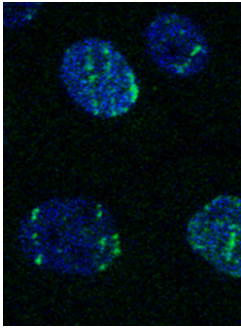




Forty-Seventh Annual Meeting Program



Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions



March 7–8, 2011

Hyatt Regency Bethesda
One Bethesda Metro Center
7400 Wisconsin Avenue
Bethesda, MD 20814

Top: Proton therapy treatment gantry (courtesy of J. Flanz, Massachusetts General Hospital).

Middle: MCF10A cells irradiated with 1 Gy 600 MeV n^{-1} iron ions, fixed 30 min after irradiation and stained with antibody to gammaH2AX (green) and DAPI (blue) (courtesy of J. Anderson and P. O'Neill, University of Oxford and F. Cucinotta, NASA Johnson Space Center).

Bottom: Astronaut in space (courtesy of the National Aeronautics and Space Administration).

Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions

Forty-Seventh Annual Meeting of the National Council on Radiation Protection and Measurements (NCRP)

Exposures to particle radiations in cancer treatments and during space missions are increasing. The 2011 Annual Meeting of the National Council on Radiation Protection and Measurements (NCRP) will focus on the scientific and policy challenges of these medical and occupational exposures.

The meeting will begin with a discussion of applications, biological interactions, and potential risks, including carcinogenesis and normal tissue damage, associated with exposure to particle radiations. The presentations will describe both results and insights gained from cell and animal experiments, clinical trials, and studies on astronauts who have participated in space missions. Discussions will include the modeling of particle radiation track structure in tissue, molecular mechanisms of cell and tissue damage, biophysical models of interactions with living systems, and evaluation of individual susceptibility of humans to radiation effects.

The practical radiation protection aspects of human exposures to particle radiations will be discussed in-depth, including those associated with medical applications and space missions. Shielding requirements for cancer treatment facilities and astronaut spacecraft will be discussed. Risk assessment modeling for decision making in operational planning and policies on dose control will also be described.

The meeting will conclude with presentations on future visions for achieving a greater understanding of the accelerator production of particle radiations, their medical applications, and potential health effects on astronauts by scientists from the U.S. Department of Energy, the National Institutes of Health, and the National Aeronautics and Space Administration.

Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions

Monday, March 7, 2011

Opening Session

- 8:15 am **Welcome**
Thomas S. Tenforde
President
National Council on Radiation
Protection and Measurements
- Eighth Annual Warren K.
Sinclair Keynote Address**
- 8:30 am **Heavy Ions in Therapy and Space:
Benefits and Risks**
Marco Durante
GSI Helmholtzzentrum für
Schwerionenforschung, Germany
- Tutorial on Charged
Particles in Medicine and
Space**
Thomas B. Borak, *Session Chair*
- 9:30 am **Physical Interactions of Charged
Particles**
Cary Zeitlin
Southwest Research Institute
- 9:45 am **DNA and Cellular Effects of
Charged Particles**
Maria Antonella Tabocchini
Istituto Superiore di Sanita, Italy
- 10:00 am **Clinical Results of Particle
Therapy**
Stephanie E. Combs
University Hospital of Heidelberg,
Germany
- 10:15 am **Space Radiation Protection Issues**
Amy Kronenberg
Lawrence Berkeley National
Laboratory
- 10:30 am **Questions and Answers**
- 10:45 am **Break**

Carcinogenesis

Polly Y. Chang, *Session Chair*

- 11:00 am **The *How* and *Why* of Radiation
Carcinogenesis: From Particles to
Gene and the Inflammatory
Signaling Cascade**
Tom K. Hei
Columbia University Medical Center
- 11:20 am **Animal Studies of Charged
Particle-Induced Carcinogenesis**
Michael M. Weil
Colorado State University
- 11:40 am **Risk of Second Tumors After
Proton Radiation: A Discussion of
the Hypotheses and Clinical Data**
Torunn I. Yock
*Massachusetts General Hospital/
Harvard Medical School*
- 12:00 pm **Questions and Answers**
- 12:15 pm **Lunch**

Normal Tissue Damage

Ritsuko U. Komaki, *Session Chair*

- 1:40 pm **A Lot to a Little or a Little to a Lot:
Insights from Studies on the Rat
Spinal Cord, Parotid Gland, and
Lung**
Peter van Luijk
University Medical Center
Groningen, The Netherlands
- 2:00 pm **Cardiovascular Effects of Charged
Particle Irradiation**
Mark P. Little
National Cancer Institute
- 2:20 pm **Normal Tissue Complications from
Proton Therapy**
Anita Mahajan
University of Texas, MD Anderson
Cancer Center

Program Summary

2:40 pm **NASCA Report 2: Longitudinal Study of Relationship of Exposure to Space Radiation and Risk of Lens Opacity**

Leo T. Chylack, Jr.
William H. Tung
Brigham and Women's Hospital
Francis A. Cucinotta
Alan H. Feiveson
NASA Johnson Space Center
Dale S. Hardy
Leif E. Peterson
Methodist Hospital Research Institute
Lisa J. Marak
Mary L. Wear
Wyle Integrated Science and Engineering

3:00 pm **Questions and Answers**

3:15 pm **Break**

Modeling

Dudley T. Goodhead, *Session Chair*

3:30 pm **Track Structure Simulations for Charged Particles**

Michael Dingfelder
East Carolina University

3:50 pm **Molecular Basis of Biophysical Modeling: Damage Complexity**

Peter O'Neill
Gray Institute for Radiation Oncology and Biology, University of Oxford, United Kingdom

4:10 pm **Biophysical Modeling for Particle Therapy**

Michael Scholz
GSI Helmholtzzentrum für Schwerionenforschung, Germany

4:30 pm **Questions and Answers**

4:45 pm **Break**

Thirty-Fifth Lauriston S. Taylor Lecture on Radiation Protection and Measurements

5:00 pm **Introduction of the Lecturer**
Polly Y. Chang

What Makes Particle Radiation So Effective?

Eleanor A. Blakely
Lawrence Berkeley National Laboratory

6:00 pm **Reception in Honor of the Lecturer**

Tuesday, March 8

8:15 am **NCRP Annual Business Meeting**

9:15 am **Break**

Individual Susceptibility

Joseph R. Dynlacht, *Session Chair*

9:30 am **Defining Molecular and Cellular Responses After Low and High Linear Energy Transfer Radiations to Develop Biomarkers of Radiation Risk or Therapeutic Outcome That Can be Personalized**

Michael D. Story
K. Kian Ang
William Brock
Kevin Coombes
Jing Wang
John Yordy
University of Texas, MD Anderson Cancer Center
Lianghao Ding
John Minna
Seongmi Park
University of Texas, Southwestern Medical Center at Dallas

Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions

| | | |
|----------|--|---|
| 9:50 am | Genetic Susceptibility Relevant to Space Travel Joel S. Bedford <i>Colorado State University</i> | Risk Assessment Modeling for Decision Making in Operations and Policy William F. Morgan, <i>Session Chair</i> |
| 10:10 am | Questions and Answers | |
| | Transport Codes and Shielding: Practical Radiation Protection John W. Norbury, <i>Session Chair</i> | 1:45 pm Biological-Based Risk Assessment for Space Exploration Francis A. Cucinotta <i>NASA Johnson Space Center</i> |
| 10:25 am | Description of Transport Codes for Space Radiation Shielding Myung-Hee Y. Kim <i>Universities Space Research Association</i> Francis A. Cucinotta <i>NASA Johnson Space Center</i> John W. Wilson <i>NASA Langley Research Center</i> | 2:10 pm Assessment of the Risk for Developing a Second Malignancy from Scattered and Secondary Radiation in Radiation Therapy Harald Paganetti <i>Massachusetts General Hospital/ Harvard Medical School</i> |
| 10:45 am | Break | 2:35 pm Questions and Answers |
| 11:00 am | Radiation Protection Calculations for Patients and Staff Wayne D. Newhauser <i>University of Texas, MD Anderson Cancer Center</i> | 2:50 pm Break |
| 11:20 am | Review of Nuclear Physics Experimental Data for Space Radiation John W. Norbury <i>NASA Langley Research Center</i> Jack Miller <i>Lawrence Berkeley National Laboratory</i> | Future Vision Noelle Metting, <i>Session Chair</i> |
| 11:40 am | Questions and Answers | 3:10 pm NCI Support for Particle Therapy: Past, Present, Future James Deye <i>National Cancer Institute</i> |
| 11:55 am | Individualizing Particle or Photon Radiation Therapy for Cancer Soren M. Bentzen <i>University of Wisconsin Madison</i> | 3:25 pm Report on Accelerators for America's Future Workshop: Medicine and Biology Jose R. Alonso <i>Lawrence Berkeley National Laboratory</i> |
| 12:15 pm | Lunch | 3:40 pm National Aeronautics and Space Administration's Needs for Research in Charged Particles Dennis J. Grounds <i>NASA Johnson Space Center</i> |
| | | 3:55 pm ENLIGHT: European Network for Light Ion Hadron Therapy Manjit Dosanjh <i>European Organization for Nuclear Research, Switzerland</i> |



