Space radiation research in Europe: flight experiments and ground-based studies

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Abstract Exposure to space radiation has long been acknowledged as a potential showstopper for long-duration manned interplanetary missions. In an effort to gain more information on space radiation risk and to develop countermeasures, NASA initiated several years ago a Space Radiation Health Program, which is currently supporting biological experiments performed at the Brookhaven National Laboratory. Accelerator-based radiobiology research in the field of space radiation research is also under way in Russia and Japan. The European Space Agency (ESA) supports research in the field in three main directions: spaceflight experiments on the International Space Station; modeling and simulations of the space radiation environment and transport; and, recently, ground-based radiobiology experiments exploiting the high-energy SIS18 synchrotron at GSI in Germany (IBER program). Several experiments are currently under way within IBER, and so far, beams of C and Fe-ions at energies between 11 and 1,000 MeV/n have been used in cell and tissue targets.

Introduction

Space exploration is a grand adventure for humankind with the potential for exciting discoveries that capture our imagination and benefits society. However, exploration and colonization of the solar system must be achievable with minimal health detriment. Exposure to galactic cosmic rays (GCR) and solar proton events presents significant but poorly understood risks for carcinogenesis and degenerative diseases (Durante and Cucinotta 2008).

NASA has acknowledged that radiation risk represents a potential showstopper for manned exploration and colonization of the Solar system in its strategic program (NASA 1998). Most of our knowledge on the biological effects of cosmic radiation is based on experiments performed at accelerators (Durante and Kronenberg 2005), and indeed, the NASA Space Radiation Laboratory (NSRL) accelerator facility in Brookhaven was totally funded by NASA to address some of the open research issues, especially to reduce uncertainties on the cancer risk estimates (Cucinotta and Durante 2006). The deterministic computer code HZETRN based on the Boltzmann transport equation was developed and constantly upgraded and coupled to a biological model for calculation of equivalent doses and risk (Wilson et al. 2002).

Europe has an active program in space experiments on the effects on microgravity and space radiation (Bücker et al. 1984), especially using excellent active dosimeters such as ALTEINO (Casolino et al. 2007) and ALTEA (Zaconte et al. 2008), and space radiation transport calculations, primarily electing to use Monte Carlo codes such as Geant4 (Ersmark et al. 2007). Moreover, a ground-based radiobiology program exploiting the high-energy SIS18 synchrotron at GSI in Germany has been successfully launched (Durante et al. 2007). This program for

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Investigations into Biological Effects of space Radiation (IBER) is complementary to the NASA program running in Brookhaven and to other space radiobiology activities ongoing at accelerators in Russia (Antipov et al. 1994) and Japan (Ando 2001).

Europe has a specific excellence in radiobiology at accelerators, driven by the ion therapy programs running in Germany and planned in other countries (Durante and Loeffler 2010). On July 6–10, 2009, the 1st ESA-IBER Investigators' Workshop was held in Cologne (Germany), in a large joint symposium together with the 20th NASA Annual Space Radiation Health Investigators' Workshop (organized by Francis Cucinotta, NASA), and the 12th Workshop on Ion Beam in Biology and Medicine (IBIBAM, organized by Gerhard Kraft, GSI). The symposium also included the 5th International Workshop on Space Radiation Research. Papers from the 4th Workshop in 2007 were previously published in this journal (Cucinotta et al. 2007). This large Heavy Ion in Therapy and Space Symposium was organized by the Radiation Biology department of the German Space Agency (DLR) with Günther Reitz as main organizer and provided a unique opportunity to have joint discussions of physicists, biologists, physicians, engineers, chemists, etc. interested in heavy-ion effects either for cancer therapy or for radioprotection in space travel. A number of papers from this symposium are published in this issue of Radiation and

Environmental Biophysics. Here, we will concentrate on the current European programs in space radiation dosimetry and biology.

Spaceflight dosimetry

Several European instruments have been used in space for dosimetry (Reitz et al. 2005; Pugliese et al. 2010), for accurate measurements of the radiation spectrum behind shielding, and for science experiments that include, for instance, investigation of the correlation between particle fluxes and light flashes (Casolino et al. 2003).

