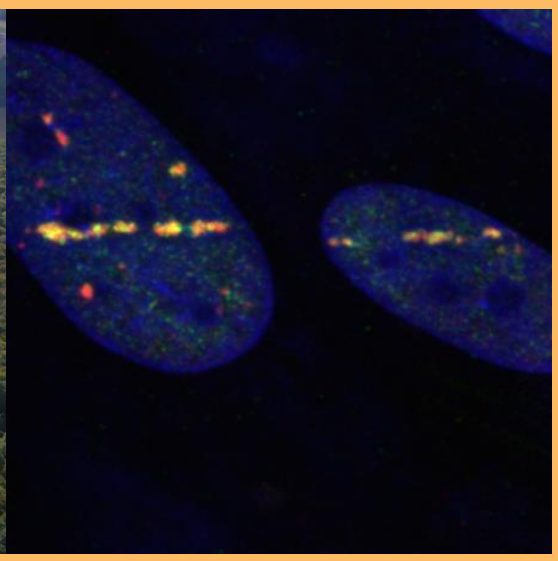
GSI REPORT 2019-3
May 2019

INTERNATIONAL BIOPHYSICS COLLABORATION MEETING

BOOK OF ABSTRACTS

GSI/FAIR, Darmstadt, Germany
20-22 May, 2019

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GSI Helmholtzzentrum für Schwerionenforschung GmbH, Planckstraße 1, 64291 Darmstadt, Germany

Cover page:

Aerial view on the FAIR construction site, September 2018 (left) and online microscopy of irradiated cells by single ions (right)

Photo: T. Middelhauve/GSI/FAIR and B.Jakob / GSI Helmholtzzentrum für Schwerionenforschung GmbH

Impressum

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Biophysics

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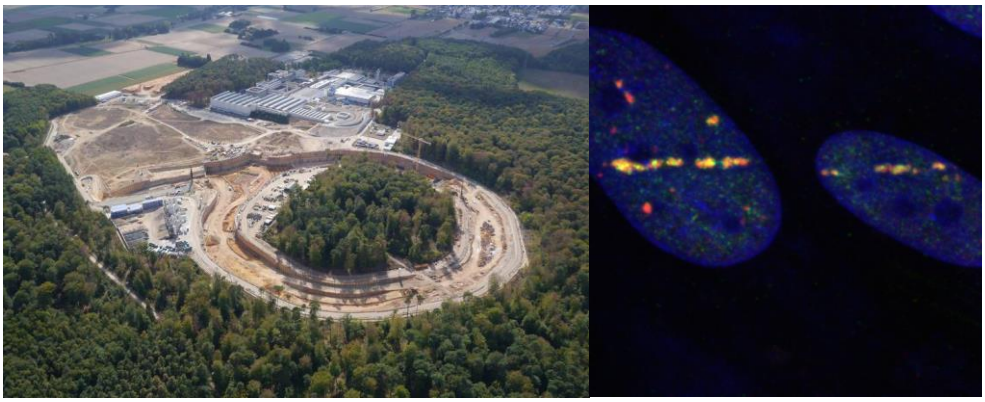

Scientific Program

www.gsi.de/bio-coll

Monday, May 20 (Opening Session)

11:30 - 12:30 **Registration, finger food in the reception**

12:30 - 14:40 **Opening Session** (plenary)
Hörsaal SB1 1.200
Chair: Marco Durante (GSI, Darmstadt, Germany)

12:40 - 12:55 *FAIR project*
Paolo Giubellino (Scientific Managing Director of GSI & FAIR, Darmstadt, Germany)

12:55 - 13:10 *Research at FAIR*
Karlheinz Langanke (Research Director of GSI, Darmstadt, Germany)

13:10 - 13:30 *Radiation biology for space research at GSI: a review*
Gerhard Kraft
(Helmholtz Professor, former Director of GSI Biophysics, Darmstadt, Germany)

Chair: Boris Sharkov (JINR, Dubna, Russia)

