density is a crucial factor for observing an AR.

F 3

PRESTIMULATION OF PI3K/AKT SIGNALING PATHWAY CONTRIBUTES TO RADIOADAPTIVE RESPONSE INDUCED BY LOW DOSES OF RADIATION

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Cellular radioadaptive response resulting from pre-irradiation with low doses is a well known phenomenon whose mechanisms have not been clarified yet. Because the PI3K/Akt signaling pathway performs a cytoprotective function in irradiated mammalian cells, we explored whether this pathway also contributes to their radioadaptive response. Cultured cells (murine fibroblasts, human vascular endothelium) were exposed to gamma-rays at priming doses (2-4 cGy) and then, after 6-9 hours, at challenging high doses (5-7 Gy). Inhibitors of PI3K, wortmannin or LY294002, and an inhibitor of the heat shock protein 90-dependent Akt activation, 17AAG, were used in our experiments. Dominant negative or constitutively activated Akt was transiently expressed in the transfected cells to manipulate the Akt activity. The data obtained show that the radioadaptive response was strongly suppressed by the above inhibitors of PI3K or Akt. The results of transfection also confirmed the importance of Akt activation for the radioadaptive response. Western blotting has revealed that the low-dose irradiation stimulates the PI3K/Akt pathway, so that the residual level of activated Akt is retained in the treated cells for several hours – till the next (high-dose) irradiation. We suggest that the low-dose radiation-induced prestimulation of PI3K/Akt pathway results in formation of the pool of activated Akt in target cells; this pool contributes to the improved cell survival following high-dose irradiation.

F 4

RADIATION INDUCED PERTURBATION OF CELL-TO-CELL SIGNALING AND COMMUNICATION

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The investigation of the bystander phenomena (i.e. the induction of damage in cells not directly traversed by radiation) is strictly related to the study of the mechanisms of intercellular communication and of the perturbative effects of radiation.
A new possible way to try to solve the bystander puzzle is through a "systems radiation biology" approach with the total integration of the experimental and theoretical activities. In particular this contribution will focus on:
1)A cybernetic communication model (based on the original Shannon-Weaver model) re-interpreted to frame cell-to-cell communication processes and possible perturbations.
2) The implementation and the development of two different modeling approaches: a stochastic model (based on a Monte Carlo code) that takes account of the local mechanisms of release and internalization of signaling molecules and an analytical model where signal molecules are treated as a population and their temporal behavior is described by differential equations.
3) "Ad hoc" experiments designed to quantify key parameters involved in intercellular signaling (focusing as pilot study on release, decay and internalization of IL-6 molecules, their modulation by radiation, and possible differences between in vivo/ in vitro behaviors).
This approach provided instruments to investigate the complex phenomena of signal transmission and the role of cell communication to guarantee (maintain) the robustness of the in vitro experimental system.

F 5

HYPER-RADIOSENSITIVITY AND INDUCED RADIO-RESISTANCE IN TERMS OF CELL SURVIVAL, MICRONUCLEI INDUCTION AND CHROMOSOME ABERRATION. DEPENDENCE ON RADIATION QUALITY

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The hyper-radiosensitivity and induced radio-resistance (HRS/IRR) phenomenon, with a deviation in the survival curve behaviour in the low-dose region, has been demonstrated to date in over 40 cell lines after low-LET irradiation (Joiner et al, 2001).
Moreover the biphasic HRS/IRR behaviour has been found for survival curves of V79 cells after alpha particle and carbon ion irradiation (Tsoulou at al, 2001; Borhnsen et al, 2001). On the other hand no deviation has been reported with other high-LET radiations, like neutron and peak pions (Marples et al, 1993, 1994). Almost the totality of data about HRS/IRR effect have been gathered using clonogenic survival assays and few cytogenetic data are currently available in literature. Anyway a complex non-linear dose-effect dependence was observed for chromosome aberrations in human lymphocyte after X/gamma-rays and carbon ion irradiations and in human melanoma and V79 cells with X/gamma-rays (Nasonova et al., 2006; Shmakova et al, 1999).
In this study, Chinese hamster V79 cells were irradiated with g-rays and with broad beams of protons of different energy (energy and LET on cell: 0.8 MeV(28.5 keV/um) and 5.0 MeV (7.7 keV/um)) in the dose range 0.1-4.0 Gy. Cellular response has been evaluated in terms of cell survival, micronuclei induction and chromosomal aberrations. Evidence of HRS/IRR substructure in terms of cell survival, micronuclei induction and chromosomal aberrations has been found after gamma but not after proton irradiation.

