Heavy ion radiobiology: from cancer therapy to space radiation protection

Research in the field of biological effects of heavy ions is needed for both cancer therapy (hadrontherapy) and protection from the exposure to galactic cosmic radiation in long-term manned space missions. Although the exposure conditions (e.g. high- vs. low-dose rate) and relevant endpoints (e.g. cell killing vs. neoplastic transformation) are different in the two fields, it is clear that a substantial overlap exists in several research topics. In addition, researchers involved either in experimental studies on space radiation protection or heavy-ion therapy exploit the same accelerator facilities. It is recommended that novel accelerator facilities under construction for oncological therapy (e.g. Heidelberg and Marburg) as well as those dedicated to advanced nuclear physics research (e.g. FAIR) will reserve beamtime for basic studies of heavy-ion radiobiology and its applications in space radiation research and therapy.

Marco Durante • Humans on Earth are continuously exposed to ionizing radiation. However, there is no experience about the exposure to high-energy heavy charged particles. In fact, most of the annual effective dose to the population comes from α-particles (from radon in air), γ- and β-rays (from natural internal and terrestrial sources), and X-rays (from nuclear diagnostic medicine). Protection from ionizing radiation on Earth is far advanced and based on solid scientific evidence of epidemiological investigations, such as the cohort of survivors of atomic bombs dropped in 1945 in Hiroshima and Nagasaki. On the other hand, crews of manned space missions are exposed to high-energy protons and heavy ions (HZE particles) during the space mission. No such exposures are known on Earth, with the notable exception of patients treated with accelerated protons or heavy ions for cancer therapy. Certainly the exposure conditions and the relevant endpoints are very different for patients and astronauts (Table 1). However, both research fields share the need for a better knowledge of biological effects of heavy ions. As noted by Eleanor Blakely (Lawrence Berkeley Laboratory, USA), “the two research topics are entwined in a
yin-yang relationship”. Apart from basic research in the biological effectiveness of heavy ions, there is a number of specific research topics which are clearly relevant for both fields (Table 1).

Individual radiosensitivity
The development of a reliable test to assess the individual response to radiation treatment (predictive assay) is still one of the main research fields in clinical radiobiology. If we would be able to predict individual response to radiation, the treatment planning could be tailored by increasing the dose in “radioresistant” patients (thus increasing the local control rate), and reducing the dose in “radiosensitive” patients (thus reducing normal tissue complications, or even suggesting alternative treatments). On the other hand, screening for individual sensitivity to radiation is important for medical surveillance of crewmembers of long-term interplanetary missions.

During the 60’s, ataxia-telangiectasia (AT) patients suffered severe or fatal radiation injuries when treated with a standard course of radiotherapy, and it was later demonstrated that AT fibroblasts are up to three times more radiosensitive than wild type. ATM (AT Mutated gene) homozygotes only represent a small fraction of the radiosensitive patients, although they appear to be the most sensitive. Clinical experience indicates that there is a heterogeneous radiosensitivity in the adult population: approximately 15% of the radiotherapy patients can be classified as “sensitive”, and approximately 5% of patients are injured during the radiotherapy course. ATM heterozygotes, who are breast cancer-prone, are suspected to represent a large fraction of the extreme radiosensitive patients. They represent about 1% of the population but about 5% of the cancer patients in USA. It has been shown that cells heterozygous for ATM mutations are slightly more sensitive to radiation than the wild-type. An increased sensitivity of ATM heterozygotes has been also proved in vivo, measuring the induction of cataracts in ATM homozygotes, heterozygotes, and wild-type mice exposed to X-rays. The coincidence of 5% of cancer patients being ATM heterozygotes and 5% of patients suffering severe side effects in radiotherapy is striking, and clinical data would be useful. It appears likely that individuals displaying hypersensitivity to sparsely ionizing radiation will be hypersensitive to heavy ions, too.

Late stochastic effects of heavy ions
NASA and ESA consider carcinogenesis as the main risk factor for astronauts caused by the exposure to cosmic radiation. Most of the research supported by Space Agencies aims to reducing uncertainty on the biological effectiveness of heavy ions for cancer induction. The topic is becoming of great interest in hadrontherapy, too. Following the pioneering work in

Figure 2
Basic studies in heavy-ion radiobiology are essential to foster human exploration of the Solar system, and to sterilize solid cancers resistant to conventional therapy. In fact, the very same particles that can represent a danger for the crews of space missions, can also be used to kill cancer cells. During an extravehicular activity, shielding is minimal and the dose caused by cosmic rays increases. Above the therapy gantry installed at GSI to treat different types of cancers, mostly chondrosarcomas.