In recent years, the MATROSHKA experiment, supported by ESA and coordinated by DLR in cooperation with 20 research institutes, has provided a valuable data-set of organ doses in space which can be used to benchmark current models (Reitz et al. 2009). MATROSHKA (Fig. 1) is designed as an anthropomorphic upper torso phantom, with 33 slices, each 25 mm in thickness. A base structure houses the electronic boxes for data acquisition and data transmission of the internal temperature and pressure as well as the active radiation detector sensors. A carbon fiber container with a mass density of $\sim 0.5 \text{ g/cm}^2$ simulates the shielding distribution of an astronauts' extravehicular activity suit (EVA suit). The phantom torso is equipped with passive thermoluminescence

Fig. 1 *Left:* The MATROSHKA facility without container; the phantom mounted on the Base Structure that houses the electronics and dressed with the Poncho equipped with a series of passive detectors

(TLDs, CR39). *Right:* the upper slides show the DOSTEL sensor head on the top of the phantom; the lower slide shows the polyethylene tubes, the passive organ dose package and an SSD in a phantom slice

Table 1 A list of high-energy ion accelerators in Europe that could be exploited for ground-based space radiation research

Accelerator	Particle	Energy (MeV/u)	Biological Exposure Setup ^a		Dosimetry ^b	Active scanning	Microbeam	Support ^c	EU Support ^d
			Cells	Animals (#)					
JYFL, Jyväskylä (Finland)	N–Xe	9.3			+				
CYCLONE, Louvain (Belgium)	C–Ar	3.75–10			+				
HIT, Heidelberg (Germany)	H	200–400	+	+	+	+			
	C								
PSI, Villigen	H	72–254			+	+			
INFN Italy: LNL, Legnaro	H	2.5–30	(+)		+		(+)		
	He	3.5			+				
	Au	1.5							
LNS, Catania	H	62–80	(+)		+				
	C	23–80							
	Ar	40							
	Au	23							
TSL, Uppsala (Sweden)	H	180	+		+				
	He	73.3							
	O	45							
	Xe	9.61							
GANIL, Caen (France)	C, O, Ne, Ar	95	+	(+)	+	+		+	+
	Ni	70							
	U	24							
GSI, Darmstadt: (Germany) UNILAC	H–U	11.4	+		+		+	+	+
SIS 18	H–U	100–2,000	+	(+)	+	+		+	+
FAIR (in progress)	H–U	<45,000	+	+	+	+		+	+

The presence of infrastructures for radiobiology is also indicated. A plus in bracket (+) indicates the presence but with limitations

^a Specialized exposure facility for biological samples like DNA probes and cultured cells, plus tissue culture laboratories available for sample preparation and processing

^b Exact dosimetry in the full range of particle fluencies of 10^5 – 10^8 /s and homogeneity better than 5%

^c Technical support (manpower) in sample exposure and laboratory work

^d Laboratory is acknowledged by the EU as an international facility, and travel and housing of guests are supported

detectors (TLD) placed in 354 polyethylene tubes, which are accommodated in the 33 slices, enabling determination of the absorbed dose and depth dose distribution at 800 measurement points in a 2.5 cm $x/y/z$ grid. Combination of TLD detectors and nuclear track etch detectors (CR39) is put together in polyethylene boxes (60 × 40 × 25 mm) at selected organ locations. For the determination of the skin dose, detectors are sewed into polyethylene stripes directly on the phantom surface. Seven active radiation detector monitors are distributed in the simulated organ regions—5 × silicon scintillators (SSDs) for the determination of the neutron component, and one silicon telescope (DOSTEL) is located on top of the head of the phantom providing particle fluences and linear energy transfer (LET) spectra. Altogether,

MATROSHKA uses more than 6,000 detectors. MATROSHKA was launched in 2004 and exposed outside the ISS—as a “simulated astronaut” performing an EVA for 539 days—followed by three exposure periods inside ISS. Simulations of the MATROSHKA experiment using the PHITS code are published in this issue (Sihver 2010).

The relationships between the skin- and organ-absorbed doses obtained in EVA show a steep gradient between the doses in the uppermost layer of the skin and the deep organs with a ratio close to 20. This decrease which is due to the body self-shielding and a concomitant increase in the radiation quality factor by 1.7 with depth in the body highlight the complexities of an adequate dosimetry of space radiation.

Fig. 2 The high-energy irradiation facility in Cave A at GSI. The robotic arm moves the samples (in flasks) to the beam position for the required exposure time. Beam delivery is by spot-scanning of the flask. This is a general-purpose facility for irradiation of *in vitro* samples with high-energy heavy ions

European accelerator-based space radiation research project

Following the recommendation of the IBER study team (IBER 2006), ESA issued in 2008 an announcement of opportunity (AO-IBER) for ground-based radiobiology research using the GSI accelerator facility.