F 6

LACK OF HYPER-RADIOSENSITIVITY AND INDUCED RADIORESISTANCE AND OF BYSTANDER EFFECT IN V79 CELLS AFTER PROTON IRRADIATION OF DIFFERENT ENERGY

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A huge body of evidence about the hyper-radiosensitivity and induced radioresistance (HRS/IRR) phenomena and the bystander effect (BE), often also contrasting, is reported in literature, in many cell types and in terms of various biological end-points, after high- and low-LET irradiation. However the mechanisms underlying these effects and the correlation of HRS/IRR and BE phenomena with radiation quality are not elucidated yet. Moreover also the possible inter-relation between HRS/IRR and BE and how they can contribute to cancer risk assessment at low doses are still open questions.
In order to study the HRS/IRR phenomena and the BE, cellular response has been evaluated in terms of cell survival after irradiation of V79 cells with broad beams of 7.7 and 28.5 keV/um protons in the dose range between 0.1 and 4 Gy. The role of intercellular communication between irradiated and not-irradiated (bystander) cells in the low-dose region has been investigated with a "partial shielding irradiation" system which prevents the irradiation of a fraction (35% in average) of the cell population by means of a 200 um-thick tantalum foil placed upstream of the cell sample .
No clear evidence of an HRS/IRR substructure neither of a consistent BE response can be identified in the low-dose region of V79 survival curves after proton irradiation of different energy.

G 1

ESTIMATION OF RADIOBIOLOGICAL EFFECTS IN CARBON ION TREATMENTS

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In radiotherapy with carbon ions, biological effects of treatment have to be predicted. Patient's cells are hit by beams composed of ions of several species (due to fragmentation) and different energies (due to straggling). To predict the effect of such a complex irradiation one usually relies on models, the Local Effect Model (LEM) developed at GSI being one of the most popular. We checked independently the reliability of the last published version of LEM in reproducing radiobiological data, both in monoenergetic and Spread Out Bragg Peak (SOBP) irradiation schemes. The results showed that LEM is able to qualitatively estimate SOBP biological effectiveness for a given cell line, once it has been calibrated on monoenergetic experimental data. We also verify that almost the same accordance in SOBP effect predictions is obtainable composing opportunely (as suggested by Zaider and Rossi, 1980) the effects of single tracks. Therefore, if it will be possible to experimentally characterize the response of few representative cell lines to monoenergetic ion irradiation, the role of models like LEM in Treatment Planning Systems will be of less importance than previously argued.

G 2

ABROGATION OF THE G_2/M ARREST ENHANCED THE CYTOTOXIC EFFECTS BY CARBON-ION BEAMS

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The aim of this study is to clarify cell cycle distribution and cytotoxicity after carbon-ion beams (C-ions). One human malignant melanoma cell line, HMV-I was exposed to X-rays or 290 MeV/u C-ions at the center of SOBP. We applied flow cytometry technique and colony formation assay. C-ions induced G_2/M arrest effectively more than X-rays at 24 h. The iso-effect dose, i.e. the 10% survival dose (5.0Gy for X-rays, 2.7Gy for C-ions) was used to examine the cell cycle kinetics. G_2/M fraction increased immediately after irradiations, and showed a peak at 15 h. G_2/M arrest cells were stayed long time after C-ions, whereas it released quickly after X-rays. In addition, the mRNA expression of molecules related with the arrest was suppressed with D10 dose and the effects were transitory after X-rays, whereas C-ions showed prolonged suppression. The arrest was released significantly by caffeine, and the cell killing by C-ions was enhanced with caffeine together. It is suggested that the release from G_2/M arrest after C-ions can enhance the cytotoxic effects. Repair of complex DNA damage by C-ions takes long time. When it released intermediate of the process, incomplete repaired damage cause cell death.

G 3

BNCT STUDIES AT LENA AND TAPIRO REACTORS: FIRST MICRODOSIMETRIC DATA COMPARISON

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By using the explanted-liver technique and the BNCT technique, liver metastasis have been successfully treated in Pavia LENA reactor. On the basis of such a success, INFN is supporting BNCT technological research aiming to implement BNCT both for lung and skin melanomas tumors. While skin melanomas can be treated with thermal neutrons lung tumors need epithermal neutrons. A study was performed to investigate the possibility of treating diffuse lung-metastases with BNCT. According to some MC simulations of human thorax irradiation, advantageous treatment is obtainable by using two opposite (anterior-posterior and posterior-anterior) epithermal collimated neutron beams as large as the lung volume. Since BNCT irradiation time is limited by healthy tissue damage, RBE assessment in mixed fields, where alpha, protons, lithium ions and gamma radiation are present at the same time, is a critical issue. Microdosimetric measurements in thermal and epithermal neutron beams, coupled with radiobiological measurements performed with small animals, will be a further tool to improve BNCT. Therefore, a twin TEPC has been constructed in order to assess RBE value both in ordinary living cells and in boron-charged cells. Twin-TEPC microdosimetric measurements have been performed both in TAPIRO reactor thermal column and in LENA reactor thermal column: two radiation fields used for BNCT radiobiological measurements. The two radiation field qualities will be compared and discussed.

