

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).

Introduction

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.

Monde	ay, March 7, 2011	
	Opening Session	11.00 a
8:15 am	Welcome Thomas S. Tenforde President National Council on Radiation Protection and Measurements	11.00 2
	Eighth Annual Warren K. Sinclair Keynote Address	11:20 a
8:30 am	Heavy lons in Therapy and Space: Benefits and Risks Marco Durante GSI Helmholtzzentrum fur Schwerionenforschung, Germany	11:40 a
	Tutorial on Charged Particles in Medicine and Space Thomas B. Borak. Session Chair	12:00 p 12:15 p
9:30 am	Physical Interactions of Charged Particles Cary Zeitlin Southwest Research Institute	1:40 r
9:45 am	DNA and Cellular Effects of Charged Particles Maria Antonella Tabocchini Istituto Superiore di Sanita, Italy	1.40 F
10:00 am	Clinical Results of Particle Therapy Stephanie E. Combs <i>University Hospital of Heidelberg,</i> Germany	2:00 p
10:15 am	Space Radiation Protection Issues Amy Kronenberg <i>Lawrence Berkeley National</i> <i>Laboratory</i>	2:20 p
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. Feivesson 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 fur 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 Ann	ual Business	Meeting
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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
10:10 am	Questions and Answers Transport Codes and Shielding: Practical Radiation Protection	1:45 pm	Biological-Based Risk Assessment for Space Exploration Francis A. Cucinotta NASA Johnson Space Center
10:25 am	John W. Norbury, Session Chair Description of Transport Codes for Space Badiation Shielding	2:10 pm	Assessment of the Risk for Developing a Second Malignancy from Scattered and Secondary Radiation in Radiation Therapy
	Myung-Hee Y. Kim Universities Space Research Association		Harald Paganetti Massachusetts General Hospital/ Harvard Medical School
	Francis A. Cucinotta NASA Johnson Space Center John W. Wilson NASA Langley Research Center	2:35 pm 2:50 pm	Questions and Answers Break
10:45 am	Break		Future Vision
11:00 am	Radiation Protection Calculations		Noelle Metting, Session Chair
	for Patients and Staff Wayne D. Newhauser University of Texas, MD Anderson Cancer Center	3:10 pm	NCI Support for Particle Therapy: Past, Present, Future James Deye National Cancer Institute
11:20 am	Review of Nuclear Physics Experimental Data for Space Radiation John W. Norbury NASA Langley Research Center Jack Miller Lawrence Berkeley National	3:25 pm	Report on Accelerators for America's Future Workshop: Medicine and Biology Jose R. Alonso Lawrence Berkeley National Laboratory
	Laboratory	3:40 pm	National Aeronautics and Space
11:40 am	Questions and Answers		Research in Charged Particles
11:55 am	Individualizing Particle or Photon Radiation Therapy for Cancer		Dennis J. Grounds NASA Johnson Space Center
	Soren M. Bentzen University of Wisconsin Madison	3:55 pm	ENLIGHT: European Network for Light Ion Hadron Therapy Manjit Dosanjh
12:15 pm	Lunch		European Organization for Nuclear Research. Switzerland

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

Welcome

Thomas S. Tenforde President, National Council on Radiation Protection and Measurements

8:30 am

8:15 am

Eighth Annual Warren K. Sinclair Keynote Address

Heavy lons in Therapy and Space: Benefits and Risks Marco Durante

GSI Helmholtzzentrum fur 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 galatic cosmic radiation in long-term manned space missions. Although the exposure conditions are different in therapy and space (e.g., high-versus lowdose 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

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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 energydependent 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.

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

9:45 am

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

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 fur 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. 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.

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

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accounting for this hetereogeneity 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, adenoidcystic-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

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 wellestablished 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 β igH3 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, $\beta i g H3$ 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 threedimensional 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.

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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 ⁵⁶Fe 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.

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 radiationinduced 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 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, threedimensional 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 conformality 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.

2:00 pm	Questions and Answers	
2:15 pm	Lunch	
	Normal Tissue Damage Ritsuko U. Komaki, Session Chair	
1:40 pm	A Lot to a Little or a Little to a Lot: Ins Cord, Parotid Gland, and Lung Peter van Luijk University Medical Center Groningen, The N	sights from Studies on the Rat Spinal
	Tumor-dose escalation would improve cure rates after radiotherapy of many can- cers. However, the risk of severe compli- cations 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 con- trast, 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.

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 B_6CF_1 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

examined the effects of fission neutrons with respect to ⁶⁰Co gamma rays for this endpoint and experimental system and reported much higher RBEs, of over 100. A single study examined cerebral hemorrhage in Fischer 344 rats neonatally exposed to ²⁰Ne or ⁵⁶Fe 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

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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, groundbased 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 nucleous.

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

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



Modeling

Dudley T. Goodhead, Session Chair

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-byevent, 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

3:30 pm

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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 radiationinduced 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 conseguence 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 fur 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 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 microdosimetrickinetic 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
	Dolly V. Chang

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 particleinduced 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 radiationinduced 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 tissuedependent 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.

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

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comparing ⁵⁶Fe, ²⁸Si, 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 thirtyseven 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 ~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 ⁵⁶Fe 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 ²⁸Si irradiated, exhibit the hallmarks of epithelial to mesenchymal transition (EMT), yet no ⁵⁶Fe-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.

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

9:50 am

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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

lonizing 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.

Tuesday morning from 10:10 am to 12:15 pm has been to attranged to accomodate a cancellation. See Summary for changes.

10:30 am	Questions and Answers	
10:45 am	Break	
	Transport Codes and Shi Radiation Protection	elding: Practical
11:00 am	Description of Transport Codes for Sp Myung-Hee Y. Kim Universities Space Research Association Francis A. Cucinotta NASA Johnson Space Center	Dace Radiation Shielding John W. Wilson NASA Langley Research 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 shield- ing, 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 radi- ation fields arise from atomic processes of charged particles with orbital electrons, and nuclear collisions leading to fragmen- tation and secondaries (<i>i.e.</i> , neutrons and nuclear recoils). The transport of space radiation fields passing through the shield- ing 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 shield- ing requirements and to resolve radiation	shielding constraints for future human missions, the radiation shielding evalua- tion 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 knowl- edge 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 char- acterized with detailed shielding and body geometry models, as well as their accu- rate atomic and nuclear interactions and fragmentation models. Finally, organ dosi- metric 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 labora- tory 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, 56Fe 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 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 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 lonizing 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-offield" 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

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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 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 highlycompetitive 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-

Abstracts: Tuesday March 8

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 (<i>e.g.</i>, 	 prodromal effects, such as nausea and vomiting) in order to determine the appropriate biological effective- ness 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 L Manjit Dosanjh <i>European Organization for Nuclear Research,</i>	ight Ion Hadron Therapy Switzerland
	The European Network for Light Ion Had- ron Therapy (ENLIGHT) was established in 2002 to coordinate European efforts in hadron therapy. The ENLIGHT network is formed by the European Hadron Therapy Comunity which consists of over 200	in particle therapy work together. ENLIGHT has been a successful initiative in forming a common European platform and bring- ing together people from diverse disci- plines and countries. ENLIGHT demonstrates the advantages of
	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	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 Issue Kathryn D. Held Massachusetts General Hospital/Harvard Med	es, and Thoughts on the Future
4:50 pm	Closing Remarks Thomas S. Tenforde President, National Council on Radiation Prot	tection 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 (http://NCRPpublications.org) (http://jicru.oxfordjournals.org)

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

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
Report No. 98	Guidance on Radiation Received in Space Activities	36
Symposium Proceedings No. 3	Acceptability of Risk from Radiation – Application to Human Space Flight	30

ICRU		
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

Please visit the NCRP website, http://NCRPpublications.org, for a complete list of publications. Reports and commentaries are available in both soft- and hardcopy formats. Book reviews of NCRP publications are also available at this website. Contact NCRP's Executive Director, David A. Schauer (schauer@ncrponline.org), for more information.

NCRP Special Liaison Organization



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.

Contracts

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 American Academy of Oral and Maxillofacial Radiology American Association of Physicists in Medicine American College of Radiology Foundation American Nuclear Society American Osteopathic College of Radiology American Roentgen Ray Society American Society for Radiation Oncology American Society of Radiologic Technologists Council on Radionuclides and Radiopharmaceuticals Health Physics Society Landauer, Inc. Lillian and Robert Brent Fund Radiological Society of North America Society for Pediatric Radiology Society of Nuclear Medicine

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PHYSICAL INTERACTIONS OF CHARGED PARTICLES

Overview

- In cancer treatment, accelerators are used to produce different radiation types – photons, protons, heavy ions.
- In deep space, there are high-energy charged particles that originate outside the solar system (Galactic Cosmic Rays or GCRs), and Solar Energetic Particles – dominantly protons – that are occasionally emitted from the sun.
- Physics is the same, regardless of source!

Charged Particle Transport for Space and Therapy

- Energetic charged particle transport is governed by two forces:
 - Electromagnetic \rightarrow ionization energy loss (including δ -rays) & Coulomb multiple scattering.
 - Nuclear
 Alteration of incident primary radiation, creation of secondary radiations.
 Sounds simple
- Sounds simple.

Particles and Interactions

Particle	Participates in Electromagnetic Interactions?	Participates in Nuclear ("Strong Force") Interactions?
Photon	Y	Ν
Electron	Y	Ν
Proton (or any other ion)	Y	Y
Neutron	Ν	Y

 Don't interpret this to mean, e.g., photons don't interact with nuclei – they do (photonuclear). But it's entirely electromagnetic.

Theoretical Underpinnings

- Electromagnetic interactions are fully understood, calculable with high accuracy.
- No fundamental theory of nuclear interactions exists

 measurements and models are needed.

Electromagnetic Processes

- Ionization energy loss (dE/dx) causes continuous slowing down as charged particles penetrate matter.
 - If no nuclear interaction, LET at depth > entrance LET.
 - Exception: heavy ions may fragment.
- Delta-ray production & Coulomb multiple scattering are strongly energy-dependent.
 No δ's, lots of scattering at low energy.
 Stochastic nature of these processes → straggling as particles come to rest.

Proton Transport



Dominated by dE/dx.

- Scattering & straggling cause lateral dose, range variations.
- Proton-nucleus collisions.
 - Target fragments, knockouts produce a high-LET component that includes neutrons.
- Distal edge dose is small.