13:30 - 14:05 *Is there a safe haven in space?*
Reinhold Ewald (Inst. of Space Systems, University of Stuttgart, Germany)

14:05 - 14:40 *Therapy with different ions: clinical perspectives*
Jürgen Debus (Heidelberg University Hospital, Germany)

14:40 - 15:00 Coffee Break
15:00 - 15:15 **Group photo**
15:30 - 16:15 **Visit to FAIR construction site**

Monday, May 20 (Session 1)

16:20 - 18:40 **Session 1a** (parallel) **– Space Radiation Research at Accelerators**
Hörsaal SB1 1.200
Chair: Jennifer Ngo-Anh (ESA/ESTEC, Noordwijk, The Netherlands)

16:20 - 16:30 *Investigating the effects of galactic cosmic rays on space electronics*
S. Metzger (Fraunhofer INT, Euskirchen, Germany)

16:30 - 16:40 *Joint research; GSI a major continued supporter to ESA's Space Radiation Research Programme*
M. Dieckmann (ESA/ ESTEC, Noordwijk, The Netherlands*)*

16:40 - 16:50 *Space radiation environment and effects activities*
G. Santin (ESA/ ESTEC, Noordwijk, The Netherlands*)*

16:50 - 17:00 *Space radiation cross section measurements at FAIR*
J.W. Norbury (NASA Langley Research Center, Hampton, VA, USA)

17:00 - 17:10 *A hybrid active-passive galactic cosmic simulator for FAIR*
C. Schuy (GSI, Darmstadt, Germany)

17:10 - 17:20 *Study of high energy particle interaction with thick targets and secondary neutron production for radiation protection on long duration space missions*
D. Boscolo (GSI, Darmstadt, Germany)

17:20 - 17:30 *European Radiation Facilities Network (ERFNet)*
L. Narici (University of Rome, Italy)

17:30 - 17:40 *Dosimetry concepts for space radiation research with high-energy ion beams*
F. Horst (GSI, Darmstadt, Germany)

17:40 - 17:50 *Space-TRiP: from ion beam radiotherapy to space radiation research*
A. Topi (GSI, Darmstadt, Germany)

17:50 - 18:00 *FAIR for space radiation research*
C.E. Hellweg (DLR, Cologne, Germany)

18:00 - 18:10 *Astrobiology studies with the ESA detailed Mars Energetic Radiation Environment Model and GSI data*
P. Gonçalves (LIP, Lisboa, Portugal)

18:10 - 18:20 *Radiation for space experiment IceCold*
E. Rabbow (DLR, Cologne, Germany)

18:20 - 18:30 *Space radiation and immune system – a FAIR connection*
A. Maier (GSI, Darmstadt, Germany)

18:30 - 18:40 *Combined effect of space radiation and microgravity on human body*
D. Leonhäuser (GSI, Darmstadt, Germany)

16:20 - 17:40 **Session 1b** (parallel) **– New Therapy Approaches**
Theorie Seminarraum SB3 3.170a
Chair: Kenneth Long (Imperial College, London, UK)

16:20 - 16:30 *Minibeam therapy with protons and light ions*
J. Eley (Vanderbilt University School of Medicine, Nashville, TN, USA)

16:30 - 16:40 *High energy ion beams for spatially fractionated radiation therapy (SFRT)*
Y. Prezado (IMNC-CNRS, Orsay, France)

16:40 - 16:50 *A preclinical small animal irradiation facility for proton minibeam therapy*
G. Dollinger (Universität der Bundeswehr München, Germany)

16:50 - 17:00 *Back to the future of antiproton dosimetry and radiobiology*
N. Bassler (University of Stockholm, Sweden)

17:00 - 17:10 *A simulated investigation on the comparison of proton, antiproton and carbon ion in radiotherapy*
D. Liu (Jeju National University, Jeju, Republic of Korea)

17:10 - 17:20 *Towards proton-boron capture therapy*
L. Manti (University of Naples Federico II, Italy)