G 4

SPECTRA OF THE LINEAR ENERGY TRANSFER AND OTHER DOSIMETRY CHARACTERISTICS AS MEASURED IN C 290 MEV/N MONO AND SOBP ION BEAMS AT HIMAC –BIO (NIRS, JAPAN) WITH DIFFERENT DETECTORS

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Acitive (MDU-Liulin) and passive (PNTD and TLD) detectors were exposed in C 209 MeV/n beam at HIMAC-BIO (NIRS, Japan). Two different types of beam configuration were used - mono energetic beam (MONO) and spread-out-Bragg-peak (SOBP); the detectors were placed at several depths from the entrance up to the depths behind Bragg peak. As far as TLD's are concerned, their relative response in beams has been studied as a function of the depth, it was reproved that it can depend on the linear energy transfer (LET) in the point of exposure.

Liulin measures energy deposition in Si; this spectra can be transformed to the spectra of lineal energy or LET. PNTD are able to determine the LET of registered particles. Both methods have its own limitations - Liulin is able to measure up to about 35 keV/µm (in water), PNTD can measure fron about 7 to 400 keV/µm. The results are compared and combined together for both beams configuration. Additional data on the TLD's response have been also obtained.

G 5

EXPERIMENTAL AND THEORETICAL EVALUATION OF THE LOCAL EFFECT MODEL

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The Local Effect Model (LEM) is a track-structure model, which is to be used to plan tumour treatments by hadrontherapy with carbon ions. To this aim, the LEM [1] assumes that cell-killing is induced by the generation of local lethal events. Based on the concept of local dose, the LEM allows one to calculate cell survival to any ionizing radiation simply from the determination of the cell survival to X-ray irradiation and from the size of the cell nucleus.

By comparing the predictions of the LEM to experimental data [2], we observed however that not only measurements for X-ray irradiations but also measurements for a beam of high-LET ions were required to fit LEM parameters. On a theoretical point of view, we pointed out some confusions and a mixing in the use of microscopic and macroscopic quantities [3]. We also showed that any pure local effect theory should only predict a linear behaviour in cell-survival curves. We concluded that the quadratic terms predicted by the LEM are due to artefacts stemming from an improper use of expected quantities (the local dose). Considering stochastic effects and non-local (non-targeted?) effects may help to improve such models.

[1] M. Scholz et al. ,Radiat. Environ. Biophys., 36:59–66, 1997.
[2] M. Beuve et al.International Journal of Radiation Oncology*Biology*Physics 71(2):635-642. (2008)
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G 6

MICRODOSIMETRIC COMPARISON OF SCANNED AND CONVENTIONAL PROTON BEAMS USED IN RADIATION THERAPY

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Multiple groups have hypothesized that the use of scanning beams in proton therapy will reduce the neutron component of secondary radiation in comparison with conventional methods with a corresponding reduction in risks of radiation-induced cancers. Loma Linda University Medical Center (LLUMC) has had FDA marketing clearance for scanning beams since 1988 and an experimental scanning beam available at the LLUMC proton facility since 2001. The facility has a dedicated research room with a scanning beam with fast switching that allows experiments during patient treatments with beam available whenever beam is not being delivered to a patient. This has provided us with an opportunity to obtain extensive dosimetric and microdosimetry data for preclinical evaluations. The facility provides conditions that approximate clinical treatments, and a variety of data are emerging for the radiation quality of the LLUMC scanning beam. Microdosimetric measurements of energy deposition have been obtained in order to provide detailed dose distributions; quality factors, i.e., Q values, of the scanned beams and conventional beams can be used here to summarize results, with lower mean Q-values being observed outside of the treatment volume with the scanned beam in comparison with passively modulated beams. Dosimetric and microdosimetric distributions will be presented, discussed, and compared with previously published results.