Heavy Ion Projectile

Fragments

- Projectile fragments retain velocity & direction of primary ion (to a good approximation).
- Range goes as (A/Z²) for a given initial velocity (A = mass number, Z = charge).
- Therefore projectile fragments go past the Bragg peak of the primary
- Important in both therapy and space.

Heavy Ion Bragg Curves



Data courtesy Brookhaven National Lab.

- Strong functions of beam ion & energy.
- Trade-off of energy loss (drives LET up) and fragmentation (drives LET down).
- At higher energies (more like GCR), fragmentation dominates as 1 GeV/nuc ⁵⁶Fe Bragg curve shows.
- There's energy deposited in distal edges (more at high E).
- Note depth scales differ.

Galactic Cosmic Rays



Calculated with Badhwar-O'Neill GCR model for near-solar maximum conditions.

 GCR's in unshielded interplanetary space give dose ~ 250 µGy/day, or ~ 10 µGy/hr.

 Flux (green bars) dominated by protons but heavy ions contribute significant shares of dose (yellow bars).

Nuclear Fragmentation and Shielding in Space

- Fragmentation → dose reduction (but maybe not much reduction in dose equivalent or risk).
- Can shielding reduce risk to crew?
 - Complications due to high energies unlike typical terrestrial environment, primaries can't be stopped with practical shielding depths.
- Considering depth-dose curves, it's not obvious how much adding mass helps.
 - Adding mass is problematic anyway due to launch costs.
 - Biological uncertainties large.

Wilson et. al Calculation and Experimental





1995 paper by Wilson et al. calculated shielding effectiveness against GCR's w/various materials.

- Hydrogen is most effective shield per unit areal density.
- Some "shields" may make exposures worse.
- Qualitatively validated by experiment.

Fluence, Dose, LET

 With 1 particle type at one point, dose D is: D (nGy) = 1.6 \oplus L

with ϕ the fluence in particles cm⁻² and L the LET in keV/µm (planar geometry). For a sphere with diameter d in units of µm

<u>Average</u> # hits = $\mu \approx 5 d^2 D(Gy) / L$

Poisson Statistics



- If d = 6 μ m, then $\mu \approx$ 180 D(Gy) / L
- If L is high and dose is modest (e.g., in a single fraction), μ is small and the distribution of hits per cell, N, is Poisson.

•
$$P(N,\mu) = \mu^{N} e^{-\mu} / N!$$

- For small μ , P(0) \neq 0, and some cells not hit.
- E.g., $\mu = 5 \rightarrow P(0) = 0.67\%$

Summary

- Electromagnetic interactions are understood.
 Complicated but can be modeled accurately.
- Nuclear interactions are inherently more complicated (many-body problem) and we must rely on models tied to data.
 - Uncertainties in data → uncertainties in physical inputs to biological systems (whose response is even less well-understood).
- Nuclear interactions play a crucial role in transport in both therapy & space applications.
 Statistical distribution of hits/cell may be an important element in heavy-ion therapy.

47th NCRP Annual Meeting Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions Bethesda, MD March 7-8, 2011



DNA AND CELLULAR EFFECTS OF CHARGED PARTICLES



Maria Antonella Tabocchini

Technology and Health Department Istituto Superiore di Sanità Rome, Italy Theoretical analysis and experimental evidence suggest that the effectiveness of charged particles in damaging biological systems is due to the production of spatially correlated and/or clustered DNA damage

Clustered DNA damage represents the signature of densely ionizing radiation

With increasing the ionization density along the track an increased complexity and severity of DNA damage is expected, with high lethal and mutagenic potential the balance between these effects determining the commitment to carcinogenesis

The features of radiation-induced clustered DNA damage may compromise the cell's ability to maintain genome integrity



Courtesy of P.O'Neil

SPATIALLY CORRELATED AND/OR CLUSTERED DNA DSB

- Various approaches have been undertaken to characterize DNA breakage and to follow the kinetics of DSB rejoining/repair in human cells irradiated with different charged particles
- Most measurements rely on gel electrophoresis (CFGE/PFGE) as the technique of choice
 - FAR analysis (based on random breakage model)
 - Fragment counting (allowing direct calculation of the DSB number without any assumption on the breakage mechanism)

γ-H2AX AS A BEACON FOR DSB advantages and shortcomings

- Physical methods for DSB quantification typically require the use of doses > 5 Gy for reliable assessment of the induced damage and repair; scoring of γ-H2AX foci allows DSB detection in a dose range where the reproductive integrity of cells is not compromised
- Physical methods for DSB detection require DNA free of histones and other proteins which is usually obtained by high temperature lysis conditions that, in turn, can produce heath labile sites; *γ-H2AX assay is a functional approach and it is not affected by this potential source of error*

The major limitation of the γ-H2AX assay is that it doesn't follow the actual fate of physical DSB but registers cellular metabolic activities initiated to facilitate and optimize DSB repair

Discrepancies were observed between the kinetics of damage processing using physical (PFGE) or functional (γ-H2AX) DSB detection

physical DSB are removed from chromatin areas that remain marked with γ-H2AX after resealing, possibly to facilitate additional processing of DNA damage

 Differential formation of γ-H2AX in regions of chromatin with different organization can be a further bias for DSB analysis based on foci detection

Further studies needed to improve knowledge from immunofluorescence assays

- Basic research on DSB induction and processing e.g., live cell microscopy analysis (co-localization of enzymes involved in damage processing, ...)
- Experimental procedures leading to a better foci resolution e.g., antibodies against different proteins, ...
- Theoretical approaches

e.g., for evaluating damage multiplicity within foci, ...



Multiple foci along a single track Multiple damage(s) within a single focus

Both dependent on radiation quality

Relevant for quantification of induced clustered DNA damage and of its repair

IN CONCLUSION

Experimental and theoretical studies are needed

- to improve the experimental detection of clustered DNA damage
- to provide quantitative information on the induction and processing of DNA damage produced by densely ionizing radiation
- to correlate cellular end points (clonogenic cell death, apoptosis, mitotic catastrophe, mutation, ...) to the levels of clustered DNA damage
- to allow predictions of biological effects in mixed radiation fields, such as those present in space and therapy

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



www.protonsforkids.org

Torunn Yock, MD MCH Massachusetts General Hospital Chief of Pediatric Radiation Oncology Assistant Professor, Harvard Medical School NCRP Meeting, March 7-8, 2011 March 7, 2011, 11:40 AM

Outline:

- Overview of costs of radiotherapy in pediatric and adult patients
- The rationale for protons
- Rates of second malignancies in children and in adults
- Math models for second tumors in pediatrics
- Neutron risk
- HCL and SEER data
- Conclusions

The Costs of Radiotherapy in Children and Adults

- Approximately 70% of pediatric cancer patients are cured and 60% of adult cancer patients are cured.
- Late effects of radiotherapy in children can be severe and are of some concern in adult populations as well.
- Radiation inhibits growth and development of whatever tissue we irradiate in a dose and age dependent manner, with the young and the old sustaining the most side effects from the therapy.
- Brain radiotherapy in children affects neurocognitive and neuroendocrine function and may also have some effects in the adults.
- Outside the brain, RT also has functional and cosmetic effects
- Second malignancy
- These effects not only impact QoL but can also be fatal.

Morbidity from Radiotherapy

- 1. Increasing dose (to normal tissues)
- 2. Increasing volume (of normal tissue)
- **3. Younger Age at irradiation** (very old affected too)
- 4. Type of tissue irradiated
- 5. Concurrent chemotherapy

2nd Malignancies also correlate with all of the above factors that increase the acute and late side effects of treatment as well.

Protons: Clinical Advantages

- Prescribed to achieve same effect as photons.
- Improved dose localization in tumor translates into a better acute and late toxicity profiles.
 - Reduces late effects--profound in the pediatric population with neurocognitive, neuroendocrine and hearing effects.
 - Reduced 2nd malignancy risk.

Proton Radiotherapy

- Unlike conventional RT which is ionizing radiation found on the EMS (below)...
- Protons are particles with charge and mass taken from H₂O
- Energized in a cyclotron
- Depth of penetration is determined by their energy.
- When the protons come to the end of their range and stop they deposit all of their radiation dose—a phenomenon called a Bragg Peak.
- RBE = 1.1 (relative biologic effectiveness compared with photons)









- Gantry head

Brass aperture (custom made)

Lucite compensator for depth penetration

IMRT vs 3D Proton comparison

PROTONS

IMRT



3D Proton vs IMRT comparison

PROTONS

IMRT



Second Malignancies (SMN)

- RT exposure increases risk of any second tumor by 2.7 compared to therapies without RT
- TY TO FLESH THIS DATA OUT BETTER



Subsequent Neoplasm Among Long-term Survivors of Childhood Cancer



Subsequent Malignancy

Unpublished 1/08

Slide courtesy of Greg Armstrong, CCSS director
2nd Tumors in Adults

- Seer Monograph data briefly covered here.
- 2nd tumors much bigger problem in kids

The Neutron Issue: 2nd cancers

- Likely Initially Overestimated: 3 major reasons.
 - 1. Experimental data, not clinical data used. Overestimates neutron production (Hall, 2006)
 - 2. Only total body dose considered; the different integral dose from photons and protons ignored.
 - 3. No clinically relevant data on carcinogenesis RBE of the energy neutrons generated by clinical proton facilities.
- The clinical data are reassuring that we are doing more good than harm by using proton radiotherapy in our patients.

2nd Malignancy Proton Study (Chung et al, IJROBP abs, 2008)

- Comparison of proton patients with SEER photon patients matched by age, histology, year, and site.
- N=1006 patients, proton f/u 6.8 yrs, photons
 5.2 yrs
- Crude rates:
 - 6.4% of proton patients developed second malignancies
 - 13.1% of patients treated with photon radiation developed second malignancies

Cumulative Incidence of 2nd Malignancy



Overall Conclusions:

- The majority of pediatric and adult patients are cured.
- Second tumors are a major source of morbidity and mortality in our radiation treated cancer survivors
- Pediatric patients carry the greatest 2nd tumor risk burden
- Although passively scattered protons create whole body dose of neutrons, the estimated effects may be somewhat overstated due to no real knowledge of the carcinogenic RBE, but further study is needed.
- Scanning techniques should replace scattered techniques in the future and dramatically reduce whole body dose from neutrons.
- Clinical 2nd tumor data appears to show that protons provide an advantage overall for decreasing second tumor effects.
- Proton radiotherapy is a quantum leap forward in terms of minimizing dose to normal tissues and scanning and intensity modulation will further improve proton delivery.