Mice heterozygous for the ATM gene are more sensitive to cataractogenesis than wild-types not only after exposure to X-rays, but also after localized irradiation with high-energy Fe-ions. However, qualitative differences in response to high- and low-LET radiation are possible. For instance, lymphoblastoid cells from AT patients undergo apoptosis after exposure to accelerated N-ions, but not after X-irradiation.

Ataxia-telangiectasia is only one among several other genetic diseases associated to radiosensitivity. In addition, clinical evidence suggests that a fraction of the population may be radioresistant. A predictive assay able to identify radiation hypersensitive or cancer-prone subjects could be useful in crew selection for long-term space flights, but this assay is not available at the moment.

• Institute for condensed matter physics at TU Darmstadt
Prof. PhD. Marco Durante, Tel. 06151/16-3681
E-Mail: marco.durante@physik.tu-darmstadt.de
www.fkp.tu-darmstadt.de/groups/ag_durante/dur/index.de.jsp
Berkeley, thousands of patients have been cured with carbon ions both in Japan and Germany. Hopefully, many more will be cured in the future, including young adults and children. The next concern will be the risk of secondary cancer for those patients who survived the primary cancer and have a significantly long life expectancy. Animal data on cancer induction by heavy ions are scanty, and more experiments are under way to reduce the uncertainty. Data accumulated so far suggest that none of the heavy ions investigated have RBE values for carcinogenesis greater than fission neutrons. Basic biology studies to unravel mechanisms of high-LET radiation-induced carcinogenesis are also obviously of great benefit for both topics.

Biomarkers of risk can be extremely useful to reduce uncertainties, despite several limitations in their sensitivity and correlation to late stochastic effects. Risk predictions are based on human epidemiological studies on cohorts exposed to sparsely ionizing radiation, and extrapolated using animal or in vitro data. Biomarkers are measured directly in subjects exposed to heavy ions, and represent early predictors of carcinogenic risk, taking into account the exposure conditions and the individual susceptibility. Epidemiological studies suggest that chromosomal aberrations in peripheral blood lymphocytes represent a biomarker of cancer risk. Measurements of chromosomal aberrations in blood’s lymphocytes have been performed both in astronauts and in radiotherapy patients. Risk estimates derived from chromosomal aberration measurements in astronauts involved in long-term missions in low-Earth orbit lie in the range predicted from physical dosimetry and standard models used to calculate the risk, thus suggesting that the current models used for risk predictions are workable and essentially sound. Aberrations in lymphocytes from radiotherapy patients are strongly dependent on the irradiated volume and on the presence of lymph nodes in the target field. Direct comparison in patients treated for the same tumors using similar target volumes indicates that the yield of aberrations is lower for patients treated with C-ions than in those treated with X-rays, despite the higher biological effectiveness of the charged particles. These results suggest that the improved physical dose distribution in hadrontherapy may decrease the risk of secondary cancers.

**Conclusions**

Both hadrontherapy and space radiation protection will benefit from more research in the field of biological effects of heavy ions. In addition, experiments in these fields will exploit the same accelerator facilities. In fact, extensive space radiation research is currently under way both at HIMAC and GSI, at
the same accelerators where patients are treated with heavy ions. Thanks to the positive clinical results obtained in Japan and Germany, more medical accelerators for proton or heavy-ion cancer treatment are planned all over the world, and especially in Europe. These facilities are very expensive, but it should be considered that they will have large applications in basic and applied research, especially for space radiation protection. Space colonization is one of the main goals of mankind for the XXI century, but human exploration of the Solar system will only be possible with a better understanding of risks connected to cosmic ray exposure, and after development of appropriate countermeasures. It is advisable that novel hadrontherapy facilities set aside a conspicuous amount of beamtime for basic research, and especially for research topics relevant to oncological particle therapy. On the other hand new very high energy research facilities, such as FAIR at GSI, should commit part of the beamtime to space radiation protection.

Marco Durante is Director of the Biophysics Department at GSI and Professor at the TU Darmstadt. He has dedicated his research efforts to the study of biological effects of heavy ions focussing on cytogenetic effects.