G 7

DIFFERENTIAL RESPONSE OF VASCULAR ENDOTHELIAL CELLS TO RADIATION EXPOSURE IN TUMOR MICROENVIRONMENT

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Micron-sized radiation beam has been utilized for basic studies in the field of radiation biology since mid 1990s to observe the individual cellular response to radiation impact, which led to the discovery of "bystander effect." During the similar time period, the synchrotron radiation of some tens of (micro)m in field size has been employed to treat brain tumors yet with animal models but ultimately for treating human patients. This new protocol, as known as microbeam radiation therapy (MRT), has been demonstrated to bring the improved therapeutic effect as compared to the conventional mm-sized beam treatment. This beneficial aspect has been presumed to come from the differential recovery of tumor vasculature from damage under the microbeam exposure. In this study, we have investigated the radiosensitivity of human umbilical vascular endothelial cell (HUVEC) in a varied pH condition of culture medium, which simulates the microenvironment of tumoral or normal tissue. The acidic tumor microenvironment seems to be inferior to the neutral normal tissue environment in keeping cells in good health. The HUVECs responded to the additional radiation stress in less sensitive under acidic environment. The comparison study with animal endothelial cells is in progress. Based on both human and animal data, we will summarize how the differential radiosensitivity of vasculature in tumor microenvironment would explain the improved therapeutic effect in MRT.

H 1

CELLULAR BURDENS AND BIOLOGICAL EFFECTS ON TISSUE LEVEL CAUSED BY INHALED RADON PROGENIES

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In case of radon exposure, the spatial distribution of the deposited radioactive particles is very inhomogeneous in the central airways. The objective of this research is to investigate the consequences of this heterogeneity on the cellular (not cell nuclear) burdens in the epithelium and to study the possible health effects on tissue level considering one type of interactions between cells. The deposition distribution in a five bifurcation unit of the bronchial airways was determined by a computational fluid dynamics program for 400 inhalations corresponding to 20 minutes of work in an uranium mine. For the quantification of cellular hits and doses, a numerical epithelium model based on experimental data was utilized. Finally, a carcinogenesis model considering cell death induced cell cycle shortening was applied to assess the biological answer of the tissue. The computations prove, that the cellular absorbed dose varies in a wide range between 0 and 2 Gy and the hit numbers in one cell can reach 25. On tissue level, the relationship between risk and the number of decays is non-linear and the shape of the curve is very different from the shape of the functions applied for cellular level. This research supports, that the deposition distribution of radon progenies may lead to inhomogeneous spatial distribution of tumours in the bronchial airways. On the other hand, in cancer risk assessment, studying single cell is not satisfactory, systems biological application is necessary.

I 1

LUNG CANCER FROM RADON AND SMOKING: A MULTISTAGE MODEL FOR THE WISMUT URANIUM MINERS, 1955-1998

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For the first time a biologically-based two-mutation carcinogenesis (TMC) model is applied to epidemiological data of the lung-cancer mortality in the large uranium-miner cohort of the WISMUT company (Germany). It comprises 35,084 miners who were first employed at WISMUT after 1954 and contains information on annual exposures to radon and its progeny. Since cohort-wide information on the tobacco consumption is missing, we developed a technique to account for the unknown smoking habits. This information has been retrieved in a WISMUT case-control study and is projected onto the cohort using a Monte-Carlo sampling method. The randomly assigned smoking behavior serves as a proxy for the missing information and is used as an input for the TMC model. TMC's free model parameters are estimated from a maximum-likelihood technique. An ensemble of 200 independent projections and subsequent TMC calculations yields frequency-density spectra of the TMC-model parameters. They are found to vary not much more than a factor ~2 from their respective mean values. This technique thus accounts for the smoking habits of the miner population and enables us to unravel risks related to the delicate interplay between radon and tobacco-smoke exposure. We will show results of the observed and expected, modeled lung-cancer mortality and present model calculations of post-exposure excess relative lung-cancer risks.

I 2

THE WST SURVIVAL ASSAY – AN EASY AND RELIABLE METHOD TO SCREEN RADIATION SENSITIVE INDIVIDUALS

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The clonogenic test has been shown to be a reliable method for the detection of radiation sensitive cell lines. Nevertheless it represents a tedious technic for the screening of hundreds of probes.
To screen hundreds of EBV transformed cell lines of young lung cancer patients for radiation sensitivity an easy, fast and reliable method was needed. The WST-1 test checks the metabolic activity of the mitochondria. Cell proliferation as well as indirectly cell death can be quantified by this method in a large scale in microtiter plates.
Cell survival was measured after 10 Gy irradiation (Cs137- source) and two time points (24h/48h) by trypan blue testing and by the WST-1 assay. An EBV cell line (GM03189/GM03323) of a radiation sensitive ATM patient in comparison to the cell line of the healthy brother was used to set up the experimental screening conditions and to establish a positive and a negative control. An optimal differentiation between the two cell lines was demonstrated for 10 Gy and 24 h cell growth after irradiation. Subsequently, 50 EBV cell lines of young lung cancer patients were screened under these conditions. 5 of them turned out to be radiosensitive. The results have additionally been confirmed by a different laboratory by means of trypan blue testing.
It was shown, that the WST-1 test represents an efficient and reliable method to screen for radiation sensitive cell lines.