Cardiovascular effects of charged particle irradiation

NCRP 47th Annual Meeting Scientific and Policy Challenges of Particle Radiation in Medical Therapy and Space Missions 7-8 March 2011 Mark P Little

Radiation Epidemiology Branch

US National Cancer Institute



Outline of talk

Introduction

- Cardiovascular radiobiology: effects of charged particle irradiation
- Possible radiobiological mechanisms
- Circulatory disease in moderate/low dose (A-bomb + occupationally exposed) groups
 Conclusions

 B_6CF_1 female mice, 4 month old at exposure, coronary artery changes after 0.8 MeV neutrons + ⁶⁰Co gamma (Yang et al Radiat Res 74:436-56;1978)` \Box 7.88 – 26.9 Gy gamma vs 0.2 – 2.40 Gy neutron (single total-body + 24 fractions) □ Smooth muscle cell degeneration and extracellular debris in heart and aorta (how assayed?) 1-24 months after exposure

Neutron dose (Gy)	Equivalent gamma dose (Gy)	Weekly fractions	RBE
0.2	8.23-26.9	24	40 - 130
0.8	>26.9	24	>35
0.8	<7.88	1	<10
2.4	>>26.9	24	>>10
			~3



B_6CF_1 female mice, 4 month old at exposure to ${}^{40}Ar$, ${}^{20}Ar$, ${}^{20}Ne$, ${}^{12}C + {}^{60}Co$ gamma (Yang &

Ainsworth Radiat Res 91:135-44;1982)`

- □ 1.6 7.0 Gy gamma vs 0.1 3.2 Gy charged particle
- Smooth muscle cell degeneration and extracellular debris in heart and aorta (how assayed?) 15 months after exposure

Dose (Gy)	Radiation type/energy	Fractional volume degenerated smooth muscle cell	Slope (/Gy)(SE)	RBE
0-7.0	⁶⁰ Co / 0.8 keV/µm	0.12-0.35	0.0299 (0.0019)	-
0-1.6	⁴⁰ Ar / 570 MeV	0.12-0.43	0.1938 (0.0258)	6.48
0-3.2	²⁰ Ne / 425 MeV	0.12-0.44	0.1350 (0.0202)	4.51
0-3.2	¹² C / 400 MeV	0.12-0.35	0.0834 (0.0129)	2.79

Endpoint of little relevance to circulatory disease?



B_6CF_1 female mice, 4 month old at exposure to 600 MeV ⁵⁶Fe (Yang Radiat Res 134:390-3;1993)`

□ 0-0.2 Gy ⁵⁶Fe (no low LET reference used)

Smooth muscle cell degeneration and extracellular debris in heart and aorta (how assayed?) 15 months after exposure

Dose (Gy)	Fractional volume degenerated smooth muscle cell (mean±SE)
0	0.12 ± 0.02
0.1	0.28 ± 0.04
0.2	0.24 ± 0.01

No information on RBE

Endpoint of little relevance to circulatory disease?

Fiescher 0344 neonatal mice, 1 day old at exposure to 670 MeV Ne or 600 MeV Fe +

225 kVp X-ray (Yang & Tobias Adv Space Res 4:239-45;1984)

Number of cerebral hemorrhages assayed 1 day after exposure

Dose (Gy)	Radiation type/energy	RBE
0 - 10.0	225 kVp X-rays	-
~2.5 - ~8.0	670 MeV Ne	1.4 - 2.0
~0.25 - ~2.0	600 MeV Fe	2.1

In some ways the most relevant radiobiological dataset



Schematic (inflammation) model of cardiovascular disease process





Cardiovascular radiation effects at moderate/low doses (< 5 Gy) >0.5 Gy: up-regulation of number of cytokines involved in inflammation, e.g., TNFa, IL-1 (Hallahan et al Cancer Res 56:5150-5;1996), inducing expression of adhesion molecules, e.g., E-selectin, P-selectin, ICAM-1, VCAM-1, PCAM-1 (Hallahan et al Biochem. Biophys Res Commun 217:784-95;1995; Hallahan et al Cancer Res 56:5150-5;1996; Quarmby et al AntiCancer Res 20:3375-^{81;2000}, leading to leukocyte "rolling" <0.5 Gy: indications of down-regulation of inflammation (Kern et al Radiother Oncol 54: 273-282;2000; Roedel et al IJRB 78:711-719;2002; Hosoi et al Int. J. Cancer 96:270-276;2001)

How would occupational dose give <u>increased</u> risk?



Known cardiovascular radiation effects from moderate/low dose (<5 Gy) epidemiology (A-bomb survivors)

- Elevated levels of IL-6 (Hayashi *et al. Int J Radiat Biol* 79:129-36;2003)
 and of TNF-α, IFN-γ and IL-10 (Hayashi *et al. Am J Med* 118:83-6;
 2005) observed in Japanese A-bomb survivors many years after exposure
- Other inflammatory markers, e.g., elevated erythrocyte sedimentation rate (Neriishi et al. Int J Radiat Biol 77:475-82;2001), C-reactive protein (Hayashi et al. Int J Radiat Biol 79:129-36;2003) also observed in this cohort



Possible other moderate/low dose (<5 Gy) radiobiological mechanisms Known effects of infections on cardiovascular disease (Ridker Circulation 97:1671-1674;1998; Whincup et al Circulation 101:1647-1652;2000; Danesh et al Eur Heart J 23:371-375;2002) Known radiation effects on immune system: reduction in certain T-lymphocyte subsets (CD4+) with increasing radiation dose in the A-bomb SURVIVORS (Kusunoki et al Radiat Res 150:227-36;1998)



Mechanisms for very low dose-rate (<0.001 Gy/day) cardiovascular disease

risk (Little *et al Radiat Res* 169:99-109;2008, Little *et al Radiat Environ Biophys* 49:139-53;2010)

- Even in A-bomb survivors average survivor dose ~0.1 Gy, i.e., most cells receive ~100 electron tracks will these effects extend to occupational settings? (<<1 electron track / cell /day)
- Role for somatic mutation in smooth muscle cells (SMC) (Benditt & Benditt *PNAS* **70**:1753-1756;1973) (based on clonality of plaques) would allow for low dose effects (analogous to cancer)
- However, evidence for clonality in SMC somewhat discredited: arterial wall is normally clonally "patchy" (Chung *et al Am J Pathol* **152**:913-23;1998)
- Mutations in SMC giving increased promotion more likely to be beneficial – now clear that SMC proliferation makes lesion development and rupture less likely (Clarke *et al Circ Res* 102:1529-38;2008), so role for SMC mutations unclear
- At <0.5 Gy evidence for down-regulation of inflammation: so how would very low dose rates (<0.001 Gy/day) lead to increased risk?



Conclusions

- Limited radiobiological data on charged particle radiation, most relevant endpoints suggesting low RBE (1.4-2.1) but some data (of questionable relevance) suggesting very high RBEs (up to 130)
- Mechanisms for low dose circulatory disease unclear: probably not mutational or directly-induced inflammation
- Radiobiology indicates that moderate-low dose (< 0.5 Gy) mechanisms may be different from those at high dose (>0.5 Gy) (but high dose RT studies have much same risk as moderate-low)
- Excess risk of circulatory diseases in number of moderate+lowdose exposed groups (A-bomb, Mayak, NRRW, Chernobyl liquidator etc)
 - Risk factors from moderate+low-dose cohorts suggest radiationassociated population risks of circulatory disease are similar to radiation-induced cancer

Normal tissue complications from proton therapy

Anita Mahajan MD 47th Annual Meeting NCRP March 2011

THE UNIVERSITY OF TEXAS MDAnderson Cancer Center

Normal Tissue Complications

- Late toxicities of cancer survivors
- Effects of low dose radiation
- Low dose reduction of proton therapy
- Potential issues of proton therapy
- Current evidence
- Summary

CCSS-what is known so far

- Long term outcomes for >14,000 5yr survivors of pediatric and adolescent cancer diagnosed b/w 1970-86
- Found to have increased risk for:
 - Late mortality
 - Second cancers
 - Organ toxicity
 - Pregnancy loss and low birth weight infants
 - Decreased education attainment
- Large number articles in the past 6 years

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Deterministic Effects

- Severity increases with dose, above a threshold
- Effect usually occurs after large doses
- Occurs hours, days, months or years after exposure
- Examples
 - Reduction in fertility
 - Cataracts



National Eye Institute

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MDAnderson Cancer Center

Stochastic Effects

- Probability increases with dose
- Severity independent of dose (all or nothing)
- Principal effect after exposure to low doses
- Examples
 - Lung Cancer
 - Genetic effects



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Patient & Treatment Factors

- Patient Factors
 - Age at initial diagnosis
 - Initial Diagnosis
 - Genetic Factors
 - Lifestyle
- Treatment Factors

 Chemotherapy
 Radiotherapy

Selected Late Effects of Low Dose Radiation

- Fertility
- Eye
- Growth
- Brain
- Lung

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Male Fertility: Testes

Dose (Gy)	Spermatogenesis	Leydig Function
<0.1	none	none
0.1-0.3	temp oligospermia 100% recovery 1yr	none
0.3-0.5	100% temp azospermia recovery 4yr	
0.5-1.0	100% azosperm 2-9 mo recovery beg. 8-26 mo	temp FSH rise
1-2	100% azospermia 1-2 mo recovery beg 11-20 mo	temp FSH & LH rise
2-3	100% azospermia 1-2mo some perm., dec testis vol.	long FSH rise, sl. inc LH

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Bone Growth

- Doses as low as 12Gy may impact growth
- Affected by cranial irradiation also
- Be aware of asymmetric bone growth
- Age of patient very important



Brain

- In children
 - Volume and dose of radiation associated with late effects
 - Current efforts to reduce volume and/or dose in children
- In adults
 - Increased risk of neurocognitive decline
 - May benefit in reduction of low dose to supratentorial brain

Lung Toxicities

- Efforts to minimize the 20Gy volume
- Chemotherapy of concern in Hodgkins lymphoma
- Baseline lung pathology in patients with lung cancer

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How do we improve outcomes?

- Reduce Irradiated Volumes...
 - Brachytherapy
 - Invasive procedure, not widely applicable
 - IMRT
 - Low dose volume of concern
 - Electrons
 - Dose homogeneity of concern
 - Protons
 - RBE, neutrons...