Program Summary

- 4:10 pm **Questions and Answers**
- 4:30 pm **Summary: Achievements, Critical
Issues, and Thoughts on the
Future**
Kathryn D. Held
*Massachusetts General Hospital/
Harvard Medical School*
- 4:50 pm **Closing Remarks**
Thomas S. Tenforde
*President
National Council on Radiation
Protection and Measurements*
- 5:00 pm **Adjourn**

Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions

Monday, March 7, 2011

Opening Session

8:15 am

Welcome

Thomas S. Tenforde

President, National Council on Radiation Protection and Measurements

8:30 am

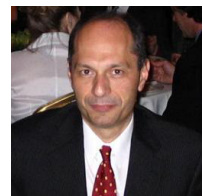
Eighth Annual Warren K. Sinclair

Keynote Address

Heavy Ions in Therapy and Space: Benefits and Risks

Marco Durante

GSI Helmholtzzentrum für Schwerionenforschung, Germany



Research in the field of biological effects of energetic charged particles is rapidly increasing. It is needed for both radiotherapy and protection from the exposure to galactic cosmic radiation in long-term manned space missions. Although the exposure conditions are different in therapy and space (e.g., high- versus low-dose rate; partial- versus total-body exposure), a substantial overlap exists in several research topics, such as individual radiosensitivity, mixed radiation fields, normal tissue degenerative effects, biomarkers of risk, radioprotectors, nontargeted effects. Late effects of heavy ions are arguably the main health risk for human space exploration, and with the increasing number of cancer patients (including young adults and children) treated by protons and carbon ions, this issue is now becoming extremely

important in particle therapy as well. Reducing uncertainty in both cancer and noncancer late risk estimates is therefore the first priority in heavy-ion radiobiology: it is necessary for a safe use of ion therapy in radiation oncology and for planning exploratory missions, especially the Mars exploration. In addition, researchers involved either in experimental studies of space radiation protection or particle therapy often use the same high-energy accelerator facilities. Several particle therapy facilities are now operating, under construction or planned in Europe, United States, and Asia. It is foreseeable that the availability of beam time and the presence of many dedicated research programs will lead to great improvements in our knowledge of biological effects of heavy ions in the coming few years.

Tutorial on Charged Particles in Medicine and Space

Thomas B. Borak, *Session Chair*

9:30 am

Physical Interactions of Charged Particles

Cary Zeitlin

Southwest Research Institute

Energetic charged particles used for radiotherapy and encountered in spaceflight

interact with matter through nuclear and electromagnetic forces. These interactions

result in the deposition of energy in the matter being traversed, both along the trajectory of the incoming particle, and (with some non-zero probability) far from that trajectory. In the therapy setting, dose localization is required, and the deposition of energy far from nominal trajectories complicates treatment planning and increases the risk of secondary cancers. Both nuclear and electromagnetic interactions produce dose outside the desired volume. Unlike therapy patients, astronauts in space receive relatively modest whole-body radiation doses from energetic charged particles and secondary radiations. A challenge for mission designers is to limit these exposures such that risk estimates remain within acceptable limits. At present, limits are defined for low-Earth orbit (LEO) but not for deep-space missions such as a hypothetical human mission to Mars. Most of the uncertainty in risk assessment for such missions comes from our lack of understanding of the biological effectiveness of the heavy-ion component of the Galactic cosmic radiation. Additional uncertainty arises from imperfect knowledge of the physics involved in the transport of high-energy particles through spacecraft walls, equipment racks, and human tissues. The same physical mechanisms are at work in these interactions as

in the particle therapy setting. In the case of heavy ions traversing matter, electromagnetic interactions are the cause of ionization energy loss, which increases the LET of the incident particle. These interactions are very well understood and can be modeled with a high degree of accuracy. Nuclear interactions can cause the fragmentation of incident ions into lighter ions, resulting in a multiplicity of charged particles, all of which have lower LET than the original ion. Neutrons are also produced in these interactions, and in some circumstances can contribute significantly to the total dose equivalent. The nuclear interactions are many-body problems and hence inherently complex; cross sections cannot typically be calculated from first principles. Nuclear interactions are accordingly not as well understood as electromagnetic interactions, and thus are the dominant source of uncertainty on the physics side of the problem. In general, the competition between fragmentation and ionization energy loss results in strongly energy-dependent Bragg curves for various ion species. This is readily accounted for in treatment planning, but presents a more difficult problem in space, where there is an extremely wide range of incident energies.

9:45 am

DNA and Cellular Effects of Charged Particles

Maria Antonella Tabocchini
Istituto Superiore di Sanita, Italy

Development of new radiotherapy strategies based on the use of hadrons, as well as reduction of uncertainties associated with radiation health risk during long-term space flights, require increasing knowledge of mechanisms underlying the biological effects of charged particles.

It is well known that charged particles are more effective in damaging biological systems than photons. This capability has been related to the production of spatially correlated and/or clustered DNA damage,

in particular two or more double-strand breaks (DSB) in close proximity, or DSB associated with other lesions within a localized DNA region. These kinds of complex damage, difficult to be repaired accurately, are rarely produced by photons and are expected to produce severe consequences at the cellular level.

In this presentation the spectrum of DNA damages, with special emphasis on complex lesions, will be described. The various approaches that have been exploited

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to characterize the charged particle induced DNA damage, in particular DNA breakage, will be reviewed. Emphasis will be given to more recent functional approaches, based on the use of fluorescent antibodies against proteins involved in the cellular processing of DNA damage; their advantages and limitations will be discussed.

Data will be shown on the relative biological effectiveness (RBE) for initial DSB induction. They will come from experimental measurements of fragmentation spectra and from theoretical evaluations obtained by performing Monte-Carlo simulations. The latter, able to reproduce the fragmentation data, provide prediction of fragmentation spectra outside the experimentally measurable range. In particular

simulations allow the study of the production of very small fragments, associated with correlated DSB. Also, data on the RBE for residual damage after repair will be shown.

Among the various cellular effects, cell death and mutation will be considered, the balance of these effects determining the commitment to carcinogenesis. Cell-death pathways play a crucial role in maintaining genomic integrity by selectively eliminating highly-mutated cells from the population. Data on the dependence of cellular effects on radiation quality will be presented. RBE for cellular effects will be compared with RBE for DNA damage (initial/after repair), also in view of possible identification of markers for radiation sensitivity.

10:00 am

Clinical Results of Proton Therapy

Stephanie E. Combs

University Hospital of Heidelberg, Germany

Over the years, particle therapy has emerged as an innovative treatment alternative in radiation oncology. While proton facilities are located in the United States, China, and Japan as well as in some European countries, carbon ions have been available in Japan since 1993 as well as in Darmstadt by the Department of Radiation Oncology of the University Hospital of Heidelberg at the Gesellschaft für Schwerionenforschung (GSI) since 1993.

The physical properties of ion beams enable precise dose delivery and sparing of normal tissue, leading to increased dose prescription possibilities especially for radioresistant tumors in close proximity to organs at risk. This special situation is found in tumors of the skull base (e.g., chordomas and chondrosarcomas). For these tumors, data from proton and carbon ion centers are comparable, showing an increase in local control rates compared to advanced photon radiotherapy.

With carbon ions, the physical properties of protons are accompanied by an enhanced radiobiological effectiveness. This has been shown in several experimental preclinical settings.

The early studies from Lawrence Berkeley National Laboratory as well as most early proton centers and carbon centers in Japan deliver their beams using passive beam delivery, achieving dose conformality to the target volumes using collimators, compensators and modulators. More precise delivery of ion beams became possible with the development of active-beam scanning. With this technique, the distinct physical characteristics of the particle beam including precisely defined dose delivery by a so-called inverted dose profile are exploited. Additionally, for carbon ions, an enhanced relative biological effectiveness has been shown which differs with respect to dose, depth, tumor type, endpoint, or normal tissue. Therefore, a special treatment planning system

accounting for this heterogeneity in biology has been generated at GSI based on the local-effect model initially published and continuously improved by Scholz and colleagues. At GSI, over 450 patients were treated with carbon ions delivered using the raster-scanning technique developed by Haberer *et al.* as well as biological treatment planning with overall excellent clinical results with very low rates of side effects.

Since November 2009, particle therapy is available at the Heidelberg Ion Therapy (HIT) Center, offering the possibility to treat

over 1,300 patients per year with proton as well as carbon ion beams. Technical characteristics including active beam delivery and treatment planning were based on the previous work.

Until November 2010, 250 patients with mainly base of skull chordomas, adenoid-cystic-carcinomas as well as atypical meningiomas and gliomas have been treated at HIT. Several clinical studies have been initiated, and will be followed in the near future for different indications to evaluate the role of particle therapy in modern radiation oncology.

10:15 am

Space Radiation Protection Issues

Amy Kronenberg

Lawrence Berkeley National Laboratory

The complex charged particle environments in space pose considerable challenges with regard to potential health consequences that can impact mission design and crew selection. The lack of knowledge on biological effects of different ions in isolation and in combination is a particular concern because the risk uncertainties are very high both for cancer and noncancer late effects. Reducing the uncertainties in the risk estimates is of high priority. Two principal components of space radiation each raise different concerns. Solar particle events (SPE) occur sporadically and are comprised primarily of low- to moderate-energy protons that may arrive at dose rates that are outside the current definitions of low dose rate. The galactic cosmic radiation (GCR) is isotropic and relatively invariant in dose rate

and is also dominated by protons, but the energy range is wider than in SPE. In addition, the contribution of other light and heavy ions to the health risks from GCR must be addressed. This tutorial will introduce four principal risks that have been identified as high priorities for research:

- risk of radiation carcinogenesis from space radiation;
- risk of acute or late central nervous system effects from space radiation;
- risk of degenerative tissue or other health effects from space radiation; and
- acute radiation risks from space radiation.