I 3

A CELL KINETIC MODEL OF GRANULOCYTOPOESIS UNDER RADIATION EXPOSURE: EXTENSION FROM MURINES TO CANINES AND HUMANS

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Space radiation poses significant challenges to space travel, and it is essential to understand the possible adverse effects from space radiation exposure to the radiosensitive organ systems that are important for immediate survival of human, e.g., the hematopoietic system. In this presentation a biomathematical model of granunocytopoiesis is described and used to analyze the blood granulocyte changes seen in the blood of mammalians under continuous and acute radiation exposure. This is one of a set of hematopoietic models that have been successfully utilized to simulate and interpret the experimental data of acute and chronic radiation on rodents. We discuss their underlying implicit regulation mechanism and the biological relevance of kinetic parameters estimation method. Extension of the model to predictions in dogs and humans systems indicates that the modeling results are consistent with cumulative experimental and empirical data from various sources, implying the potential to integrate into one united model system to monitor the hematopoietic response of various species under irradiation. Based on the evidence of threshold responses of dogs for extended periods of low daily dose exposures, we discuss the potential health risks of the space traveler under chronic stress of low-dose irradiation and the possibly encountered Solar Particle Events.

I 4

IDENTIFICATION OF RADIO-RESPONSIVE MICRORNA IN HUMAN LYMPHOCYTES UNDER DIFFERENT GRAVITY CONDITIONS

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In space environment ionising radiation (IR) is combined with a condition of weightlessness, (i.e. microgravity) with potential synergistic action on cells. Many data showed that microgravity, experienced by astronauts during space flights or modeled on Earth, causes apoptosis, cytoskeletal alteration, cell growth inhibition, increased frequency of mutations and chromosome aberrations.
In this study we have examined miRNAs expression profile in gamma-irradiated human peripheral blood lymphocytes (PBL) incubated in modeled microgravity (MMG) and in parallel ground gravity (1g) during the repair time. miRNAs are small noncoding RNA that control gene expression post-trascriptionally by regulating mRNA translation or stability in the cytoplasm. The aim is to identify lead radio-responsive miRNAs affected by MMG that might alter the mechanisms of cell response to DNA damage, in particular those involved in DNA repair and apoptosis. miRNA expression profile was analysed in PBL irradiated with 0.2-2Gy and incubated for 4h and 24h in MMG and in parallel ground conditions (1g). Significant changes were observed according to the dose: 20 miRNAs resulted differentially expressed after 0.2Gy and 58 after 2Gy, indicating a dose-dependent expression pattern. Moreover, the cluster analysis showed a higher separation between 4 and 24h with a evident opposite expression levels for all IR-responsive miRNAs. MMG alone affected the expression of 44 miRNAs, whereas when it was associated with

I 5

RADIATION PROTECTION ISSUES FOR THE SPES PROJECT OF THE LNL

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The SPES (Selective Production of Exotic Species) project will be built at the National Laboratories in Legnaro (Italy). Its goal will be the development of radioactive ion beams and the consequent re-acceleration with the already existing Linac, to perform forefront reasearch in the frame of nuclear physics. Radiation protection aspects play along with every stage of the project e.g. civil construction planning, control system design and special technological plants. The first action is the evaluation of the direct radiation sources, due to the interaction of the beam with the target, the personnel and the environment have to be protected from. Based on this, one can design the shielding system, evaluate the activation of air in critical areas and control the possible leakages of radioactivity in the environment. In the present work some of these aspects are presented. The studies have been performed by means of the Monte Carlo transport code FLUKA. The interaction of a proton beam with 70 MeV energy and 300 microA current with an uranium carbide target has been studied and the dose levels outside the shielding have been assessed during the irradiation of the target and after a certain cooling time. The activation of the air in the target room has also been evaluated both in the presence and absence of a ventilation system. The production of radioactivity in the soil below the shielding has been evaluated in order to prevent the ground water to be contaminated.