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Possible Outcomes of Proton Therapy

	TUMOR CONTROL		
ΤΟΧΙΟΙΤΥ	No Change	Increase	Decrease
No Change	SO SO	GOOD	BAD
Increase	BAD	SO SO	BAD
Decrease	GOOD	GOOD	BAD

Questions About of Proton therapy

- Physical Dose ≠ Biologic Dose
- RBE, current accepted value is 1.1
 - Variation with Bragg Peak
 - Variation with Tissue, ie α/β values
 - Variation with Energy and Depth
 - Effect on cell: Double stranded breaks, apoptosis
- Neutron scatter: Dependent on delivery system

RBE: BEST GUESS GIVEN THE PUBLISHED DATA

What about Neutrons?







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Protons



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Neutrons

Taddei et al., submitted

What can be done?

- Improve stray radiation exposure data
 - Monte Carlo
 - Measurements
- Improve delivery of scattered beams
- Improve local shielding
- Implement scanned beams


Our Experience....

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Proton Therapy for craniopharyngioma





Photon Therapy for craniopharyngioma







Retinoblastoma



electron



IMRT



Hosolute 1000,0 cgy 500,0 cgy

lat photon



hv+lens block



ant + lat hv

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GTV CTV Hypothalamus Thyroid Brain Body Lt Lac Gland **Lt Cochlea**



5Gy	Ρ	X
Brain	45	55
Body	43	67
Thyroid	15	35
Lt Cochlea	0	100
Lt Lac Gland	100	100

Evidence to support the Good outcomes

- Good outcomes for skull base tumors – MGH
- Early ototoxicity after MB therapy – Moeller et al ASTRO, 2010
- Decrease esophagitis, pneumonitis, higher dose for lung cancer
 - Sejpal et al Cancer, 2011
- Decreased cytopenias during CSI

 Nguyen et al SNO 2009
- Decreased SMN's
 - Yock et al ASTRO, 2008

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Goal of proton therapy

	TUMOR CONTROL		
ΤΟΧΙΟΙΤΥ	No Change	Increase	Decrease
No Change	SO SO	GOOD	BAD
Increase	BAD	SO SO	BAD
Decrease	GOOD	GOOD	BAD

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Summary

- Number of survivors is increasing
- Consider long term effects of all treatments
- Decrease treatment volume and dose if possible
- Consider the irradiated volume
- Educate patients and caregivers regarding long term toxicities

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Modeling

Track Structure Simulations for Charged Particles

Michael Dingfelder East Carolina University

Molecular Basis of Biophysical Modeling: Damage Complexity

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

Biophysical Modeling for Particle Therapy

Michael Scholz GSI Helmholtzzentrum fur Schwerionenforschung, Germany



2 nm





Track structure simulations for charged particles

Michael Dingfelder,

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Forty-Seventh Annual Meeting

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

March 7-8, 2011 Hyatt Regency Bethesda, Bethesda, MD.

Sponsors:



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Introduction

Track structure and transport codes: an overview Track structure:

- event-by-event (detailed) description
- only electromagnetic interaction
- secondary electrons followed
- materials: liquid water DNA, proteins, ...

Transport codes:

- condensed history
- electromagnetic interaction
- nuclear interaction
- energy loss / nuclear fragmentation
- materials: atomic cross section data bases



Charged particles:

- electrons
- protons, alphas,
- light ions: carbon
- heavy ions: HZE particles

Low-energy electrons:

- track ends
- damage / indirect effects



Energy Deposition

Track Structure



Time evolution





Track Structure

East Carolina University.



Follow

- primary particle
- produced secondary particles
- from start/ejection energy down to total stopping

step by step

- total cross sections (IMFP)
- energy/angle differential cross sections
- secondary electron spectra
- ionization / excitation
- elastic
- other



Cross Sections and Transport Models:

Cross sections:

- mean free path
- single differential
- double differential
- triple differential

Transport models:

- angular dependencies
- secondary electron emission
- auto ionization / Auger
- charge changing, multi-ionization, etc



CROSS SECTIONS

general

Plane Wave Born Approximation



Cross Sections: Remarks

- PWBA: momentum dependence
 - proto
 - corrections/approximations
 - other materials than water
 - relativistic energies

- low-energy electrons
- protons, ions

Bethe approximation:

- asymptotic (higher energies)
- only optical information needed

- Semi-empirical models:
- experimental data
- other materials



HEAVY IONS

HZE PARTICLES

HZE Interaction Cross Sections

- Plane wave Born approximation
- Bethe approximation
- Scaling laws (velocity and charge)
- Calculated from proton cross sections

$$\frac{\mathrm{d}\sigma_{\mathrm{ion}}}{\mathrm{d}W\mathrm{d}Q}(v) \,=\, Z_0^2\,\frac{\mathrm{d}\sigma_{\mathrm{proton}}}{\mathrm{d}W\mathrm{d}Q}(v)$$



Consider heavy ion as point particle

Partially dressed ions

- screening of nuclear charge by other electrons
- effective charge scaling

$$\frac{\mathrm{d}\sigma_{\mathrm{ion}}}{\mathrm{d}E} = Z_{\mathrm{eff}}^2(E) \,\frac{\mathrm{d}\sigma_{\mathrm{proton}}}{\mathrm{d}E}$$



Ions are atomic systems



Ionization:

- target, projectile
- simple, multiple

Excitation:

- target, projectile
- simple, multiple

Charge changing:

- electron loss
- electron capture
- single, multiple

single, multiple



Heavy Ions

- Charge changing events
 - excitation $p + X \rightarrow p + X^*$
 - ionization $p + X \rightarrow p + e + X^+$
 - electron capture $p + X \rightarrow (p + e)^* + X^+$ to bound state
 - $p + X \rightarrow p + e + X^+$ to continuum state
 - electron loss $H + X \rightarrow p + e + X^*$ H = (p+e) $H + X \rightarrow p + e + X^+ + e$
 - simultaneous capture/loss and ionization/excitation of target and/or projectile
- Charge states
- proton: p, H, H⁻
- alpha: He²⁺, He⁺, He
- carbon: C⁶⁺, C⁵⁺, C⁴⁺, C³⁺, C²⁺, C⁺, C

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THE MC CODE PARTRAC



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Transport medium: liquid water

• electrons:	10 eV – 10 MeV
• protons:	1 keV – 1 GeV
• alpha particles:	1 keV – 1 GeV
• ions:	1 MeV/u - 1 GeV/u

Considered: Excitations (5 discrete levels) Ionizations (5 ionization shells; single ionizations only) Elastic scattering (electrons only) Charge changing (protons, alphas only; 1,2 electron capture/loss)

Some tracks ...



Electrons, 10 keV



Heavy ions (relativistic)





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Remarks:

- track structure simulations: low energies = non relativistic models
- extension: non-relativistic to relativistic.
- extension: from electrons to protons to alphas to ions.
- *relativistic* Bethe surface ?
- *relativistic* sum rules, ... ?
- for relativistic energies: use Bethe formalism.



LOW ENERGY ELECTRONS AMORPHOUS SOLID WATER

low energy condensed phase transport sub-ionization sub-electronic-excitation track ends test of Monte Carlo methods

Test of MC code / input data



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Biological Tissue
Low energy electrons

- Low energy excitations (condensed phase)
 - phonon excitations (translational, librational)
 - vibrational excitations
 - electronic excitations (dissociative attachment)
- extent electron transport down to 1 eV
 - experimental data in amorphous ice (Michaud et al. Radiat. Res 159 (2003) 3)
 - modify transport model







Simulation of tracks – slab geometry



- proton ion
- proton exc
- electron ion
- electron exc
- electron stop
- electron low



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Comparison: Experiment vs. Simulation



Summary

Transport medium: liquid water

• electrons:	10 eV – 10 MeV
• protons:	1 keV – 1 GeV
• alpha particles:	1 keV – 1 GeV
• ions:	1 MeV/u – 1 GeV/u

Open Questions:

- low-energy electron transport
- heavy ions: dressed ions; relativistic theory; multi-ionizations, etc. nuclear transport
 other materials – DNA, proteins, ...



Molecular basis of biophysical modelling - damage complexity

Peter O'Neill

•OH

e

Gray Institute for Radiation Oncology & Biology University of Oxford, UK

(+



Formation of clustered damage by direct effect



Types of complex DNA damage

Clustered damage

TWO or more lesions formed within 1 or 2 helical turns of the DNA by a single radiation track



Complex DSB

additional lesions close to ends of DSB



Types of complex DNA damage

Clustered damage

TWO or more lesions formed within 1 or 2 helical turns of the DNA by a single radiation track



Complex DSB

additional lesions close to ends of DSB



1Gy ⁵⁶Fe ions – DSB detection by γH2AX



Tracks of DSB (γH2AX foci) appear to remain at longer times -•repair factories? •heterochromatin?

Does loss of γH2AX foci reflect repair dynamics of DSB induced by ion-particles?



Variation in LET along the path of a charged particle



Damage complexity- all damage substrates are not the same





Biophysical Modelling for Particle Therapy

Michael Scholz

GSI Darmstadt



Approaches for Treatment Planning in Ion Beam Therapy



GSI

GSI Approach: Basics of Local Effect Model (LEM)



NCRP 2011 Bethesda

GSI Approach: Basics of LEM

Basic Assumption: Increased effectiveness of particle radiation can be described by a combination of the photon dose response and microscopic dose distribution

Local Effect (Photons) = Local Effect (lons)



LEM: Transfer of low-LET experience to high-LET



Treatment Planning: GSI approach



Idea of LEMIV-concept

Pattern of DSB distribution Pattern of DSB distribution after ion irradiation in 2D after X-irradiation in 2D 10 10 8 a [H ypos [µm] ypos ... 2 • . 2 0 2 8 10 0 8 10 6 xpps [µm] xpos [µm] n_{DSB}=0 DSB distribution in single track can be n_{DSB}=1: isolated DSB interpreted as cut-out of X-ray distribution! n_{DSB}≥2: clustered DSB

Input Parameters

- Physics:
 - Radial Dose Distribution:

$$D(r) \propto \frac{1}{r^2} R_{Track} \propto E^{1.7}$$

- Biology:
 - Photon SSB+DSB yield

$$\boxed{N_{SSB} = Y_{SSB}D \mid N_{DSB} = Y_{DSB}D}$$

- **Photon** Dose Response Curve: $\frac{-\ln S(D) = \alpha D + \beta D^2}{\text{Linear shape for } D > D_t}$
- Target Size (Nuclear Size): experimental Data



Application to Cancer Induction: Basics

• Competition between induction and killing:



- Application of LEM to neutron radiation:
 - Determine secondary charged particle recoil spectrum (PHITS)
 - Apply LEM as for any other mixed particle radiation field
 - At present: secondary particle spectra for monoenergetic neutrons

Application to Cancer Induction:

Induction of lung tumors in mice (Coggle et al. 1988)



(LEM calculations: G. lancu, T. Friedrich, unpublished)

Comparison with Microdosimetric-Kinetic-Model

- MKM: Two types of lesions in domains with μ m size
 - L_I: lethal, unrepairable
 - L_{II} : sublethal, repair / conversion to lethal lesions (4 rate const.)
- Yield of L_I and L_{II} only depends on specific energy deposition z_{1D} in domain per particle traversal





Conceptual Differences





- LEM is able to reproduce the RBE(LET) dependence
- LEM is applicable to *in-vitro*, *in-vivo* and clinical endpoints
- LEM has been implemented in treatment planning
- Neutron effects can be predicted on the basis of secondary charged particle recoil spectra
- Promising results for application to cancer induction
- MKM also reproduces experimental data relevant for application in ion beam therapy
- LEM and MKM share similarities, but also show conceptual differences, which are testable

Thank you!