Specific gaps in our knowledge will be discussed for each of these principal risks.

10:30 am

Questions and Answers

10:45 am

Break

Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions

Carcinogenesis

Polly Y. Chang, *Session Chair*

11:00 am

The *How* and *Why* of Radiation Carcinogenesis: From Particles to Gene and the Inflammatory Signaling Cascade

Tom K. Hei

Columbia University Medical Center

Cancer is generally considered to be a multi-stage process with sequences of genetic events governing the phenotypic expression of a series of transformation steps leading to the development of metastatic cancer. Although radiation is a well-established human carcinogen, the mechanism of how radiation induces cancer is not clear. High linear energy transfer (LET) particles such as those used in radiotherapy and found in the natural radiation environment in space are potent clastogens that induce chromosomal breakages and present a potential mechanism for the loss of tumor suppressor genes. This is consistent with the observation that activation of the *ras* oncogenes, mediated through a point mutation, is an infrequent event in radiation-induced animal tumors and in radiation-induced malignantly-transformed human epithelial cells. Using an immortalized human bronchial epithelial cell line, it has been shown that high-LET radiation, including alpha and HZE particles, induces a step-wise neoplastic transformation and that the *βigH3* gene, a transforming growth

factor- β inducible gene, is consistently down-regulated by six- to sevenfold among radiation-induced tumorigenic human cells when compared with controls. To demonstrate its tumor suppressive effects, *βigH3* gene was ectopically reintroduced into tumor cells and resulted in a significant reduction in tumor growth as well as *in vitro* anchorage independent growth. The unequivocal demonstration that targeted cytoplasmic irradiation resulted in mutations in the nucleus of the same hit cells and that extracellular targets can modulate the radiobiological response in mammalian cells, in three-dimensional human tissue models and in whole organisms present an additional challenge in understanding the defined signaling process in radiation carcinogenesis. The observation that cyclooxygenase-2, a tissue inflammatory enzyme, is frequently found to be increased in many human cancers and in nontargeted tissues of irradiated animals highlights the contribution of tissue matrix and inflammatory cascade in the carcinogenic process.

11:20 am

Animal Studies of Charged Particle-Induced Carcinogenesis

Michael M. Weil

Colorado State University

The distribution of energy deposition in cells and tissues by HZE ions differs considerably from that of low linear energy transfer (LET) radiation raising concerns that charged particle exposure may be more efficient in inducing radiogenic cancers or may induce a different spectrum of tumors. In the absence of data on human

exposures, risk assessments for heavy ion irradiation will likely be modeled incorporating experimental results obtained using animals, *ex vivo* tissues, and cultured cells, and it is in these model systems that the question of potentially novel carcinogenic effects of HZE ion exposures will be explored.

A limited number of animal studies with carcinogenesis endpoints have been performed to evaluate the effectiveness of HZE ions. These include the induction of skin and mammary tumors in the rat; and Harderian gland tumors, acute myeloid leukemias, and hepatocellular carcinomas in the mouse. In general, high relative biological effectiveness (RBEs) have been found for solid tumor induction. RBE dependence on HZE radiation quality has been most extensively characterized in studies of mouse Harderian gland tumorigenesis. In this model, RBE increases with LET and plateaus in the 100 through 400 keV μ^{-1} range.

Unlike the results of solid tumor studies, a leukemogenesis study found 1 GeV n^{-1} ^{56}Fe ions no more efficient than gamma-rays for acute myeloid leukemia (AML) induction. Based on molecular and cytogenetic criteria, HZE induced AML are

indistinguishable from gamma-ray induced AML.

The tumor types that arise in HZE irradiated animals are the same as those that occur spontaneously or following low-LET radiation exposures. Genetic background is critical, the tumor types induced in HZE irradiated mice depends on their strain background, and the extent of HZE induced mammary carcinogenesis in the rat is also strain dependent.

There is evidence from the Harderian gland tumor studies and from hepatocellular carcinoma induction in HZE irradiated CBA mice that charged particles may play a unique or enhanced role in tumor promotion. In addition, data from studies of mice genetically engineered to develop lung cancer suggest that HZE exposure enhances malignancy in this model system.

11:40 am

The Risk of Second Tumors After Proton Radiation: A Discussion of the Hypotheses and Clinical Data

Torunn I. Yock

Massachusetts General Hospital/Harvard Medical School

Cure rates for pediatric and adult malignancies are now ~80 and 60 %, respectively, due to dramatic improvements in surgery, chemotherapy and radiotherapy. However, radiotherapy is the cause of many of the adverse late effects of treatment, which are now being well documented in the literature. The most sinister side effect of radiotherapy that affects both children and adults is radiation-induced second malignancies.

Second malignancies are a major source of morbidity and mortality in pediatric cancer survivors and are rarer but an important source of morbidity and mortality in adults. Because protons decrease the volume and dose to normal tissues compared with photon techniques, they are thought to decrease the risk of second tumor formation. The second malignancy

rates in children from incidental normal tissue dose are on the order of 2 to 10 % by 15 to 20 y after photon radiotherapy and <3 % in adults. There are little clinical data on the actual rates of second tumor formation after proton radiotherapy. However, math modeling studies do demonstrate an expected benefit with reduced rates of carcinogenesis from proton radiotherapy compared with photon techniques.

Mirabell *et al.* demonstrated expected second malignancy risks in a math modeling study comparing proton and photon techniques in children and found the expected risks for second malignancy using protons to be significantly less by a factor of 2 to 15 depending on the case and the photon technique, three dimensional versus IMRT. Similarly, in adults

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Yoon *et al* also found second tumor rates to be equal or less than those induced by photons.

Not everyone is convinced based on these models that protons will result in fewer radiation-induced second tumors. Hall *et al.* proposed that neutron scatter from current treatments at clinical proton facilities may eliminate the benefit of proton radiotherapy in the pediatric population and may, in fact, be worse. However, this assertion only considers the scatter dose outside of the field paths, for IMRT, three-dimensional conformal photons and protons and does not take into account the entrance and exit dose to normal tissues that increase the second malignancy risk in these tissues. Such an omission leaves out the largest source of risk for second malignancies. Furthermore, the amount of neutron production from clinical cyclotrons is much lower than the data used to generate the risk calculation from the neutron production. However, scanning techniques of proton radiotherapy can

dramatically reduce neutron scatter to the patient and are likely to improve conformity with fewer beams needed. This technique is employed regularly in one institution (Paul Sherrer Institute, Switzerland) and is occasionally used at some of the major centers in the United States. However, passively-scattered techniques are by far the technique used the most.

Unfortunately, there is little (but not zero) published literature on the second malignancy rates in patients treated with proton radiotherapy. Data from the Harvard Cyclotron Cohort looks promising with low rates of second tumor formation. A comparison of proton and photon treated patients using a SEER photon cohort will be coming out shortly, but has only been published in abstract form. This study demonstrates that protons do appear to reduce the subsequent risk of second tumors in a mixed pediatric and adult population. Some of those data will be presented in more detail at this meeting.

12:00 pm

Questions and Answers

12:15 pm

Lunch

Normal Tissue Damage

Ritsuko U. Komaki, *Session Chair*

1:40 pm

A Lot to a Little or a Little to a Lot: Insights from Studies on the Rat Spinal Cord, Parotid Gland, and Lung

Peter van Luijk

University Medical Center Groningen, The Netherlands

Tumor-dose escalation would improve cure rates after radiotherapy of many cancers. However, the risk of severe complications in co-irradiated normal tissues often prohibits this. Therefore, photon-based intensity modulated radiotherapy (IMRT) and particle therapy (PT) were developed to minimize the amount of co-irradiated normal tissue.

Dose distributions obtained by IMRT and PT show marked differences. IMRT reduces dose by using more beams as compared to older techniques. Besides a reduction of the amount of normal tissue irradiated to a high dose, this results in spreading of dose to large volumes that are now irradiated to a low dose. In contrast, PT exploits the advantageous depth-dose distribution to achieve dose

reduction with a limited number of beams, resulting in small volumes receiving a high dose and a reduction of the large volume receiving a low dose. To determine which, potentially results in best organ sparing a lot to a little or a little to a lot, the effect of (partial) irradiation of three differently structured organs of the rat, whose responses to radiation are known to depend on very different mechanisms, was determined. In these tissues the effect of additional low dose administered in large volumes was investigated using nonuniform dose distributions.

First, radiation damage in the spinal cord depends mainly on white matter necrosis and vascular injury. The spinal cord tolerated a very high dose in a small volume (*i.e.*, 51 and 88 Gy for 4 and 2 mm cord length, respectively). However, the addition of a subtolerance dose as low as 4 Gy to the surrounding tissue reduced the tolerance dose by 36 and 25 %, respectively. This clearly demonstrates the damaging effect of low doses in large volumes of the spinal cord.

Loss of parotid gland function is mainly due to loss of function of saliva producing cells and the stem/progenitor cells

required to replace them. Irradiation of 50 % of the gland to a local irradiated tissue dose of 30 Gy reduced saliva production by only 20 %. However, addition of a dose as low as 1 Gy to the other 50 % of the gland resulted in an additional loss of 20 to 40 %. This clearly demonstrates the devastating effect of low dose regions added to a high dose region.