17:20 - 17:30 *Radiosensitizating effect of gadolinium oxide-based nanoparticles on NSCLC cells under low and high LET irradiation*
W. Chen (Institute of Modern Physics, Lanzhou, China)

17:30 - 17:40 *High Z nanoparticles as radioenhancers for different radiation qualities*
M. Fuß (GSI, Darmstadt, Germany)

17:40 - 18:40 **Session 1c** (parallel) **– Research Programs**
Theorie Seminarraum SB3 3.170a
Chair: Horst Wenninger (CERN, Switzerland)

17:40 - 17:50 *TREASURE (Training Researchers of south-EASt eURope with Enlight for the Future)*
M. Dosanjh (CERN, Switzerland)

17:50 - 18:00 *Opportunities for life-science research at the Dalton Cumbrian Facility (DCF)*
F. Currell (University of Manchester, UK)

18:00 - 18:10 *High-resolution dosimetry R&D at LIP for medical and space applications*
J. Sampaio (LIP, Lisboa, Portugal)

18:10 - 18:20 *CNAO facilities for radiobiological experiments*
A.Facoetti (CNAO, Pavia, Italy)

18:20 - 18.30 *Radiation biophysics research at iThemba LABS*
C.Vandevoorde (iThemba, Cape Town, South Africa)

18:30 - 18:40 *Radiobiological research at Joint Institute for Nuclear Research*
A.N. Bugai (JINR, Dubna, Russia)

18:40 - 20:30 **Welcome reception (GSI foyer)**
20:30 - 21:00 Bus to Darmstadt center

Tuesday, May 21 (Session 2)

09:00 - 10:30 **Session 2** (plenary) **– New Accelerators**
Hörsaal SB1 1.200
Chair: John W. Norbury (NASA Langley Research Center, Hampton, VA, USA)

09:00 - 09:30 *The FAIR accelerator*
Udo Weinrich (GSI, Darmstadt, Germany)

09:30 - 10.00 *Status and perspectives of medical accelerators*
Thomas Haberer (HIT, Heidelberg, Germany)

10:00 - 10:30 *Applied nuclear physics experiments at new accelerators*
Vincenzo Patera (University of Rome, Italy)

10:30 - 10:50 Coffee break

10:50 - 12:30 **Session 2a** (parallel) **– New Accelerators**
Hörsaal SB1 1.200
Chair: Sandro Rossi (CNAO, Pavia, Italy)

10:50 - 11:00 *JINR particle accelerators for radiation biology*
B. Sharkov (JINR, Dubna, Russia)

11:00 - 11:10 *South East European International Institute for Sustainable Technologies (SEEIIST)*
S. Damjanovic (GSI, Darmstadt, Germany)

11:10 - 11:20 *Plans for heavy ion therapy in The United States*
A. Pompos (UT Southwestern Medical Center, Dallas, TX, USA)

11:20 - 11:30 *New infrastructure for image guided preclinical research in particle therapy*
S. Brandenburg (University of Groningen, The Netherlands)

11:30 - 11:40 *The ELIMED/ELIMAIA open Users beamline for laser-driven ion beams and first planned irradiation activities*
G.A.P. Cirrone (INFN-LNS, Catania, Italy)

11:40 - 11:50 *From CERN technologies to medical applications*
M. Cirilli (CERN, Geneva, Switzerland)

11:50 - 12:00 *INFN-LNS Hadrontherapy facility: clinical outcome, radiobiological studies and preclinical molecular imaging approaches*
G. Cuttone (INFN-LNS, Catania, Italy)

12:00 - 12:10 *The new CNAO irradiation facility for research applications*
M. Necchi (CNAO Pavia, Italy)

12:10 - 12:20 *LhARA; the Laser-hybrid Accelerator for Radiobiological Applications*
K. Long (Imperial College, London, UK)

12:20 - 12:30 *The LARAMED project at LNL: radionuclides from the nuclear physics to medicine*
J. Esposito (LNL-INFN, Legnaro, Italy)

10:50 - 11:40 **Session 2b** (parallel) **– High Intensity Beams**
Theorie Seminarraum SB3 3.170a
Chair: Frank Van den Heuvel (University of Oxford, UK)