Thomas Friedrich Rebecca Grün Uwe Scholz Adrian Seeger **GSI** Biophysics Olaf Steinsträter Marco Durante Thilo Elsässer Siemens PT Marburg University Gheorghe Iancu

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SIEMENS Siemens Healthcare



Defining Molecular and Cellular Responses After Low and High LET Radiations to Develop Biomarkers of Risk or Therapeutic Outcome

Michael Story

- MD Anderson
- K. Kian Ang
- John Yordy
- Jing Wang
- Kevin Coombes
- Uma Raju
- John Heymach

- UT Southwestern
- John Minna
- Liang-hao Ding
- Seongmi Park
- Amit Das

Challenges in Particle Radiations in Medical Therapy and Space Missions

- Medical Therapy
 - Extension of Radiotherapy Research, (PI) Ang
 - Project 2: Gene expression as a predictor of normal tissue and tumors to radiotherapy
 - SPORE in Lung Cancer, (PI) Minna
 - Gene expression defining individualized drug and radiation combinations for lung cancer therapy
- Space Radiation Exposures
 - Risk Estimates and Mechanisms of Lung Cancer Pathogenesis after Space Radiation
 - Project 1:HZE Particle Exposure and the Risk for Human Lung Carcinogenesis

Low LET: Individual Susceptibility

- Inter-individual radioresponse
 - Therapy
 - Normal tissue
 - Acute or late effects of radiotherapy
 - Second cancers from therapeutic exposures
 - Tumor tissue
 - Intrinsic tumor radiosensitivity
 - » Radioresistance
 - Physiologic (hypoxia)
 - Genetic
 - Terrestrial and extra-terrestrial exposures
 - Carcinogenesis
 - Low dose or dose rate exposures
 - Medical Imaging
 - Security

Genetic drivers of radiosensitivity

- Examples of inherited human syndromes of excess cancer and radiosensitivity
 - Ataxia telangiectasia
 - Cockayne's syndrome
 - Fanconi's anemia
 - Nijmegan breakage syndrome
- Heterozygosity
 - Slightly more radiosensitive
 - Increased risk for cancer

General Population

- Intrinsic susceptibility likely a complex trait
- In complex traits: many loci with individually small effects that are cumulative
 - Will not be found by family linkage studies
 - The common disease- common variant hypothesis is not going to apply

Radiosensitivity as a Complex Trait

•Radiosensitivity defined by SF2

- 90 primary skin fibroblasts
- 18 with adverse late effects from radiotherapy
- DNA repair fidelity compromised
- •Discrete events
- The sum of small effects?



Radiosensitivity of 90 skin fibroblast cell lines as measured by surviving fraction at 2 Gy. Insert) Diminished DNA repair capacity of cell line C42 (red box) compared to other skin fibroblast cell lines S23 and C29, blue and green arrows, respectively, and a radiosensitive AT cell line.



Gene Expression Analysis

Cell

• Principal component analysis

- -Normal and resistant occupy the same space
- Each of the sensitive cell lines occupies its own space
- Explicit sets of genes responsible for spatiality
- -Define normal at least in terms of NT response (constitutionality)







Tumor cell lines (HNSCC)

Preliminary analysis

- Normally distributed SF2 values in 49 cell lines
- Divide into 2 groups by expression analysis: sens < 0.45 < resistant
- Signature does not predict for lung adenoma
- •Other generalized radiation sensitivity signatures did not predict





Clinical Response

72 probes (50 named genes)

116 probes (74 named genes)



- Gene expression analysis in 90 samples from highrisk HNSCC patients treated by PORT
 - Largely defined by epithelial to mesenchymal transition


Low LET Summary

- Genetic drivers of susceptibility
 - Normal tissue
 - Tumors
- Specific to tissue or tumor type
- Large sample sets required
- Significant debate on usefulness of cell lines
 - Do they translate?
- Validation in tissue required

High LET: Individual susceptibility

- Particle therapy
 - Tumor response
 - Adverse normal tissue response
 - Second cancers from radiotherapy
- Environmental exposures

Space environment

Early days

UTSW NSCOR in Lung Carcinogenesis

Define Genetic and Epigenetic Changes in Human Bronchial Epithelial Cells Following Exposure to HZE Particle Irradiation

Determine the Effectiveness of HZE Particle Irradiation on Initiation and Progression of Human Epithelial Cells to Lung Cancer

Define the Genetic and Epigenetic Changes Associated with HZE Particle Associated Initiation and Progression to Lung Cancer Non-oncogenically immortalized human bronchial epithelial cells

- HBEC3 KT: 1 of 60 normal human epithelial cells lines
 - normal non-smoking female
 - Immortalized by CDK4 and hTERT overexpression
 - Do not make tumors upon implantation in immune compromised mice
 - Unlike HBEC3 immortalized by HPV (HBEC 3ET)
- From HBEC 3KT a series of cell lines with defined molecular alterations were created
 - p53 knockdown, RAS^{V12} overexpression, p53/RAS combination
 - Overexpression of EGFR^{wt} and EGFR TK domain mutants
 - EGFR^{wt}, EGFR^{L858R}, EGFR^{E746-750E}

HBEC3 KT characterization

 Cell survival and gene expression as a function of LET





Molecular profiling: Gene expression

- For a given cell line are there unique gene expression patterns associated with HZE particle spectrum?
 - Unique genes or unique temporal response?
- Does genetic background alter gene expression patterns associated with HZE particle spectrum?
 - Are there consequences?
 - Survival
 - Carcinogenesis
- Physical dose vs equivalent biological dose
- Biomarkers of short term response
- Biomarkers of carcinogenic potential

Gene expression in HBEC3 KT cells reveals a uniform response to radiation

- p53 response genes
- Functional and metabolic signaling pathways







Radiation Type Contributes Differences of Radiation Responses in 3KT Cells





Experiment factors were built in ANOVA model. The mean F Ratio represents signal to noise ratio of each factor against all variables. The figure shows Beam quality is the factor that contributes most to the variation.

Mapping of experimental conditions using Principal Component Analysis (PCA). Areas of Ellipses were calculated based on contribution to each component by different beam types.

Metabolic and signaling pathway changes unique to specific radiations







Radiation-Induced Cellular Transformation



•Acute dose peaks at 0.25 Gy for Fe and Si (not shown)

Clone Isolation and Characterization

- 196 clones isolated
 - Short term culture
 - Frozen
 - 93 re-tested for soft agar growth
 - Half recapitulate the growth in soft agar
 - Characterize growth, morphology etc
 - Distinct morphology seen in some cell lines

Markers of EMT in HBEC3-KT Cells

RadiationN/ADose0 GyClonef.0d

Fe (1GeV) 0.5 Gy f.5f



Fe (1 GeV) 0.5 Gy f.5g



E-cadherin Vimentin







Markers of EMT in HBEC3-KTR53



Other Proteins

Other Proteins in HZE Irradiated HBEC 3KT

- MDM2 upregulated
 - p53 levels being examined by western
 - p53 sequencing ongoing
- CDK6 upregulated /(miR-107 down-regulated)
- No kRAS mutations identified
 - Radiation-induced vs smoking associated lung cancers

Inter-individual radioresponse to HZE particle exposure

- Sixty cell lines from individuals
 - Smokers
 - Never smokers
 - Male and female



Fractionated dose or low dose rate

HZE Summary

- Normal tissue in treatment field
 - Adverse acute or late tissue effects
 - May be exaggerated by HZE particles in some individuals
 - May be limited due to superior tissue targeting
 - *Banking of clinical samples absolutely necessary
- Cancers from therapy or environmental exposures
 - Cellular transformation suggests enhanced risk at very low doses followed by decline
 - Fractionated exposure suggests increased risk
 - -* Oncogenic potential of transformed cells unknown
 - -* Better quantitation of cellular transformation

Survival in EGFR series

EGFR^{wt}, EGFR^{L858R}, EGFR^{E746-750E}

- Increasing LET diminishes difference in cell survival
- Common mutation in never smoker lung cancer



Beam Quality or LET on Molecular Response



- No clear picture yet
 - O @ 120MeV and Si @ 1 GeV cluster
 - O @120 and 1GeV are divergent
- Contrast Fe @ 1 GeV and γ -
- Physical modeling of dose deposition required

Radiation-induced cellular transformation (ability to grow on soft agar)



- 10-12 x 10⁶ cells irradiated at 70% confluence at BNL or UTSW
- Cultures propagated for at least 4 months
- Inoculated into soft agar in quadruplicate plates monthly
- Foci counted after 2-4 weeks growth in soft agar
- Regularly isolate foci, submit to short-term culture, freeze



Description of Transport Codes for Space Radiation Shielding

Myung-Hee Y. Kim¹, John W. Wilson², and Francis A. Cucinotta³

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NCRP 2011 Annual Meeting

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

March 7-8, 2011



Introduction

- Radiation transport codes, when combined with Risk Projection models, are the main tool for shielding study and design.
- Approaches to assess the accuracy of Transport Codes:
 - Ground-based studies with defined beams and material layouts
 - Inter-comparison of transport code results for matched boundary conditions
 - Comparisons to flight measurements
- NASA's HZETRN/QMSFRG code has a very high degree of congruence for each of these criteria.
 - QMSFRG developed by Cucinotta et al. as quantum model of fragmentation
 - GERM code is a time-dependent Monte-Carlo code using QMSFRG