The choice of the GSI facility was based on a careful evaluation of the different accelerators available in Europe for these studies (Table 1). GSI has an outstanding reputation in the field of heavy-ion radiobiology and can provide the following irradiation facilities to external investigators:

- High-energy (<2 GeV/n) Cave A (Fig. 2)
- High-energy (<2 GeV/n) Cave M
- Low-energy (<15 MeV/n) UNILAC facility
- Low-energy microbeam (spatial resolution about 1 μm)
- X-ray machine (250 kVp, dose-rate <6 Gy/min)

The main topics recommended by the IBER study team for ground-based investigations in Europe are provided in Table 2 (IBER 2006). Fourteen proposals have been selected within the AO-IBER, and the topics are summarized in Table 3. It is noteworthy that most topics are

related to noncancer effects, whereas the NASA program in Brookhaven has a strong emphasis on cancer risk. Noncancer effects should be carefully addressed before the mission to Mars, and they are even less understood than carcinogenesis (NASA 2009). The use of innovative biological test models is highly desirable, and in this issue, innovative models of the mouse aorta (Soucy et al. 2010) in the NASA program and organotypic brain slices from the ESA program (Merz et al. 2010) are described.

In the first IBER experiments performed at GSI in the Summer 2009, investigators used ^{12}C and ^{56}Fe ions at energies between 11 and 1,000 MeV/n. These ions were not selected by chance—experiments with carbon are also important for heavy-ion therapy, whereas iron is the major contributor to dose equivalent in space. Nickel and nitrogen ions have also been used in the spring 2010 run. In future experiments, it will be important to exploit the GSI microbeam (Fig. 3). In space, astronauts are exposed to charged particles from $Z = 1$ (H) up to $Z = 28$ (Ni), but the probability of a hit to a specific single cell in the human body is low. In fact, about 50% of the human cells (nuclear cross-section approximately 100 μm^2) are hit by a particle of the CNO group during 1-year travel to Mars in solar minimum. Particle microbeams can deliver single charged particles of different charge and energy to single cells from different tissues, and microbeam studies are therefore very useful for improving current risk estimates for long-term space travel. In principle, 2D *in vitro* cell cultures can help establishing basic molecular mechanisms, but they are not sufficient to extrapolate risk, given the substantial evidence proving tissue effects to be essential in determining the response to radiation insult. Instead, 3D tissue or animal systems represent a more promising target for space radiobiology using microbeams (Durante 2009).

Conclusions

Space radiation research is becoming a high priority in Europe, as already it is in the USA. The uncertainty on space radiation risk must be reduced to reach an “acceptable” level (Schimmerling 2010) for human colonization of the Solar system, and ground-based research is a key step in this process. The current roadmap for radiation protection studies in Europe (Belli et al. 2010) gives great emphasis on studies on quality factors, dose-rate effects, noncancer effects, and the shape of the dose–response curve at low doses, all topics extremely relevant for space radiation protection as well. In addition to consolidated activities in modeling of the space radiation environment and dosimetry and spaceflight experiments on ISS, the recent ground-based IBER radiobiology program has the potential to attract many European groups with expertise in radiobiology

Table 2 Research topics of interest for the European ground-based program [IBER study group 2006]

Area	Topic	Subtopics	Practical impact in space	European competence	Relationship to NASA SRHP	Spinoff in hadrontherapy
Cancer risk	Molecular mechanisms of carcinogenesis by charged particles	1. DNA repair 2. Genomic instability 3. Epigenetic changes 4. Nontargeted effects	High impact for risk assessment; Low impact for mission criticality	Concentrates on low dose, low LET	Several projects supported by NASA in this field	Basic mechanisms are also relevant for therapy
	Innovative experimental models for cancer risk assessment at low doses and low dose rates	1. Animal and tissue models 2. 3D cultures 3. Specific models for leukemia and breast, thyroid, colon, and lung cancers	High if accompanied by appropriate modeling to translate in accurate risk coefficients	Good	Animal models are widely used in SRHP. Human tissues/3D cultures are insufficient	Prediction of the risk of secondary cancers
	Individual susceptibility and biomarkers of risk	1. Genes or proteins responsible for radiosensitivity 2. New methods in biodosimetry	Potentially high for prevention and intervention	Good	One large research study on ATM heterozygosity	Potential for individualization of the treatment planning
	Accelerated aging induced by energetic charged particles	1. In vitro senescence mechanisms 2. Development of animal models 3. Extrapolation to risk of cardiovascular diseases	High impact for risk assessment; Low impact for mission criticality	Good	Only few research projects specifically address this issue	Important for predicting late normal tissue morbidity
Noncancer risk	CNS damage	1. Behavioral endpoints 2. Molecular studies	High for a go/no-go decision	Good	Both animal and in vitro studies currently ongoing	Interest for the treatment of brain tumors with heavy ions
	Risk of radiation sickness induced by very intense SPE	1. Simulations of SPE 2. Prodromal syndrome for protons at low dose rate	Very high for mission criticality	Excellent from radiotherapy	Only one project is studying this problem	Interest for acute effects in proton therapy
Acute effects	Risk of transgenerational genetic alterations induced by cosmic radiation	1. RBE of heavy ions for the induction of hereditary damage 2. Combined effects of radiation and other stressors on reproduction in space	Especially relevant for future human colonization of space. Impact on pregnancy planning of astronauts	Excellent	No specific ground-based programs, a few spaceflight experiments	Interest for treatment of pediatric tumors