10:50 - 11:00 *Investigating the mechanism behind FLASH radiation effects*
F. Van den Heuvel (University of Oxford, UK)

11:00 - 11:10 *Radiobiology of high dose-rate particle beams*
E. Beyreuther (HZDR, Dresden, Germany)

11:10 - 11:20 *Radiobiology of the laser-accelerated ions at ultra high dose rates*
P. Chaudhary (Centre for Cancer Research and Cell Biology, Belfast, UK)

11:20 - 11:30 *The basic mechanism behind FLASH radiotherapy: measuring DNA damage and oxygen depletion at ultrahigh dose rates*
B. Jakob (GSI, Darmstadt, Germany)

11:30 - 11:40 *FLASH irradiation by tumour conformal beam application with 3D modulators and biological verification*
Y. Simeonov (THM, Gießen, Germany)

11:40 - 12:30 **Session 2c** (parallel) **– Radioactive Beams and Detection**
Theorie Seminarraum SB3 3.170a
Chair: Christian Graeff (GSI, Darmstadt, Germany)

11:40 - 11:50 *Simultaneous cancer treatment and online imaging with radioactive ion beams at FAIR*
T. Steinsberger (GSI, Darmstadt, Germany)

11:50 - 12:00 *Real-time PET imaging for range verification in proton and ion radiotherapy*
P. Dendooven (KVI-CART, Groningen, The Netherlands)

12:00 - 12:10 *Toward hybrid γ-PET imaging of radioactive ion beams at FAIR*
G. Dedes (LMU Munich, Germany)

12:10 - 12:20 *PET real-time imaging of ion beams*
V. Rosso (University of Pisa, Italy)

12:20 - 12:30 *A multimodal imaging system for in vivo range verification in particle therapy*
M.G. Bisogni (University of Pisa and INFN Pisa, Italy)

12:30 - 13.30 Lunch break

Tuesday, May 21 (Session 3)

13:30 - 15:50 **Session 3a** (parallel) **– Dosimetry**
Hörsaal SB1 1.200
Chair: Anatoly Rozenfeld (University of Wollongong, Australia)

13:30 - 13:40 *Radiation quality of therapeutic ion beam from unconventional accelerator modalities*
G. Magrin (EBG MedAustron, Wiener Neustadt, Austria)

13:40 - 13.50 *Microdosimetry as a tool for radiation risk assessment*
C. La Tessa (University of Trento, Italy)

13:50 - 14:00 *Recent development of solid-state microdosimetry for RBE study of ion therapeutic beams and radiation protection for astronauts in space*
A. Rozenfeld (Centre for Medical Radiation Physics, Wollongong, Australia)

14:00 - 14:10 *Relative Biological Effectiveness (RBE) of a clinical eye proton therapy beam: experiments and Monte Carlo approach*
G. Petringa (LNS-INFN, Catania, Italy)

14:10 - 14:20 *Investigating ion track structure at FAIR*
T. Friedrich (GSI, Darmstadt, Germany)

14:20 - 14:30 *BioDynaMo: a platform for computational modelling and simulation of biophysical dynamics*
R. Bauer (Newcastle University, Newcastle upon Tyne, UK)

14:30 - 14:40 *Preliminary results from a synchrotron dedicated prompt gamma spectroscopy system: experiments with ^{1}p, ^{4}He, ^{12}C, ^{16}O beams*
R. Dal Bello (DKFZ, Heidelberg, Germany)

14:40 - 14:50 *High-energy neutron field characterization with the Bonner sphere spectrometer NEMUS*
M. Zboril (PTB Braunschweig, Germany)

14:50 - 15:00 *Neutron production in heavy ion therapy*
M. Nandy (Saha Institute of Nuclear Physics, Kolkata, India)

15:00 - 15:10 *An integrated system for 3D energy deposition measurements in a water phantom for hadron therapy*
J. Leidner (CERN, Geneva, Switzerland)