Early loss of lung function is mainly due to inflammation. In a study on the rat lung, early loss of function was induced starting at doses as low as 10 Gy, even though a small fraction of the lung (25 %) could be irradiated up to 40 Gy without any loss of function.

Though these organs develop damage through different mechanisms, low dose in large volume invariably results in enhanced damage and reduced tolerance. In conclusion, these results in three organs demonstrate that in general spreading dose to large, low-dose regions may result in less organ sparing. As such, from the normal tissue damage perspective, concentrating dose in small, high-dose regions using particle therapy is preferable over spreading dose in large low-dose regions using photon-based IMRT.

2:00 pm

Cardiovascular Effects of Charged Particle Irradiation

Mark P. Little

National Cancer Institute

There have been many epidemiological studies, extending over a considerable period, documenting excess cardiovascular risk associated with high dose (>5 Gy) radiotherapeutic exposure to low linear energy transfer (LET) radiation, in particular after treatment for Hodgkin's disease and breast cancer. More recently, excess risk has been observed in groups exposed to much lower levels (<5 Gy) of low-LET radiation doses, such as the Japanese atomic-bomb survivors and various occupationally exposed groups.

There is as yet little human evidence of circulatory risk associated with charged particle irradiation. The few *in vivo* experimental studies that examine effects of charged particle irradiation on the circulatory system for the most part examine acute tissue changes. With respect to the endpoint of arterial smooth muscle cell degeneration, two studies documented effects of exposure of B₆CF₁ mice to beams of ¹²C, ⁴⁰Ar, ²⁰Ne, or ⁵⁶Fe and estimate relative biological effectiveness (RBE) with respect to ⁶⁰Co gamma rays that is generally two or less. A single study

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examined the effects of fission neutrons with respect to ^{60}Co gamma rays for this endpoint and experimental system and reported much higher RBEs, of over 100. A single study examined cerebral hemor-

rhage in Fischer 344 rats neonatally exposed to ^{20}Ne or ^{56}Fe and observed an RBE with respect to 225 kVp x rays in the range 1.4 to 2.1.

2:20 pm

Normal Tissue Complications from Proton Therapy

Anita Mahajan

University of Texas, MD Anderson Cancer Center

Proton therapy is an attractive option for the reduction of toxicities of radiotherapy because of the reduction of integral radiation dose to normal structures. This reduction in dose should lead to fewer toxicities. This benefit is of particular interest in the pediatric population since children are more vulnerable to the potential risks of radiation and significant progress has been made in improving survival in many different pediatric malignancies.

At this time, a relative biological effectiveness of 1.1 is used in clinical situations to calculate the equivalent biologic dose for protons relative to photons. The unit of dose is commonly referred to as a cobalt gray equivalent (CGE). The interaction of a proton at a cellular level is postulated to lead to a higher frequency of double stranded breaks, so in theory there could be a higher probability of cell kill and a lower probability of mutagenesis. At this time, however, once the physical properties of the interaction of protons with matter are accounted for, there are no definite data that 1 CGE has any different biologic outcome than 1 Gy delivered with

photons. In the Bragg peak, there is greater uncertainty of dose deposition and associated biologic effect. In clinical practice, therefore, one avoids placing the Bragg peak on critical structures such as the brainstem, spinal cord, or optic chiasm.

Normal tissue damage in the brain, cardiovascular system, and eye will be discussed by the other speakers. This presentation will address the potential differences afforded by proton therapy in these organs and consideration of other organ systems that may be affected by radiation therapy. In general, the low dose bath is reduced or on occasion eliminated with the use of proton therapy which can result in a reduction of late and early toxicities related to low dose radiotherapy such as vomiting, mucositis, cardiovascular complications, pulmonary injury, and developmental effects in children.

The differences of the low dose bath in a variety of different situations will be reviewed and consideration of the potential benefits and risks will be considered.

2:40 pm

NASCA Report 2: Longitudinal Study of Relationship of Exposure to Space Radiation and Risk of Lens Opacity

Leo T. Chylack, Jr.

William H. Tung

Brigham and Women's Hospital

Francis A. Cucinotta

Lori J. Chappell

Alan H. Feiveson

NASA Johnson Space Center

Dale S. Hardy

Leif E. Peterson

Methodist Hospital Research Institute

Lisa J. Marak

Mary L. Wear

Wylie Integrated Science and Engineering

The National Aeronautics and Space Administration (NASA) Study of Cataract in Astronauts (NASCA) was a 5 y longitudinal study of the effects of low doses of space radiation exposure on the severity/progression of nuclear (N), cortical (C), and posterior subcapsular (PSC) lens opacities. It began in 2003 and was completed on December 31, 2009. Participants included 171 consenting astronauts who flew at least one mission in space, and comparison subjects made-up of three groups, (1) 53 astronauts who had not flown in space, (2) 95 military aircrew personnel, and (3) 99 non-aircrew, ground-based subjects.

Continuous measures of the severity of opacification for N (pixel density), C (percent of area opaque), and PSC (percent of area opaque) were derived from Nidek EAS 1000 digitized images. Primary outcome measures were maximum (right eye, left eye) for each lens opacity type. Age, demographics, general health, nutritional intake, and solar ocular exposure were measured at baseline. In the cross-sectional analyses of baseline data, astronauts who flew in space were matched to comparison subjects (astronauts who had not flown in space, military aircrew, and ground-based controls) using propensity scores based on demographic characteristics and medical history, stratified by gender and smoking (ever/never). Various forms of regression analysis were used (depending on the statistical properties of each outcome measure) to quantify effects of space radiation exposure, while controlling for remaining differences in sunlight exposure levels, age at baseline, nutritional intake (β -cryptoxanthin and polyunsaturated fats) after matching. In the longitudinal analyses using median regression the longitudinal data was collapsed into robust estimates of slopes of opacity versus time for each eye of each subject. Median regression, with the dependent variable being the maximum of the two slopes (right eye and left eye) per

subject, was then used to quantify and test for a radiation effect, adjusting for confounding variables age, nutritional and sun-exposure histories. In addition, a partial-correlation analogue of Kendall's Tau with standard errors adjusted for repeated observations on each eye for each subject was used to make inference on the likelihood of increased individual slopes for subjects with radiation exposure in cases where a regression model on the maximum slopes could not be adequately estimated.

- *C lens opacification*: median regression models controlled for age showed a statistically significant increase in the rate of C progression in the worst eye associated with dose of space radiation exposure. The C progression rate from space radiation was 0.372 ± 0.158 % increase in lens area opaque per sievert per year ($P = 0.019$);
- *PSC*: median regression showed that subjects with space radiation exposure were more likely to have higher rates of increase in the numbers of PSC centers ($P = 0.037$), but no relationship was found between radiation and progression of the aggregate area opaque of PSC; and
- *N*: median regression suggested higher rates of increase of average pixel densities for the entire nucleus ($P = 0.105$) and for the posterior embryonal nuclear region ($P = 0.065$) with radiation exposure, but not for other regions of the nucleus.

There were no detectable adverse effects of radiation exposure on high- or low-contrast visual acuity. The 5 y follow-up period in NASCA is short in the life history of a cataract. Longer follow-up might reveal additional associations between space radiation exposures and measures of lens opacification and visual function. The findings of the NASCA study are significant, since they were found in astronauts with relatively low lens doses, with

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the majority of exposures below 100 mSv. These findings raise concerns for future, longer space missions where higher lens

doses will occur, such as those to the International Space Station, Earth's moon, and Mars.

3:00 pm

Questions and Answers

3:15 pm

Break

Modeling

Dudley T. Goodhead, *Session Chair*

3:30 pm

Track Structure Simulations for Charged Particles

Michael Dingfelder
East Carolina University

Charged particle track structure simulations are a useful tool for the interpretation and understanding of early physical and chemical stages of radiation actions on matter. These Monte-Carlo-based simulations provide detailed information on properties of the interactions including spatial distributions of energy deposition, interaction types (e.g., ionization, excitation, elastic scattering, charge change, etc.) and radical species produced. This information is used in radiation biology to explore and estimate the effects of radiation quantity and quality on the biological response and to provide detailed information on the initial patterns of radiation damage.

Monte-Carlo track structure simulations follow the primary, as well as all (produced) secondary particles, event-by-event, from starting or ejection energies to total stopping. This requires reliable interaction probabilities (cross sections) for all considered scattering events, including ionization, excitation and charge changing events of the incident charged particles (i.e., electrons, protons, alpha particles, light and heavy ions) with the atoms and molecules of the material under consideration. Liquid water is of special interest

since it serves as a substitute for soft tissue.

In general, ionization probabilities for charged particles are obtained within the framework of the first Born approximation. Within this approximation the probabilities can be calculated as a product of a kinematical factor describing the projectile and a function fully characterizing the target material under consideration. This function, called the dielectric response function of the material, is modeled and obtained for liquid water by using scarcely available experimental data and theoretical models and constraints.