Table 2 continued

Area	Topic	Subtopics	Practical impact in space	European competence	Relationship to NASA SRHP	Spinoff in hadrontherapy
Combined effects	Interaction between space environment and radiation	1. Bioreactors to simulate μg on ground	Potentially high for prevention/intervention if protection or enhancement is proven	Excellent in stress response and flight experiments	No specific programs	The effect of stress and combined chemotherapy treatment on radiation effects is of interest for therapy
		2. Effect of stress on radiation response (adaptation, sensitization?)				
		3. Radiation and stressors on planetary surfaces				
	Mixed radiation fields	1. Simultaneous high/low-LET radiation exposures	Potentially high if adaptive response or synergism is proven	Excellent	Some experiments at NSRL	Hadron therapy is always characterized by mixed radiation fields, although doses and dose rates are much higher than in space
		2. Effect of pre-exposure to low dose rate protons on response to single heavy ions				
		3. Biophysical modeling of mixed radiation fields				
Counter measures	Shielding	1. Nuclear fragmentation	Very high for the spacecraft and habitat modules design	Good	NASA has his own shielding program, mostly operational	Therapeutic beams go through shielding material
		2. Material testing				
		3. Biological effects and shielding				
	Radioprotectors	1. Drugs to prevent acute radiation sickness	High to mitigate SPE risk	Good from radiotherapy	Very limited at the moment	Very important if can be applied in clinical trials
		2. New molecules to decrease late morbidity				
		1. Antioxidants as radioprotectors	High for prevention	Good	A few studies on specific compounds	Not very relevant for therapy, where doses are very high
	Dietary supplements	2. Tests with heavy ions, low dose rates, and different endpoints				

SRHP Space Radiation Health Program, *CNS* central nervous system, *SPE* solar particle event, *ATM* ataxia telangiectasia mutated, *RBE* relative biological effectiveness, μg microgravity, *LET* linear energy transfer, *NSRL* NASA Space Radiation Laboratory

Table 3 Topics of the experiments selected within the ESA-IBER project

Experiment topic	Area (Table 2)	Topic/subtopic # (Table 2)
Effects of heavy ions on neural stem cells of the hippocampus	Noncancer risk	CNS damage/2
Molecular mechanisms of heavy-ion-induced mucositis as studied in organotypic cultures	Noncancer risk	Accelerated aging induced by energetic charged particles/2
Effects of heavy ions on photoreceptors	Noncancer risk	Accelerated aging induced by energetic charged particles/2
Low-energy electrons in solids	Countermeasures	Shielding/2
Germ-cell mutagenesis in mice	Hereditary risk	Risk of transgenerational genetic alterations induced by cosmic radiation/1
Radioprotection by pTyr	Countermeasures	Radioprotectors/2
Backup repair pathways	Cancer risk	Molecular mechanisms of carcinogenesis induced by charged particles/1
Signaling pathways and DNA repair	Cancer risk	Molecular mechanisms of carcinogenesis induced by charged particles/3
Heavy-ions effects in osteoblasts	Noncancer risk	Accelerated aging induced by energetic charged particles/1
Late cardiovascular effects of space radiation	Noncancer risk	Accelerated aging induced by energetic charged particles/3
MATROSHKA	Combined effects	Mixed radiation fields/1
Heavy ions and ion channels	Noncancer risk	Accelerated aging induced by energetic charged particles/1
Heavy ions and gene splicing	Cancer risk	Individual susceptibility and biomarkers of risk/1

Fig. 3 The microbeam at GSI can deliver single heavy ions at low energy with a resolution of about 1 nm. The figure shows the delivery of 5 carbon particles in the nuclei of human cells (*left*) and subsequent detection of the hits by immunofluorescence of repair proteins (*right*)

or biomedicine in the field of heavy-ion research and space radiation protection. Greater involvement of the international community is needed, especially with the goal of developing effective countermeasures before sending a manned mission to Mars, which hopefully will occur in this century.

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