15:10 - 15:20 *Electrons @ FAIR*
M. Krämer (GSI, Darmstadt, Germany)

15:20 - 15:30 *Dry DNA stability after irradiation with swift heavy ions*
M. Karganov (Institute of General Pathology and Pathophysiology, Moscow, Russia)

15:30 - 15:40 *From basic radiobiology towards medical applications at IFIN-HH & ELI-Nuclear Physics*
M. Radu (IFIN-HH, Magurele, Romania)

15:40 - 15:50 *Development of an analytical model for the depth dose profile produced by gamma radiation*
S. Elj (CNSTN, Tunis, Tunisia)

13:30 - 15:50 **Session 3b** (parallel) **– Radiobiology**
Theorie Seminarraum SB3 3.170a
Chair: Charlot Vandevoorde (iThemba, Cape Twon, South Africa)

13:30 - 13:40 *Normal tissue biological models to investigate radiation-induced side effects*
P. van Luijk (University Medical Center, Groningen, The Netherlands)

13:40 - 13:50 *The impact of lipid metabolism in radiation resistance*
J. Seco (DKFZ, Heidelberg and University of Heidelberg, Germany)

13:50 - 14:00 *A pointillist view on particle tracks and DNA-repair in 3D-conserved cell nuclei by means of super-resolution localization microscopy*
M. Hausmann (Kirchhoff-Institute for Physics, University of Heidelberg, Germany)

14:00 - 14:10 *lncRNA-actin cytoskeleton axis regulates cellular response to heavy particles*
G. Zhou (Soochow University, Suzhou, China)

14:10 - 14:20 *Ion beam stimulation therapy for iron-oxide mineral forming neurodegenerative disease*
J.-K. Kim (University of Daegu, Daegu City, Republic of Korea)

14:20 - 14:30 *Radiobiology data with low energy neutrons*
M. Pedrosa-Rivera (ILL, Grenoble, France and University of Granada, Spain)

14:30 - 14:40 *Radiation metabolomics: biomarkers and beyond*
S.K. Manna (Saha Institute of Nuclear Physics, Kolkata, India)

14:40 - 14:50 *Novel in vitro models for the prediction of space radiation and radiotherapy risks*
I. Schroeder (GSI, Darmstadt, Germany)

14:50 - 15:00 *(Brain) tissue slice cultures as a system to study radiation effects*
F. Rapp (GSI, Darmstadt, Germany)

15:00 - 15:10 *Preliminary gene expression results of cancer cells in hypoxic and normoxic environment under irradiation*
J. Jansen (DKFZ, Heidelberg and University of Heidelberg, Germany)

15:10 - 15:20 *Human induced pluripotent stem cell derived in vitro models for space radiation biology*
M. Mayer (University of Applied Sciences Aschaffenburg, Germany)

15:20 - 15:30 *Effect of deep space-related conditions on central nervous system performance in multicellular organisms as a function of their genetic background*
F. di Cunto (University of Torino, Italy)

15:30 - 15:40 *Blocking DNA activity in ion beam therapy of cancer cells*
S.N. Volkov (Bogolyubov Institute for theoretical Physics, NAS, Kiev, Ukraine)

16:00 - 17:00	Bus to Castle Frankenstein
17:00 - 18:00	**Castle excursion**
18:00 - 20:00	**Social dinner**
20:00 - 21:00	Bus to Darmstadt center and GSI

Wednesday, May 22 (Session 4)

09:00 - 10:00 **Session 4** (plenary) **– Medical Physics & Radionuclides**
Hörsaal SB1 1.200
Chair: Naruhiro Matsufuji (NIRS-QST, Chiba, Japan)

09:00 - 09:30 *Particle therapy now - have we reached the future?*
Jay Flanz (MGH, Boston, MA, USA)

09:30 - 10:00 *Radioisotope production at new accelerators*
Ulli Köster (ILL, Grenoble, France)

10:00 - 10:20 Coffee break

10:20 - 12:20 **Session 4a** (plenary) **– Medical Physics & Radionuclides**
Hörsaal SB1 1.200
Chair: Yolanda Prezado (CNRS, Orsay, France)