Of special interest for modeling and interpreting the initial patterns of radiation damage are low-energy electrons and heavy ions. In both cases, the standard formalism of the first Born approximation is not applicable and alternative descriptions need to be applied. Low-energy electrons appear on the end of the charged particle tracks and are important in the modeling of the chemical stage (radical production and transport) and the simulation of indirect effects. Heavy ions are of interest in space radiation (high energies) and carbon therapy (especially at the Bragg peak). Heavy ion ionization

cross sections can be related to proton cross sections *via* charge and velocity scaling for moderate and high speeds. However, at low to moderate speeds

additional interaction types (*i.e.*, electron capture and electron loss) need to be considered.

3:50 pm

Molecular Basis of Biophysical Modeling: Damage Complexity

Peter O'Neill

Gray Institute for Radiation Oncology and Biology, University of Oxford, United Kingdom

Predictions from biophysical models of interactions of radiation tracks with cellular DNA indicate that clustered DNA damage sites, defined as two or more lesions formed within one or two helical turns of the DNA by passage of a single radiation track, are formed in mammalian cells. These complex DNA damage sites are regarded as a signature of ionizing radiation exposure particularly as the likelihood of clustered damage sites arising endogenously is low. The induction of radiation-induced non-double-strand breaks (DSBs) clustered DNA damage sites in mammalian cells has been confirmed experimentally, with both high and low linear energy transfer (LET) radiations. For instance it was predicted from biophysical modeling that ~30 to 40 % of low-LET-induced DSBs, a form of clustered damage, are complex with the yield increasing to >90 % for high-LET radiation, consistent with the reduced reparability of DSB with increasing ionization density of the radiation. The increased biological effects such as mutagenesis, carcinogenesis and lethality with increasing complex DNA damage are consistent with these predictions. The molecular basis for biophysical models will be discussed based on the ability of ionizing radiation to produce clustered DNA damage sites, including

DSB, against a plethora of endogenous damage induced. It is these clustered damage sites which lead to the biological effects of ionizing radiation even for low fluence of particle tracks.

This overview will concentrate on developing the theme arising from biophysical models that damage complexity is important and is consistent with the hypothesis that radiation-induced clustered DNA damage sites and complex DSB are less repairable. For non-DSB clustered damage the reparability is less than that for isolated single lesions (*e.g.*, those caused by aerobic metabolism) and as a consequence the clustered damages are either highly mutagenic, a “foe” if induced in a normal cell, or harmful to cells, a “friend” if in a tumor cell. With particle radiation it is also important to consider delta rays which may cause clustered damaged sites that may be highly mutagenic.

In summary, the aim is to emphasize the link between the spatial distribution of energy deposition events related to the track, the molecular products formed, and the consequence of damage complexity contributing to biological effects and to present some of the outstanding challenges, particularly with particle radiation.

4:10 pm

Biophysical Modelling for Particle Therapy

Michael Scholz

GSI Helmholtzzentrum für Schwerionenforschung, Germany

One major rationale for the application of heavy ion beams in tumor therapy is their increased relative biological effectiveness (RBE) in the Bragg peak region. For dose

prescription, the increased effectiveness and corresponding differential effects between tumor and normal tissues have to be taken into account in treatment

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planning. The accurate description of these complex dependencies of RBE on the dose level, biological endpoint, position in the field, etc., requires biophysical models.

Different approaches have been developed for this purpose [e.g., the Katz track structure approach, the microdosimetric-kinetic model, and the local effect model (LEM)]. The basic features of these models will be presented and compared with respect to their applicability in ion beam therapy.

LEM will be described and discussed in more detail, since it is the only model currently implemented in treatment planning for ion-beam therapy. The model is based on the knowledge of charged-particle track structure in combination with the

response of the cells and tissues under consideration to conventional photon radiation. The effects of ion radiation are determined from the analysis of the microscopic spatial distribution of initial DNA double-strand breaks as derived from the local dose distribution within the particle tracks. The model is able to accurately describe the RBE values over the whole clinically relevant range from protons to carbon ions.

The model is applicable to describe the effects in the tumor as well as in healthy normal tissue, and the accuracy of the model will be demonstrated by comparison to experimental data *in vitro* and *in vivo*. An extension of the application to the effects of neutron radiation will be briefly discussed.

4:30 pm

Questions and Answers

4:45 pm

Break

Thirty-Fifth Lauriston S. Taylor Lecture on Radiation Protection and Measurements

5:00 pm

Introduction of the Lecturer

Polly Y. Chang

What Makes Particle Radiation So Effective?

Eleanor A. Blakely

Lawrence Berkeley National Laboratory

The scientific basis for the physical and biological effectiveness of particle radiations has emerged from many decades of meticulous basic research. A diverse array of biologically relevant consequences at the molecular, cellular, tissue, and organism level have been reported, but what are the key processes and mechanisms that make particle radiation so effective, and what competing processes define dose dependences?

There is a diverse array of biophysical processes across the electromagnetic (EM) spectrum that underlies differences in energy absorption and biological effects depending on wavelength and frequency. On Earth, particle accelerators use EM fields to propel well-defined charged particle beams to high velocities in a spiral trajectory, while the sun and cosmos provide unpredictable, complex fields of particle radiations in outer space. Charged particles therefore represent the most



energetic extreme of the EM spectrum, whether encountered in the clinic or in space travel. Each ion beam's depth-dose energy deposition profile demonstrates significant differences in energy absorption compared to conventional radiation, depending on the particle atomic number and velocity.

Original measurements of particle-induced DNA strand breaks by molecular pioneers had trouble reconciling their data with the cellular radiobiologists who found higher biological effectiveness. This spurred the development of improved technologies that nearly matched the effectiveness of molecular/cellular endpoints. Cell biologists learned that there are several modes of cell death, each dependent on radiation quality. The development of antibodies to identify radiation-induced foci composed of specific DNA repair proteins that interact in a prescribed sequence and are recruited to specific damage repair locations has resulted in an explosion of information regarding how repair processes work. Chromosomal techniques with a rainbow of colors have elucidated unknown rearrangements missed by earlier approaches. Recent years have brought genomics and proteomics to the forefront, revealing significant details of the differential gene networks triggered by radiations of increasing ionization densities.

Recombinant technologies have supported an understanding of the consequences of the loss or gain of specific genes to an organism's response to particle radiation. New studies indicate that individual genotypes control radiation-regulated genes and pathways in response to radiations of varying ionization density. The fact that densely ionizing radiations can affect different gene families than sparsely ionizing radiations, and that the effects are dose- and time-dependent has opened up new areas of future research. The complex microenvironment of the stroma, and the significant contributions of the immune response have added to our understanding of tissue-specific differences across the linear energy transfer (LET) spectrum. The relative contributions of targeted and nontargeted effects is thorny and elusive, but important contributor to chronic low doses of radiations of variable LET. This remains an area requiring research to help inform and guide our understanding of health protection considerations in medicine and in space. Cancer incidence is also LET- and tissue-dependent suggesting different mechanisms of action across the gradient of ionization density. This presentation will chronicle the step-by-step acquisition of experimental clues that have refined our understanding of what makes particle radiation so effective.

6:00 pm

Reception in Honor of the Lecturer

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Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions

Tuesday, March 8

8:15 am **NCRP Annual Business Meeting**

9:15 am **Break**

Individual Susceptibility

Joseph R. Dynlacht, *Session Chair*

9:30 am **Defining Molecular and Cellular Responses After Low and High Linear Energy Transfer Radiations to Develop Biomarkers of Radiation Risk or Therapeutic Outcome That Can be Personalized**

Michael D. Story

K. Kian Ang

William Brock

Kevin Coombes

Jing Wang

John Yordy

University of Texas, MD Anderson Cancer Center

Lianghao Ding

John Minna

Seongmi Park

University of Texas, Southwestern Medical Center at Dallas

While it has been known that there are extreme cases of normal cell radiosensitivity and resulting morbidity after radiotherapy that are a result of rare genetic disorders, smaller genetic variations among individuals may contribute to the variability of normal and tumor tissue response to radiotherapy and perhaps to carcinogenic risk from terrestrial and space radiation exposures. Using primary cell cultures from nearly 200 radiotherapy patients we have shown that the range of radiosensitivity varies almost fourfold. Those considered as radiosensitive displayed modest DNA double-strand breaks or chromosome repair defects and correlated with severe adverse normal tissue responses from select donors. Gene expression analysis readily segregates samples based upon their radiosensitivity suggesting that response is driven by underlying genetic mechanisms. This is also seen in cell lines from both head and neck and lung tumors where gene expression can define radiosensitivity. Attempts

are being made to develop biomarkers that would identify the radiosensitivity of both normal and tumor tissues for use in clinical settings.