Components of Space Radiation Shield Design





NSRL for Biophysics Applications

Approximate Composition

N_{101.7}O_{33.1}Al₃₆ Density: 0.00194 g/cm³ Thickness: 1.2166 g/cm² N: 2.09×10²² atoms/g O: 6.81×10²¹ atoms/g Al: 7.41×10²¹ atoms/g





^{0.05379 ~ 0.08604} g/cm²







Space Weather Prediction Center, NWS, NOAA

NOAA/SWPC Boulder, CO

Feb 3

aal Time

2011 Feb 1 0000 UTC

12BIT 1x1



Updated 2011 Februa 16:25:12 UTC

GOES Solar X-ray Flux

NOAA Scales Activity Range 1 (minor) to 5 (extreme)

NOAA Scale	Past 24 hours	Current
Geomagnetic Storms	none	none
Solar Radiation Storms	none	none
Radio Blackouts	none	none

Satellite Environment

energiane ei ibisi likeense versetinte taasin tee sie eriste adelle tek ike ik

na haine di Malaka kala kasala na dika di kasa kasa dah kana kasala kasa kasa



Space Environmental Models of Proton Spectrum Functional Forms to Fit Data

- Exponential in Rigidity or Energy: $\Phi(>R)=J_0 \exp(-R/R_0)$ or $\Phi(>E)=J_0 \exp(-E/E_0)$
- Sum of Two Exponentials : $\Phi(>E)=J_1 \exp(-E/E_1) + J_2 \exp(-E/E_2)$
- Weibull Function in Energy : $\Phi(>E)=J_0 \exp(-\kappa E^{\alpha})$



E, MeV

Band Function with 4 Parameters (J_0 , γ_1 , γ_2 , R_0): Double Power Law in Rigidity

 $\Phi(>R) = J_0 R^{-\gamma_1} e^{-R/R_0} \qquad \text{for} R \le (\gamma_2 - \gamma_1) R_0$ $\Phi(>R) = J_0 R^{-\gamma_2} \left\{ \left[(\gamma_2 - \gamma_1) R_0 \right]^{(\gamma_2 - \gamma_1)} e^{(\gamma_1 - \gamma_2)} \right\} \qquad \text{for} R \ge (\gamma_2 - \gamma_1) R_0$



Interplanetary Galactic Cosmic Ray Energy Spectra Advanced Composition Explorer/Cosmic Ray Isotope Spectrometer



Badhwar-O'Neill Model fit of ACE CRIS oxygen energy spectra measurements near solar minimum and near solar maximum Solar modulation parameter: ACE CRIS oxygen measurements (line); IMP-8 (Z>8) channel 7 measurements (\bigcirc)



Shield Geometry Model and Shielding Analysis by CAD







Structural Distribution Model for Layers of Spacecraft Using ProE[™]/Fishbowl





Ray Tracing inside Spacecraft

Color-coded Representation of Directional Shielding



Human Geometry Models/Active Marrow Distributions





Inter-Comparisons of Transport Codes





Heinbockel JH et al., NASA TP 2009-215560, 2009





Evaluation of Detector Response - TEPC Response for Trapped Protons on STS-89 -



without TEPC response

with TEPC response



Phantom Torso Experiment (PTE) of ISS/STS **TLD Dose Contours of Brain Slice**

2300



100 300

600

Badhwar GD et al., 2002





Organ Dose Equivalent using CK-39/TLD, mSV										
Tissue	Measured	HZETRN/QMSFRG	Difference (%)							
Skin	4.5±0.05	4.7	4.4							
Thyroid	4.0±0.21	4.0	0							
Bone surface	5.2±0.22	4.0	-23.1							
Esophagus	3.4±0.49	3.7	8.8							
Lung	4.4±0.76	3.8	-13.6							
Stomach	4.3±0.94	3.6	-16.3							
Liver	4.0±0.51	3.7	-7.5							
Bone marrow	3.4±0.40	3.9	14.7							
Colon	3.6±0.42	3.9	8.3							
Bladder	3.6±0.24	3.5	-2.8							
Gonad	4.7±0.71	3.9	-17.0							
Chest	4.5±0.11	4.5	0							
Remainder	4.0±0.57	4.0	0							
Effective dose	4.1±0.22	3.9	-4.9							

Yasuda et al., 2002

0	Active Dosimetry Data, mGy/d								
0	Organ	Trapped		GCR		Total		Difference	
0		Expt	Model	Expt	Model	Expt	Model	(%)	
0 0 0	Brain Thyroid Heart Stomach Colon	0.051 0.062 0.054 0.050 0.055	0.066 0.072 0.061 0.057 0.056	0.076 0.074 0.075 0.076 0.073	0.077 0.077 0.076 0.077 0.076	0.127 0.136 0.129 0.126 0.128	0.143 0.148 0.137 0.133 0.131	13.3 9.4 6.7 5.5 2 5	

Cucinotta FA et al., 2008



Predictions for Mars Mission



Radiation type



Annual Effective Dose for Male





Model-based Prediction of SPE Occurrence






Model-based Prediction of SPE Fluence

Hazard Function as an Offset $\boldsymbol{\beta}$ Distribution Density Function

$$\lambda(t) = \frac{\lambda_0}{4000} + \frac{K}{4000} \frac{\Gamma(p+q)}{\Gamma(p)\Gamma(q)} \left(\frac{t}{4000}\right)^{p-1} \left(1 - \frac{t}{4000}\right)^{q-1} \quad (0 \le t \le 4000)$$





Effective dose on Mars Surface with MOLA Topography



Altitude km	T, °C	p, kPa	Atmospheric shielding thickness, g/cm ²		
			Low density model	High density model	
8.0	-41.16	0.34	0.14	0.19	
4.0	-34.99	0.49	6.73	9.25	
2.0	-33.00	0.58	10.97	15.08	
0.0	-31.00	0.7	16.00	22.00	
-2.0	-29.00	0.84	19.04	26.17	
-4.0	-27.01	1.00	22.64	31.13	
-8.0	-23.02	1.44	32.00	44.00	



Conclusions

- Highly accurate space environment models are available:
 - ➤ Near Earth GCR accuracy:
 - ✓ abundant elements ~5%
 - ✓ all major components <10%
 - ✓ solar modulation parameters 98.9% correlation with measurements
 ➤ Managing SPE risk:
 - ✓ Probabilistic SPE occurrence model as a tool
 - ✓ GLE fluences and spectra using satellites and NM data for shielding design application
- Validation of transport codes in ground based experiments:
 - QMSFRG model: absorption X-section within +5%, elemental fragment Xsection within <u>+</u>25% to H.I. experiments
 - Good agreement from inter-comparisons of transport codes
 - \checkmark Good agreement for p, n, He energy spectra
 - \checkmark MC codes tend to over-estimate triton flux
 - ✓ QMSFRG X-sections in HZETRN/GERMCode superior to GEANT4, FLUKA and PHITS models



Conclusions

- Comparison of HZETRN to flight measurements:
 - ✓ Secondary particle energy and LET spectra < \pm 30%
 - ✓ Dose and Dose Equivalent < \pm 20% by TEPC, TLD/CR-39
 - ✓ Excellent agreement with Phantom Torso on ISS/Shuttle
- Areas not well tested are mesons and EM cascades
- NASA Space Radiation Risk Assessment Tools:
 - Environmental models, shielding and body geometry models, atomic and nuclear interaction and fragmentation models incorporated
 - Reliable and realistic radiation simulation in the early design process for exploration missions
 - Probabilistic Risk Assessment for Cancer and Acute radiation risks for varying space scenarios
 - ✓ ISS, Deep space, Moon, and Mars

Radiation Protection Calculations For Patients and Staff

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The University of Texas Graduate School of Biomedical Sciences

at Houston

THE UNIVERSITY OF TEXAS **MDAnderson Cancer** Center

Making Cancer History[®]





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I <u>do not</u> have any conflicts of interest

Objectives of This Lecture

Guiding principles

Calculations for protection of patients
 Pediatric case study

Calculations for protection of staff
 Shielding calculations

Research status and future directions

Guiding Principles of Radiation Protection

Prevent occurrence of serious radiationinduced conditions in exposed persons. These include acute and chronic deterministic effects.

Reduce stochastic effects in exposed persons to a degree that is acceptable in relation to the benefits to the individual and society from the activities that generate such exposure.

After NCRP Report 116, 1993

Exposure of Patients to Radiation



Monte Carlo Method: The Gold Standard for Dose Calculations





Stanisław Ulam in the 1950s [1].

John von Neuman in the 1940s [2].

[1] Immediate source: <u>http://www.zwoje-scrolls.com/zwoje16/text03.htm</u> Ultimate source: Likely from Ulam's autobiography, *Adventures of a mathematician* [2] http://www.lanl.gov/history/atomicbomb/images/NeumannL.GIF 6 Personalized Protection Calculations: Which *quantities* are needed?

Is "dose" enough?

Absorbed dose? Equivalent dose? Effective dose? Integral dose? Ambient dose equivalent?

Is "risk" enough?

Incidence? Mortality? Absolute? Relative? Timepoint?

Radiation Absorbed Dose



Risk of SMN Incidence



Risk of SMN Mortality

From Newhauser and Durante (in review)

Basic Risk Quantities

Relative Risk

$$RR = \frac{R_{\rm e}}{R_{\rm u}}$$

Excess Relative Risk

ERR = RR - 1

Ratio of Relative Risk



Calculation of Radiogenic Second Cancers: Organ Specific Risk



Risk model Linear nonthreshold Endpoint-specific BEIR VII (2006)

Equivalent dose $H_{\rm T} = W_{\rm R} \cdot D_{\rm T}$

Radiation weighting factor Related to RBE for carcinogenesis

Absorbed dose Tx: Pencil beam algorithm Stray: MC algorithm Current Status of Radiation Protection Protection Calculations for Patients
Predicted SMN risk lower after proton therapy after than photon therapy
Uncertainties are large but tractable

Open questions
 How much detail to model
 Most appropriate dose/risk quantities
 Interpatient variation in radiosensitivity

Protecting Staff: Neutron Shielding Calculations Complexity Many sources and barriers Radiation transport physics **Regulatory requirements** Uncertainty Facility usage patterns Equipment performance Basic data

Protection of Staff: Neutron Shielding Calculations **Neutron Source Neutron Shield Dose Calc Point**



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Future Directions of Research

Goals: Expand evidence base for making clinical decisions and health care policy decisions.