In contrast to the risks from typical terrestrial radiation exposures are exposures of astronauts to heavy particles in free space and now secondary effects from heavy particles increasingly used in cancer therapy. To address some of these concerns a model system of nononcogenically immortalized human bronchial epithelial cells (HBECs) has been developed to determine the acute responses (*i.e.*, cellular survival, gene expression) and long term effects (*i.e.*, cellular transformation and oncogenesis, genomic and epigenomic alterations) from heavy particle exposures. Our goals are to determine how cells respond to heavy particles of varying energies, charge, dose, and dose rate in a series of HBECs from at least 60 individuals, and within individuals, the fate of oncogenically-progressed cells. Our initial approach examined gene expression

comparing ^{56}Fe , ^{28}Si , and gamma rays. Interestingly, there was no association of dose with gene expression, and while there was some contribution from time after radiation, the dominant parameter that defined gene expression patterns was radiation type. Five hundred and thirty-seven genes could be used to segregate samples based upon radiation type. In addition, it would appear that there is a relationship between particle charge and energy that will be discussed. To address carcinogenic risk, cellular transformation after heavy particle exposure of these HBEC cells was used as a surrogate for oncogenesis. The frequency of transformation is $\sim 10^{-6}$ for unirradiated normal HBECs, only slightly increases after low linear energy transfer (LET) radiations up to 5 Gy, but increases four- to fivefold after

very low doses of iron and silicon: the most effective dose being 0.25 Gy, and rapidly dropping to near control values by 1 Gy. This result was confirmed in a second independent HBEC cell line. Like low dose, fractionated ^{56}Fe exposures (five daily, 0.20 Gy fractions), also enhanced cellular transformation fourfold. At the cellular level, transformed cells, particularly progressed cells (*i.e.*, cells modified to express a mutant form of RAS) that were ^{28}Si irradiated, exhibit the hallmarks of epithelial to mesenchymal transition (EMT), yet no ^{56}Fe -irradiated cells displayed EMT and no heavy particle irradiated normal HBECs exhibited EMT. While early, these results identify inter-individual responses to radiation that may drive therapeutic response and carcinogenic risk after either low- or high-LET radiation exposures.

9:50 am

Genetic Susceptibility Relevant to Space Travel

Joel S. Bedford

Colorado State University

Cellular studies have established that radiosensitivities, as measured for several biological effects, including mutation, chromosomal aberration induction, and cell killing, are under genetic control. This control involves variations in the efficiency of radiation damage processing systems normally operating to allow cells to cope with such damage. The systems and extent of variations are generally dependent on radiation quality, and the radiation environment in space differs from that on Earth. While DNA damage from radiations largely underlies these cellular radiation effects, and genetic changes at the cellular level are an essential component of radiation carcinogenesis, there are also tissue and organ specific factors that play a role in susceptibility. Studies with various mouse strains, including congenic or recombinant inbred strains have shown that genetic factors can result in enormous

variation in susceptibility to cancer induction by radiation. Some fairly recent human epidemiological studies on clustering of radiation-induced cancers in families lends direct evidence that genetic variations in radiation sensitivity are not simply confined to potentially unrelated cellular damage endpoints or a putative irrelevancy of inbred mouse strains. Many of the exposures experienced by astronauts in the space environment are from low linear energy transfer (LET) radiations such as protons, where the genetic based variations in effect are likely to be the same as seen for sparsely ionizing x or gamma radiations already studied extensively. Evidence available to date for other HZE radiations, having very different patterns of local energy deposition or track structure, however, suggest that quality factors are not always the simple function of LET that has been assumed. Important

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has been rearranged to accommodate a
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deviations have been demonstrated. As more information becomes available on the proportions of individuals in the population and degree of genetic-based

variations in susceptibility for various components of the space radiation environment, the prediction of radiation risk to astronauts may need to be reevaluated.

10:10 am

Individualizing Particle or Photon Radiation Therapy for Cancer

Soren M. Bentzen

University of Wisconsin Madison

Ionizing radiation is unique among the anti-cancer agents because it can be carefully titrated and modulated in the four dimensions of space and time. The programming of radiation therapy (*i.e.*, the biology of dose-time-fractionation) has historically been one of the most fruitful arenas for research into improving the therapeutic ratio (*i.e.*, the trade-off between the benefits and risks from ionizing radiation). Increasing use of drug/radiation combinations and a willingness to explore nonstandard dose-fractionation schedules in the clinic have revitalized clinical radiation research on dose fractionation in recent years. Spatial modulation is the other main pathway for improving the therapeutic ratio and this has been the driver behind many technological advances in radiation therapy including Intensity modulated (photon) radiation therapy, intensity modulated proton therapy, and carbon-ion therapy. Inverse optimization of radiation treatment plans is a powerful tool for individualizing radiation therapy and thereby maximizing the individual benefit:risk ratio. Two huge challenges remain in order to get the full benefit from new treatment planning and delivery technologies. The first one is to improve the target volume selection and delineation where much of the current hope centers around novel molecular and functional imaging tools. Novel strategies, such as dose-painting by numbers, where individual voxel-level dose prescriptions are used, are the topic of preclinical and clinical research and may potentially lead to a new paradigm for the prescription, planning and delivery of radiation therapy.

The second challenge is to understand better the relationship between radiation dose distribution in normal tissues and organs on one hand and patient-level side effects on the other. The recent Quantitative Analysis of Normal Tissue Effects in the Clinic collaborative network (sponsored by the American Society for Radiation Oncology and the American Association of Physicists in Medicine) produced an impressive overview of the advances in this clinical research field, but also highlighted many remaining limitations to our knowledge. In particular the interaction between cytotoxic or molecular targeted agents and dose distribution is poorly researched. The same is true for dose-distribution effects for nonstandard radiation dose-fractionation schedules. The unique physical characteristics of hadron radiation beams would potentially be a powerful tool for further optimizing radiation therapy. However, a rational prescription of these therapies is currently limited by our incomplete understanding of four-dimensional (spatio-temporal) radiation biology. As radiation therapy is a loco-regional treatment modality, predictive biomarkers specific for the competing risks of loco-regional or distant failure are of great potential interest when trying to select the optimal combination of systemic and local therapy modalities for an individual patient. Finally, a brief overview will be presented of research into predictive and prognostic biomarkers and surrogate endpoints, including imaging based assays, for clinical effects of radiation therapy for cancer.

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Abstracts: Tuesday March 8

10:30 am

Questions and Answers

10:45 am

Break

Transport Codes and Shielding: Practical Radiation Protection

John W. Norbury, *Session Chair*

11:00 am

Description of Transport Codes for Space Radiation Shielding

Myung-Hee Y. Kim

Universities Space Research Association

John W. Wilson

NASA Langley Research Center

Francis A. Cucinotta

NASA Johnson Space Center

Exposure to ionizing radiation in the space environment is one of the hazards faced by crews in space missions. Three main sources of space radiations are the trapped particles in the Van Allen belts, galactic cosmic radiation (GCR), and solar particle events (SPE). As space radiations pass through spacecraft or habitat shielding, their energies and the composition are altered by interactions with the shielding. Further modification is made at critical organ sites by overlaying body tissue shielding. These modifications to the radiation fields arise from atomic processes of charged particles with orbital electrons, and nuclear collisions leading to fragmentation and secondaries (*i.e.*, neutrons and nuclear recoils). The transport of space radiation fields passing through the shielding can be simulated using Monte-Carlo techniques or deterministic solutions of the Boltzmann equation. Any high-energy transport code incorporates several basic features of physics: the nuclear elastic and inelastic interactions, decay and atomic interactions (ionization, excitation, and Coulomb scattering). To determine shielding requirements and to resolve radiation

shielding constraints for future human missions, the radiation shielding evaluation of a spacecraft concept is required in the early design process. The reliable and realistic radiation transport simulation can be accomplished only after incorporating all the components of space radiation shielding design. First, accurate knowledge of space environmental models is critical to define the appropriate external space radiation as a boundary condition. Then, radiation shielding transmissions into areas of internal shielding and at each critical body organ can be properly characterized with detailed shielding and body geometry models, as well as their accurate atomic and nuclear interactions and fragmentation models. Finally, organ dosimetric quantities or biological risks can be assessed by applying the corresponding response models for space radiation shielding against the particle spectra, which have been accurately determined from the transport code. Current transport codes will be reviewed and their accuracy analyzed through comparison to laboratory and spaceflight data.

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11:20 am

Radiation Protection Calculations for Patients and Staff

Wayne D. Newhauser

University of Texas, MD Anderson Cancer Center

Predictions of exposure to charged particle radiation are commonly performed for patients receiving radiotherapy and occupational workers in accelerator facilities and astronauts. This presentation will review the physical interactions and bioeffects modeling approaches used to perform calculations of radiation dose to individuals exposed to charged particle radiation. The discussion of physical interactions include Coulombic energy loss, multiple Coulomb scattering, range straggling, and nuclear interactions and the production of secondary charged and uncharged particles. Modeling approaches

discussed will include analytical algorithms (*i.e.*, broad beam and pencil beam algorithms) and fast Monte-Carlo methods using supercomputing techniques. Modeling of the particle source, shielding, and human anatomy will be discussed, including the use of generic humanoid phantoms versus more realistic, personalized phantoms. Dosimetric and risk concepts and quantities of relevance to radiation protection will be discussed. The review will conclude with a brief summary of currently available dose computing capabilities, unmet needs, and possible directions for future research initiatives.

11:40 am

Nuclear Physics Measurements for Improving Transport Code Calculations

Giacomo Cuttone

INFN Laboratori Nazionali del Sud, Italy

The study of fragmentation processes is relevant in different fields of the physics concerning both basic research and applications. The energy range 10 to 1,000 A MeV is of fundamental importance for shielding in space radiations and hadron therapy and is interesting for different aspects concerning nuclear physics, astrophysics, radiobiology, radiation medicine, and radiation protection. An accurate description of the fragmentation of heavy ions is important for understanding the effects of the high-Z component of galactic cosmic radiation (GCR) on humans in space, for radiation-induced damage in microelectronics circuits (single event upsets), and for shielding in accelerator environments. The energy spectrum of the GCR peaks around 1 A GeV, and among the different heavy ions, ^{56}Fe attracted the greatest interest, because its contribution in terms of dose equivalent can be even greater than that attributed to galactic protons.

Moreover, the interaction and transport of light energetic ions ($Z < 9$ and $E < 400 \text{ MeV n}^{-1}$) in tissue-like matter is extremely important for cancer therapy with charged particles, a field in rapid expansion and pioneered in Europe at GSI. Normally, <50 % of the carbon projectiles actually reach the tumor in therapy, and this makes very clear that a precise knowledge of the fragmentation cross sections is necessary for treatment planning.

Both in hadron therapy and space radiation protection, specific computer codes are used to calculate the beam transport in matter. Deterministic codes are quick and are commonly used in practical situations. However, total and partial fragmentation cross sections are the critical inputs for transport codes, and the limited experimental data on cross sections make up the highest uncertainty in these codes. To check that the physics in the models and codes is correct, it is essential to understand the reactions and transport of

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particles and ions and the production of fragments and evaporation products (e.g., protons and neutrons). Experiments for the determination of double differential cross sections for reactions of heavy ions on different target material present in tissue, spacecraft shielding and electronic devices need to be performed. The multiplicity distributions of secondary particles and the production of evaporation residues and light fragments should be validated to make sure the physical models included in the transport codes can reproduce the observations. The total reaction cross sections are essential in the determination of the mean free paths of the transport particles in the transport codes, and must therefore be calculated with great accuracy. However, measurements of total reaction cross sections including all reactions channels (e.g., de-excitation through gamma ray emission and target excitation) are missing and should be performed.

Deterministic codes often contain many parameters adjusted on a limited domain

and therefore not usable safely outside of this domain. In addition, they are generally not able to describe correlations between particles. Monte-Carlo transport codes use physics models to calculate the characteristics of all the particles and fragments produced in the nuclear interactions. To guarantee that these codes are predictive and reliable in all the domains of application, it is mandatory that they are built on solid nuclear physics bases and validated against constraining experimental data. Coincidence experiments, in which the different reaction products, from neutrons to heavy fragments, are measured simultaneously, are a unique way to reach a deep understanding of the reaction mechanism and consequently severely constrain the physics models. An intense experimental program is going to be carried out at GSI and INFN-LNS in Catania on this topic as part of a collaboration between GSI, INFN, IN2P3, ESA, and University of Siviglia in this field.

Status and future perspectives will be extensively reported.

12:00 pm

Questions and Answers

12:15 pm

Lunch

Risk Assessment Modeling for Decision Making in Operations and Policy

William F. Morgan, *Session Chairman*

1:45 pm

Biological-Based Risk Assessment for Space Exploration

Francis A. Cucinotta

NASA Johnson Space Center

Exposures from galactic cosmic radiation [made up of high-energy protons and high-energy and charged (HZE) nuclei], and solar particle events, comprised largely of low- to medium-energy protons, are the primary health concern for astronauts for long-term space missions. Experimental studies have shown that

HZE nuclei produce both qualitative and quantitative differences in biological effects compared to terrestrial radiation, making risk assessments for cancer and degenerative risks, such as central nervous system effects and heart disease, highly uncertain. The goal for space radiation protection at the National Aeronautics

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and Space Administration is to be able to reduce the uncertainties in risk assessments for Mars exploration to be small enough to ensure acceptable levels of risks are not exceeded and to adequately assess the efficacy of mitigation measures such as shielding or biological countermeasures. The recent Biological Effects of Ionizing Radiation (BEIR VII) and the 2006 United Nations Scientific Committee on the Effects of Atomic Radiation models of cancer risks and their uncertainties are reviewed. These models are shown to have an inherent twofold uncertainty as

defined by ratio of the 95 % confidence level to the mean projection, even before radiation quality is considered. In order to overcome the uncertainties in these models, new approaches to risk assessment are warranted. New computational biology approaches to modeling cancer risks are considered. A basic program of research that includes stochastic descriptions of the physics and chemistry of radiation tracks and biochemistry of metabolic pathways, to emerging biological understanding of cellular and tissue modifications leading to cancer, will be described.

2:10 pm

Assessment of the Risk for Developing a Second Malignancy from Scattered and Secondary Radiation in Radiation Therapy

Harald Paganetti

Massachusetts General Hospital/Harvard Medical School

Radiation therapy treatment planning aims at reducing doses outside of the target to minimize side effects. Such side effects can be short or long term. With the average age of radiation therapy patients decreasing, there is an increasing concern for long-term side effects, like second cancers.

The volumes in patients receiving radiation dose can be separated into three (overlapping) regions: the tumor (treated with the therapeutic dose), organs at risk in the tumor vicinity intersecting with the beam path (receiving low to intermediate doses), and the rest of the patient body (receiving very low doses). Of concern in terms of scattered and secondary radiation are only the regions outside of the tumor.

Each of the areas defined above has to be considered separately in terms of risk assessment. Organs relatively close to the target are considered in the treatment planning process by using dose constraints. They typically receive doses in excess of 1 % of the prescribed target dose. The dose absorbed in this region is often termed “in-field” dose (*i.e.*, the dose

visible in the treatment plan that is not associated with the target). The dose deposited outside of the volumes considered for treatment planning by secondary or scattered radiation is termed “out-of-field” dose.

Risk assessment is based on different toolsets when analyzing in- and out-of-field components:

- dosimetric information for in-field regions can typically be obtained from the treatment planning program. Biological weighting factors are small when dealing with photons and protons. While the dosimetry is straightforward, risk modeling can be complicated for various reasons (*i.e.*, the fact that in-field organs receive inhomogeneous dose distributions, the competing biological effects of cell survival and mutation, as well as cell repopulation).
- in contrast, out-of-field dosimetry is not as straightforward because whole-body computed tomography information is typically not available. Furthermore, dose calculation

algorithms in treatment planning codes are not intended for scattered and secondary doses. Consequently, for out-of-field dosimetry Monte-Carlo simulations and whole-body computational phantoms are often applied. Secondary doses often include neutron radiation, which is associated with considerable uncertainties in terms of radiation weighting factors. While dosimetry for out-of-field organs might be challenging, risk modeling

is typically relatively simple as it is assumed that dose-response relationships at low doses follow the linear-no threshold formalism (at least for solid cancers).

This presentation will outline the dosimetry for in- and out-of-field risk assessment. Furthermore, it will summarize the formalism of risk models for in- and out-of-field use. Finally, results based on this formalism for proton and photon radiation therapy will be presented.

2:35 pm

Questions and Answers

2:50 pm

Break

Future Vision

Noelle Metting, *Session Chairman*

3:10 pm

NCI Support for Particle Therapy: Past, Present, Future

James Deye
National Cancer Institute

In light of the rising worldwide interest in particle therapy, and proton therapy specifically in the United States, the National Cancer Institute (NCI) is being asked more often about funding for such research and facilities. Many of the questions imply that NCI is naive to the exciting possibilities inherent in particle therapies and thus they wish to encourage NCI to initiate and underwrite such programs.

In fact NCI has a long track record of support for the translation of hadrons from the physics laboratory to the therapy clinic by way of technology development and scientific investigations of physical and biological processes as well as clinical outcomes.

Early work has included:

- continuous funding since 1961 of proton treatments for more than 15,000 patients and facility

construction at the Harvard / Massachusetts General Hospital (MGH) site;

- treatment of 227 patients with the pi-meson facility at Los Alamos between 1974 and 1981;
- funding of more than \$69M for seven neutron therapy centers between 1971 and 1989;
- many funded projects in boron neutron capture radiation therapy through the present time; and
- numerous radiobiology projects over the past 50 y.

NCI continues to play an active role in the incorporation of protons into randomized clinical trials through the Children's Oncology Group, Radiation Therapy Oncology Group and the Program Project Grant (P01) that is co-directed by the MGH and MD Anderson Cancer Center. This has required funding development

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and implementation of guidelines that enable inter-comparison of dosimetry and treatment between facilities. NCI has also funded recent efforts that wish to develop new physical processes for the production of particles such as protons.

With regard to the future, while it is true that there are no specific funding opportunity announcements directed to particle therapy research, it is also true that NCI remains open to reviewing any research that is compatible with an established mechanism. However given the very substantial resources that these facilities currently require along with the highly-competitive economic environment that now exists, it is clear that scientific review of such grant applications will look to

leverage the scientific pursuits which are the NCI mandate with the reality of the clinical practices just as is the case for photon radiation research. Such leveraging should be enhanced by the growing opportunities and need for international collaborations. On the other hand, these collaborations are complicated by the fact that these particle therapies are now fully reimbursable modalities which makes it difficult to separate research (the NCI mission) from clinical practice development.

This presentation seeks to illuminate these new realities in order to encourage the pursuit and funding of the scientific underpinnings of physical methods, radiobiology and clinical practice with particle therapy.

3:25 pm

Report on Accelerators for America's Future Workshop: Medicine and Biology

Jose R. Alonso

Lawrence Berkeley National Laboratory

Medicine and biology was one of the five working groups convened for the Accelerators for America's Future Workshop held in October 2009. The recently-released report from the Workshop stresses that the leadership position of the United States in fields where accelerators play an important part is being seriously eroded because of a lack of coordinated agency support of advanced research and development directed towards accelerators. This is particularly true in the field of medicine and biology.