Patients: Personalized calculations of dose and risk to <u>reduce incidence of late effects</u>.

Staff: Improved shielding calculation tools and novel shielding designs will <u>reduce costs</u> and improve utility of new facilities.

Future Directions: Amdahl's Law + Moores Law





In parallel computing to predict the theoretical maximum speedup using multiple processors

Rapidly falling cost of computing enables hospitals and clinics to use supercomputing. 8192 CPUs being assembled for MDACC.

Radioprotection calculations will play an increasingly important role in realizing the full potential of advanced radiotherapies! 14 Assessment of the Risk for Developing a Second Malignancy from Scattered and Secondary Radiation in Radiation Therapy



H. Paganetti PhD

Associate Professor of Radiation Oncology, Harvard Medical School Director of Physics Research, Massachusetts General Hospital, Department of Radiation Oncology

INTRODUCTION



INTRODUCTION

- Most modeling studies have focused on <u>out-of-field</u> cancer risks (e.g. due to neutrons in proton therapy) with doses <0.1 Gy.
- <u>In-field</u> organs (OAR) receive large doses (even > 10 Gy). Small portions of an OAR might receive the full target dose.
- Clinical data suggest that second primary malignancies are <u>mainly observed</u> in tissues having absorbed doses <u>above 2 Gy</u> and their incidence increases with dose.

METHODS

Differences between the analysis of in-field and outof-field doses:

- <u>In-field</u> organs are imaged and considered in <u>treatment planning</u>. Organs receive large heterogeneous doses.
- <u>Out-of-field</u> doses are typically small and homogeneous. We need <u>Monte Carlo</u> for dose calculation. Organs are not imaged for treatment planning.

METHODS (out-of-field dosimetry) Scattered and Secondary Radiation

Monte Carlo treatment head model: Paganetti et al. Med. Phys. 2004 Monte Carlo treatment head model: Bednarz et al. Phys. Med. Biol. 2009



METHODS (out-of-field dosimetry)



Table 2. Elemental compositions (% by mass) and tissue densities $(g \text{ cm}^{-3})$ of individuals at the ICRP reference ages.

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Group 1 (cranium/mandible)

5.272

4.280

19.154

49.850

Newborn

5.551

19.150

4.259

51.209

1

Phantom age (years)

5.173

20.180

4.230

46.759

10

5.340

21.953

44.757

4.019

15 (male)

5.434

3.831

23.442

43.526

Ca	12.892	13.852	15.619	15.801	15.773		
Na	0.031	0.025	0.104	0.103	0.177		
Mg	0.260	0.268	0.187	0.181	0.176		
Р	6.303	6.969	7.435	7.544	7.346		
S	0.287	0.287	0.283	0.276	0.271		
Cl	0.018	0.012	0.007	0.006	0.006		
К	0.027	0.019	0.011	0.009	0.006		
Fe	0.013	0.012	0.011	0.012	0.011		
Density	1.458	1.490	1.520	1.519	1.525		
Group 2 (vertebrae—cervical, thoracic, lumbar)							
Н	8.760	8.390	7.997	7.901	7.993		
С	16.209	17.885	21.884	27.069	29.956		
N	2.844	3.020	3.230	3.319	3.247		
0	64.925	61.789	55.514	49.237	46.486		
Ca	3.048	4.345	6.469	7.575	7.637		
Na	0.337	0.289	0.246	0.180	0.193		
Mg	0.088	0.114	0.116	0.141	0.146		
Р	2.908	3.383	3.918	4.110	3.933		
S	0.663	0.598	0.485	0.369	0.325		
Cl	0.194	0.163	0.112	0.062	0.045		
к	0.006	0.006	0.004	0.004	0.003		
Fe	0.016	0.019	0.024	0.033	0.036		
Density	1.157	1.184	1.219	1.232	1.230		

METHODS (neutron dosimetry) Neutron radiation weighting factor $H = D \times w_R$ [particle, energy]



Neutron radiation quality factor $H = D \times Q[LET_{\infty}]$

METHODS (neutron dosimetry)



METHODS

Differences between the analysis of in-field and outof-field doses:

- Low-dose risk models based on atomic bomb survivor data might not be applicable for doses > 2 Gy.
- <u>High-dose risk models</u> are non-linear and need to consider inhomogeneous dose distributions.

METHODS (modeling)

Converting organ (equivalent) doses to risk



METHODS (modeling) Low-dose BEIR VII risk models

- $\rho(D)$: linear or quadratic function of dose for solid tumors
- β_s : base excess relative risk per Sievert
- γ , η : describe the dependency on age and age at exposure
- a: attained age
- e: age at exposure

In addition: Dose and Dose Rate Effective Factor – DDREF

METHODS (modeling) High-dose risk model

Schneider, Med. Phys. 36 1138-43 (2009)

$$EAR(D_{average}) \longrightarrow EAR\left(OED = \sum_{i} \left[D_{voxel}, R, mutation, kill\right]\right)$$

Cell kill: $\alpha' = \alpha + \beta \times d_F$ linear-quadratic model d_F fractionated dose Repopulation: R [0;1]

RESULTS (in-field) In-field risk considering optic glioma patient



In-field versus out-of-field risks



SUMMARY

Out-of-field

 Younger patients show a higher risk due to model predictions and geometrical factors

• Most out-of-field risks are lower than the baseline risks

•Risks from passive scattered proton therapy and IMRT are comparable (on average). Proton beam scanning shows a significant advantage

In-field

Younger patients show a higher risk due to model predictions
Most of the <u>in-field risks for IMRT are higher than the baseline risks</u>
Most of the in-field risks for passive scattered <u>proton therapy are lower</u> than the baseline risks. Proton beam scanning might show a slight advantage

•In-field risks depend on the treatment plan



Symposium held in Washington DC October 25-28, 2009

Chairmen: Walter Henning, ANL Charles Shank, LBNL

> Jose Alonso, LBNL 8 March 2011



Questions:

- Is US falling behind in advanced technology areas where accelerators play important role?
- If so, why?
- What can be done about it?



Working Groups:

Biology and Medicine
Discovery Sciences
Energy Sciences
National Security
Industrial Applications


Full Report:

http://www.AcceleratorsAmerica.org

Download as .pdf

Google: "Accelerators for America"





Medicine & Biology Working Group



Medicine & Biology

Co-Chairs:

Herman Suit (Mass General Hospital) Jose Alonso (LBNL)

Sub-Groups: External Beam Applications (Therapy) Radioisotopes



Radioisotope Group

Tom Ruth (TRIUMF) Don Geesaman (Argonne) Leonard Mausner (Brookhaven) Wolfgang Runde (Los Alamos) Martin Brechbiel (NCI/NIH) Jerry Nolen (Argonne) Yves Jongen (IBA)



External Beam Group

MDs

Herman Suit (Mass General Hospital) George Laramore (U Washington) Jim Cox (MD Anderson) Jorgen Debus (Heidelberg) Medical Physics/Biology Ellie Blakely (LBNL) **Tony Lomax (Paul Sherrer Institute)** Anders Brahme (Karolinska) ACCELERATORS

External Beam Group

Accelerator Andy Sessler (LBNL) Steve Peggs (BNL) Jay Flanz (MGH) John Cameron (ProCure) Laddie Derenchuk (Indiana) Dave Whittum (Varian) Paul Bolton (JAEA-Kyoto)



Our Conclusions:

- Is US falling behind in advanced technology areas where accelerators play important role? YES!!!
- If so, why?
 ... (our views)
- What can be done about it?
 ... (also our views)



External Beam Therapy: Emphasis on protons and light ions

Advantages of Particles: **Dose localization** Sparing of normal tissue High LET component for ions













Graphic: ProCure

GSI

Proton Therapy in US

Number of hospital-based facilities is growing steadily

- 8 in operation
- > 4 under construction
- ? In planning stages
- ALL privately funded!

ALL (but earliest... Loma Linda, IUCF) use foreign technology Sub-optimal (passive) beam-delivery technology is generally used (Active) beam scanning not yet in wide clinical use Gantries (for one) are BIG and EXPENSIVE

ACCELERATORS

SYMPOSIUM

FORAMERIC



Light Ion Therapy Facilities

In US: ZERO

In Asia:

3 in operation: Chiba, Harima, Gunma (Japan)

~3 under construction: Shanghai (China), 2+ Japan In Europe:

- 2 in operation: Heidelberg (Germany), Pavia (Italy)
- 5 under construction: Wiener Neustadt (Austria)
 - Lyon, Caen (France), Marburg (Germany), Kiel (Germany)

GSI/Siemens: Heidelberg

ACCELERATORS

SYMPOSIUM



Observations:

US Industry is not in the game yet Major particle-therapy system providers are European or Japanese IBA, Siemens, Hitachi, ACCEL(now Varian)

No path for Federal assistance to potential customers, Industry or R&D centers (e.g. DOE Labs) Requires private financing for acquisition/operation of treatment facilities

Entry price is steep hurdle for new facilities Business model requires reimbursable treatments, No time for R&D

Entry price is prohibitive for light-ion facilities



Digging Deeper:

• DOE labs have expertise, and keen interest

- But... roadblocks, and no funding
- "can't compete with private sector"
- CRADA difficult to implement
 - * Limited funding, all private
 - * Restrictive intellectual property and risk-sharing conditions



Digging Deeper:

- No Agency one can turn to for support for hadron-therapy accelerator or systems R&D
 - DOE does not fund health-care-related initiatives
 - NCI funds clinical research, not technology development or facility construction



What can be done?



Encourage new Technologies



Still River's single-room solution



LLNL/Tomotherapy's DWA linac



Laser-generated proton concepts (Japan, Germany)



Support Critical R&D:

Scanning technology Low-mass, faster dosimetry and beam-diagnostic instrumentation Real-time organ-motion tracking Treatment verification: real-time imaging Radiobiological characterization, mainly for ions Reduced cost of facilities, particularly gantries Streamlining of operations/maintenance costs



STEPS TO REMEDY THE PROBLEM

Identify a Program Office with mission to support technology development in hadron therapy

Establish directed SBIR and other grant support avenues to promote R&D in medical accelerator and related instrumentation

Develop an EFFECTIVE Public/Private partnership model for funding R&D and new facilities

Develop a roadmap for a light-ion-capable facility in the US





NASA's needs for Research in Charged Particles - Future vision

March 8, 2011





NASA's Needs for Charged Particle Research







Among the health risks for the human exploration of the Solar system, space radiation is generally recognized as a main obstacle to interplanetary travel.