Radiation therapy with beams of protons or light ions was pioneered in the United States, but in the case of light ions is now only performed overseas. Japan and Europe (Germany, France, Italy, Austria) all have ion-beam facilities either operating or in construction, while the United States has no serious projects planned. Proton therapy is now available in the United States in a number of centers, but all but one of the operating facilities contain

accelerator and beam-delivery components manufactured abroad by IBA (Belgium) or Hitachi (Japan). Fermilab built the first clinical proton facility installed at Loma Linda, operating since 1990, but no others followed. Two U.S. companies are soon to provide proton therapy capability: Varian using a superconducting cyclotron manufactured in Germany, and Still River – the only truly US. endeavor – with a compact superconducting synchrocyclotron directly mounted on a gantry. These U.S. companies will need to fight hard to overcome the dominance of overseas technology in this field.

Why has the United States lost its lead in this field? Our working group addressed this issue, and found that in large measure this can be traced to federal policies for funding research and development and for subsidizing design and construction of clinical facilities. While national laboratories possess the expertise to provide the accelerator and beam-

delivery technology, they were specifically forbidden to “compete with the private sector.” Then, while elsewhere in the world, central governments were subsidizing efforts of their private industries to develop these technologies, the Cooperative Research and Development Agreement (CRADA) process in the United States was slow to be implemented and has been largely ineffectual in building a competitive advantage for U.S. industry.

Funding for building clinical facilities in the United States has had to be raised from private sources, again in contrast to overseas projects that have received substantial subsidies or direct investments from government entities. As a result, proton

facilities, by virtue of having to recover investment costs, are touted in the U.S. press as “the poster-child for health care costs gone amok” while they are flourishing overseas. And while proton facilities are beginning to appear, the financial hurdle for starting a light-ion facility in the United States have been totally prohibitive for the private-equity market.

While technological advances are being made that will provide some reduction in necessary capital costs, the field will not flourish in the United States until the federal agencies, National Institutes of Health and U.S. Department of Energy in particular, recognize the critical need for investment of federal funds in this field.

3:40 pm

National Aeronautics and Space Administration's Needs for Research in Charged Particles

Dennis J. Grounds
NASA Johnson Space Center

Among the health risks for the human exploration of the solar system, space radiation is generally considered the main obstacle to interplanetary travel. It remains a most formidable obstacle because large uncertainties are associated with the projected health risk estimates, and no simple and effective countermeasures are available.

Ground-based research at particle accelerators is the main tool to overcome the obstacles of space radiation on human exploration. The usage of ground-based simulations by the National Aeronautics and Space Administration (NASA) leads to important areas of collaboration between NASA and the U.S. Department of Energy, and potentially other government agencies and nations.

NASA designs missions to keep crewmembers below the acceptable safety standards at the 95 % confidence level. The techniques available to design safe missions are: considering the solar cycle, optimizing operational parameters such as

the length of space missions and crew selection for age and gender, or applying mitigation measures, such as radiation shielding. However, with current information, a nominal 3 y mission to Mars currently remains outside acceptable limits. In 2006, the National Council on Radiation Protection and Measurements released a report identifying the major areas of information needed for radiation protection for missions beyond low-Earth orbit. This presentation intends to briefly describe NASA's research needs in these areas:

- determine the carcinogenic effect of protracted exposures of relevant energies of protons, neutrons, and heavy ions and the resulting quality factors;
- conduct experiments to underpin the risk estimates such as cell and molecular biology experiments using realistic cell and tissue models;
- determine whether or not there is a significant risk of effects on the

Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions

- function of the central nervous system from space radiations;
- determine the effect of protracted exposures of relevant energies of protons, neutrons, and heavy ions on other tissues, such as the ocular lens, bone marrow, cardiovascular and immune systems;
- develop methods of using experimental data for estimating risks of late and early effects in humans;
- conduct studies of the effects of solar particle event dose rates on early radiation responses (e.g., prodromal effects, such as nausea and vomiting) in order to determine the appropriate biological effectiveness factors to use in establishing gray equivalent limits to apply to organs and tissues for early effects;
- evaluate biomarkers for their ability to detect adverse effects;
- evaluate biomarkers to estimate cumulative doses; and
- assess countermeasures for their efficacy in preventing adverse effects.

3:55 pm

ENLIGHT: The European Network for Light Ion Hadron Therapy

Manjit Dosanjh

European Organization for Nuclear Research, Switzerland

The European Network for Light Ion Hadron Therapy (ENLIGHT) was established in 2002 to coordinate European efforts in hadron therapy. The ENLIGHT network is formed by the European Hadron Therapy Community which consists of over 200 participants from 20 European countries.

A major success of ENLIGHT has been uniting traditionally separate communities so that clinicians, physicists, biologists and engineers with experience and interest

in particle therapy work together. ENLIGHT has been a successful initiative in forming a common European platform and bringing together people from diverse disciplines and countries.

ENLIGHT demonstrates the advantages of regular and organized exchanges of data, information, and best practices, as well as determining and following strategies for future needs in research and technological development in the hadron therapy field.

4:10 pm

Questions and Answers

4:30 pm

Summary: Achievements, Critical Issues, and Thoughts on the Future

Kathryn D. Held

Massachusetts General Hospital/Harvard Medical School

4:50 pm

Closing Remarks

Thomas S. Tenforde

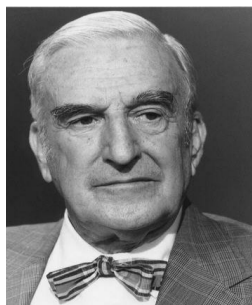
President, National Council on Radiation Protection and Measurements

5:00 pm

Adjourn

Mission Statement

To support radiation protection by providing independent scientific analysis, information and recommendations that represent the consensus of leading scientists.



Lauriston S. Taylor
1929–1977



Warren K. Sinclair
1977–1991



Charles B. Meinhold
1991–2002



Thomas S. Tenforde
2002–





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Registration

Monday, March 7, 2011 7:00 am – 5:00 pm

Tuesday, March 8, 2011 7:00 am – 1:00 pm

(no registration fee)

Register online: <http://registration.ncrponline.org>

2012 Annual Meeting

Contemporary and Emerging Issues in Radiation Protection

March 12 –13, 2012
Bethesda, Maryland

Publications

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| NCRP | Title | Price |
|-----------------------------|---|-------|
| Report No. 153 | Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit | 75 |
| Report No. 142 | Operational Radiation Safety Program for Astronauts in Low-Earth Orbit: A Basic Framework | 40 |
| Report No. 137 | Fluence-Based and Microdosimetric Event-Based Methods for Radiation Protection in Space | 25 |
| Report No. 132 | Radiation Protection Guidance for Activities in Low-Earth Orbit | 45 |
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| Report 84 | Reference Data for the Validation of Doses from Cosmic-Radiation Exposure of Aircraft Crew | 198 |
| Report 78 | Prescribing, Recording, and Reporting Proton-Beam Therapy | 192 |
| Report 63 | Nuclear Data for Neutron and Proton Radiotherapy and for Radiation Protection | 90 |

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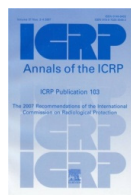
ICRP Symposium on the International System of Radiological Protection

October 24-26, 2011

**Bethesda North Marriott Hotel and Conference Center
North Bethesda, Maryland**

The International Commission on Radiological Protection (ICRP), an independent organization that issues recommendations on protection against ionizing radiation, will hold its next meeting together with its standing committees in North Bethesda, Maryland, October 2011. This meeting, held only once every 2 y, brings together the scientists and policy makers from around the world who are members of ICRP. The recommendations of ICRP form the basis of radiation safety standards, regulations, policies, guidelines, programs, and practice worldwide.

A unique event is being organized in parallel with this meeting: the first *ICRP Symposium on the International System of Radiological Protection*. With participation from North and South America, Europe, Africa, Asia, and Australia, this Symposium will be of interest to everyone in the field of radiological protection.



The overall System of Radiological Protection recommended by ICRP is described in ICRP Publication 103. This is an opportunity for anyone with an interest in radiological protection to hear about the System directly from those who have developed it. Participants will learn not only about how the System operates, but also its ethical foundations, the logic behind it, and how it has been applied in practical situations.

The opening plenary session will provide useful information on the System of Radiological Protection, and insight into the ongoing work of ICRP in relation to other key organizations in radiological protection. Other sessions will cover topical issues such as: protection against radon in homes and workplaces, protection of medical patients, environmental protection, and radiological protection related to security screening.

Presentations will be made by ICRP Main Commission and committee members, senior members of other international organizations, and officials and industry representatives from around the world. Time for open discussions will ensure an interactive exchange of ideas.

This Symposium is made possible in part through support from the U.S. Nuclear Regulatory Commission and the U.S. Environmental Protection Agency. Please contact Christopher Clement, ICRP Scientific Secretary, at sci.sec@icrp.org if your organization may also be interested in supporting this ground-breaking event.

Further information will be available at www.icrp.org



Contracts/Grants/Contributors/Sponsors

These organizations have supported the work of the National Council on Radiation Protection and Measurements during the period of January 1 to December 31, 2010.

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- Centers for Disease Control and Prevention
- Defense Threat Reduction Agency
- National Institute for Occupational Safety and Health
- U.S. Department of Homeland Security
- U.S. Department of Veterans Affairs
- U.S. Navy
- U.S. Nuclear Regulatory Commission

Grants

- National Aeronautics and Space Administration
- National Cancer Institute
- U.S. Department of Energy

Contributors

- American Academy of Health Physics
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