Galactic cosmic rays (GCR) remain 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 NASA leads to important areas of collaboration between NASA and DoE, and potentially other government agencies and nations.

Space Radiation Environments



- Galactic cosmic rays (GCR) penetrating protons and heavy nuclei - a biological science challenge
 - shielding is not effective
 - large biological uncertainties limits ability to
 evaluate risks and effectiveness of mitigations
- Solar Particle Events (SPE) largely medium energy protons – a shielding, operational, and risk assessment challenge
 - shielding is effective; optimization needed to reduce weight
 - improved understanding of radiobiology needed to perform optimization
 - library of over 400 events allows for Probabilistic Risk Assessment (PRA) for mission planning
 - accurate event alert and responses is essential for crew safety





Categories of Space Radiation Risks

Four categories of risk of concern to NASA:

- Carcinogenesis (morbidity and mortality risk)
- Chronic & Degenerative Tissue Risks
 - ✓ cataracts, heart-disease, etc.
- Acute Radiation Risks sickness or death
- Acute and Late Central Nervous System (CNS) risks
 - ✓ immediate or late functional changes

Differences in biological damage of heavy nuclei in space compared to x-rays, limits Earth-based radiation data on health effects for space applications

<u>New knowledge on risks must be obtained</u>

Risks estimates are subject to change with new knowledge, and changes in regulatory recommendations from NAS, UN, NCRP, etc.



Lens changes in cataracts



First experiments for leukemia induction with GCR

Major Sources of Uncertainty



Radiation quality effects on biological damage

- Qualitative and quantitative differences of Space Radiation compared to x-rays
- Dependence of risk on dose-rates in space

✤Biology of DNA repair, cell regulation

- Predicting solar events
 - Onset, temporal, and size predictions
- Extrapolation from experimental data to humans
- Individual radiation-sensitivity
 - Genetic, dietary and "healthy worker" effects





Nature Rev. Cancer (2008)

Minor Sources of Uncertainty

NASA

Data on space environments

Knowledge of GCR and SPE environments for mission design

Physics of shielding assessments

 Transmission properties of radiation through materials and tissue

Microgravity effects

 Possible alteration in radiation effects due to microgravity or space stressors

Errors in human data

 Statistical, dosimetry or recording inaccuracies



Lunar Surface EVA Cancer Risk versus SPE Size (100 MeV protons fluence)

Space Radiation Research- 20 Year Plan



Agency Mission	2008–2014	2015–2020	2021–2030	Contributions to National Priorities
Lunar Sortie Missions by 2020	Perform research on dose-rate effects of protons, develop shielding design tools; apply probabilistic risk assessment to lunar missions	Validate radiation environment and transport models using lunar data; Validate models of proton dose-rate effects	Develop and deploy operational strategies for managing SPE risks; Apply biomarker methods to samples from lunar crews	Contribute to increased understanding of solar physics; Apply biomarker technologies to problems on Earth
Lunar outpost Missions up to 240 days	Use NSRL to simulate space radiation to understand their biological effects; Compete radiation transport codes and design tools	Continue NSRL research on risks; perform research on biological countermeasures; optimize shielding designs for Mars missions	Finish NSRL research on countermeasures; Develop diagnostics of radio-sensitivity and gene therapy for prevention and/or treatment of radiation damage	Design exploration missions; Apply new knowledge of radiation effects and NASA computational biology models to human diseases on Earth
Mars Exploration Missions by 2030	Reduce uncertainties in risk projections to less than 2-fold; Determine if CNS and degenerative risks from GCR will occur	Reduce uncertainties in risk projections to less than 50%; lunar- instruments to measure Mars surface environment at solar minimum	Apply knowledge on individual risk assessments and biomarkers; develop accurate long-term solar weather predictions	Apply countermeasure knowledge to diagnosis, prevention and treatment of diseases on Earth



- Current NASA focus is research using simulated space radiation at the NASA Space Radiation Lab (NSRL) at Brookhaven, Upton NY
 - 40 Single Investigator Awards from US Universities and Govt Labs
 - 12 Joint Awards with the Department of Energy (DOE) Low Dose Program

Areas of potential collaboration

- Differences in biological damage of heavy nuclei in space compared to x-rays, limits Earth-based radiation data on health effects for space applications. However new theraputic uses of high Z ions including Carbon, creates new possibilities with exposures of normal tissues in the range of interest to NASA.
- Research regarding secondary tumor formation could yield valuable information.
- Advances in biomarkers, biodosimetery, and biological counter-measure effectiveness are also of interest.

ENLIGHT

European Network for Light Ion Hadron Therapy





ENLIGHT

- Why did we need a network?
- What was necessary for a network?
- Which activities were needed to catalyse ENLIGHT?
- Which were the key starting points?



- ENLIGHT was launched at CERN in Feb 2002
- In 2002, ENLIGHT was composed of
 - ESTRO, the European Society for Therapeutic Radiology and Oncology
 - ETOILE, Lyon, France
 - Karolinska Institute, Sweden
 - GSI/GHIP (German Heavy-Ion Project), Germany
 - Med-Austron, Austria
 - TERA, Italy
 - CERN, Switzerland
- ENLIGHT was funded as a network by the European Commission between 2002 - 2005

ENLIGHT was established to.....

- Create common multidisciplinary platform
- Share knowledge
- Share best practices
- Harmonise data
- Provide training, education
- Identify challenges
- Innovate
- Lobbying for funding



Challenges for the network

Multidisciplinary and cutting-edge technologies:

- Clinical Studies
- Radiobiology
- Treatment planning for Particle Therapy
- Adaptive ion therapy and treating of moving organs
- Novel imaging PET systems
- Feasibility study for innovative gantry designs
- Improved gantry design





- A heterogeneous group many different disciplines
- How to balance between basic research and the clinical needs?
- Many partners. How to give space to each and make progress with the main objectives?
- How to strike a balance between agenda of the single centres and the ENLIGHT++ goals?
- Can we show ion therapy is more effective?



 A major achievement of ENLIGHT is bringing together of various communities so that clinicians, physicists, biologists and engineers interested in particle therapy are working together for research, funding and lobbying





- In 2006 ENLIGHT became
 - + More than a network....research
 - + More inclusivemore institutions, more countries
- The network itself continued even without funding
 - Develop strategies for securing the funding for specific projects under the umbrella of ENLIGHT, along two major axes
 - Research in areas needed for improving hadron therapy
 - Networking, to establish and implement common standards, protocols for treating patients, training and education
- Now we have >300 participants from 20 European countries

In 2011, under the umbrella of ENLIGHT, there are now 4 EC funded projects:

- Three ongoing projects: PARTNER, ULICE and ENVISION with a total funding of 24 M Euros
 - midterm PARTNER at Karolinska in Sept 2010
- The newest training project , ENTERVISION, started in February 2011 in Lyon



PARTNER

Particle Training Network for European Radiotherapy

- 4-year Marie Curie Training project
 - Funded by the EC with 5.6 M Euros
 - Started in September 2008
- Aims at the creation of the next generation of experts



- Brings together key academic institutes and research centres and the two leading European companies in particle therapy (IBA and Siemens)
- Research and training opportunities for 25 young biologists, engineers, physicians and physicists

PARTNER is funded by the European Commission under Grant Agreement Number 215840

Multidisciplinary PARTNERships to fight cancer

- Clinical Studies
- Epidemiology & Patient Selection
- Radiobiology
- Treatment Planning
- Simulation and Dosimetry
- Image Guided Hadron Therapy
- PET prototype, In-situ Monitoring
- Novel Gantry
- ICT and prototype
- GRID Novel accelerator study





CERN | CNAO | ETOILE | GSI | IBA | IFIC | KI | MEDAUSTRON | SIEMENS | TERA | UKL-HD | UNIS
ULICE Union of Light Ion Centres in Europe

Addresses two complementary issues:

- Development of appropriate instruments for high-performance hadron therapy
- Need for close collaboration among the existing and planned centres





- The ULICE project started in September 2009
- Funded for 4 years by the EC with 8.4 M Euros
- 20 European institutions

ARC|AUH,AS|CERN|CNAO|ESTRO|ETOILE|GSI| IBA|IFJPAN|INFN|KI|MEDA|MUW|RUNMC|SAG|TUD|UCL|UKL-HD|UNIMAR|UOXF



The 3 pillars of ULICE

Joint Research Activities

 aims at improving the performance of hadron therapy facilities by research and development

Networking Activities

 Communication among the 20 partners and with the external world

Transnational Access

 provides access for external researchers to the recently opened ion therapy facilities



The ULICE project is co-funded by the European Commission under FP7 Grant Agreement Number 228436

Accurate positioning is a crucial challenge for targeting moving organs during treatment



ENVISION aims at developing solutions for:

- real-time monitoring
- quantitative imaging
- precise determination of delivered dose
- fast feedback for optimal treatment planning
- real-time response to moving organs
- Simulation studies

adapted from Parodi et al, IJROBP 68 (2007) 920-34

The ENVISION project is co-funded by the European Commission under FP7 Grant Agreement N. 241851



ENVISION

A 4-year EU funded project started in February 2010, ENVISION is a collaboration of 16 leading European research centres and industrial partners for 6M Euros.



Five work packages

- Time-of-Flight in-beam PET
- In-beam single particle tomography
- In-vivo dosimetry and moving target volumes
- The combination of in-vivo dosimetry, treatment planning, and clinical relevance
- Monte Carlo simulation of in-vivo dosimetry

CERN | CNRS | CISC | GSI | IBA | INFN | MAASTRO | MUW | OXFORD | POLIMI | TERA | TUD | UCBL | UCLM | UGENT | UKL-HD



Research Training in Imaging for Cancer Radiation Therapy

- ENTERVISION fills the need for reinforcing research and training of young researchers in all aspects of imaging
- Interdisciplinary and multinational initiative
- Many training courses open to external young researchers
- ENTERVISION brings together ten academic institutes and and the two leading European companies in particle therapy, IBA and Siemens.
- The network will train 16 Researchers during a 4-year period.

The ENTERVISION project is co-funded by the European Commission under FP7 Grant Agreement N. 264552



- ENLIGHT provides a powerful multidisciplinary European collaboration amongst interested partners
- ENLIGHT acts as a platform for defining research needs
- Developing projects and getting them funded
- Lobbying politically (e.g. France, Poland, UK)
- ENLIGHT is a useful resource for communities interested in hadron therapy and establishing facilities

Clear desire for continuing to collaborate on new and existing research topics and helping new initiatives....