10:20 - 10:30 *Radiotherapy studies with multiple ion beams*
O. Sokol (GSI, Darmstadt, Germany)

10:30 - 10:40 *Beam scanner development for the biophysics researches*
V. Skachkov (ITEP, Moscow, Russia)

10:40 - 10:50 *Medical-physics challenges from radiation therapy with Facility for Antiproton and Ion Research (FAIR)*
N. Matsufuji (NIRS-QST, Chiba, Japan)

10:50 - 11:00 *Online beam and range monitoring in a static toroidal gantry delivery configuration*
P. Cerello (INFN, Torino, Italy)

11:00 - 11:10 *A High-granularity digital tracking calorimeter optimized for proton CT*
P. Piersimoni (University of Bergen, Norway)

11:10 - 11:20 *PRIOR – proton microscope for FAIR*
D. Varentsov (GSI, Darmstadt, Germany)

11:20 - 11:30 *The PaNTERA project - proton radiography towards medical applications*
M. Schanz (GSI, Darmstadt, Germany)

11:30 - 11:40 *A novel approach for the monitoring of ion beams: where we are*
S. Giordanengo (INFN, Torino, Italy)

11:40 - 11:50 *Hadron beam time tracker for time-of-flight measurements of prompt-gamma*
P. Magalhaes Martins (DKFZ, Heidelberg, Germany and University of Lisbon, Portugal)

11:50 - 12:00 *MoVe IT - modeling and verification for ion beam treatment planning: new insights from FAIR beams?*
E. Scifoni (TIFPA-INFN, Trento, Italy)

12:00 - 12:10 *Research on the production of therapeutic ^{105}Rh with deuteron beam*
M. Sitarz (GIP ARRONAX, Saint-Herblain, France)

12:10 - 12:20 *The ISOLPHARM project: production at SPES of high specific radionuclides as radiopharmaceutical precursors*
S. Corradetti (INFN Laboratori di Legnaro, Italy)

12:20 - 13.00 **Final Session** (plenary) **–**
– Discussion / Election of Spokesperson and Deputy Spokesperson
Hörsaal SB1 1.200
Chair: Marco Durante (GSI, Darmstadt, Germany)

13:00 Adjourn

International Biophysics Collaboration Meeting

Book of Abstracts

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Content

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Introduction

The Biophysics Collaboration: biomedical research at new accelerators

M. Durante[1,2], R. Pleskac[1], and C. Graeff[1]
[1]GSI Helmholtzzentrum für Schwerionenforschung, Biophysics Department, Darmstadt, Germany;
[2]Technische Universität Darmstadt, Institut für Festkörperphysik, Darmstadt, Germany

Several new large-scale particle accelerators are under construction all around the world (e.g. FAIR, SPIRAL2, ELI, SPES, SEEIIST in Europe; FRIB in USA; NICA in Russia; RAON in Korea). These machines offer new opportunities including high intensity, high energy, use of different ions, radioactive ion beams, ultra-short pulses. Many of these accelerators have cost in the range of 10^9 €, and the primary science objective is basic nuclear physics. However, most of them include programs in applied nuclear sciences, especially biomedical research. Applications to energy, medicine, materials, space, security and environment are indeed the fields with the largest expansion potential in nuclear physics [1]. They also give a social justification for the high investment cost of the new facilities.

At the Facility of Antiprotons and Ion research (FAIR) in Darmstadt [2], applied physics has been always part of one of the four pillars (APPA [3]). The necessity to transform the FAIR Biophysics Collaboration into a truly International, worldwide collaboration stems from the interest in the same activities in many new facilities. An International Collaboration, linking the different new facilities, can guarantee the quality of the science and the complementarity of the activities. Even if the scheme is similar to the traditional high-energy physics collaborations, the Biophysics Collaboration can cover many different research topics (*Figure 1*), and therefore, rather than competition to reach first a specific goal, this Collaboration will be characterized by collaboration and complementarity.

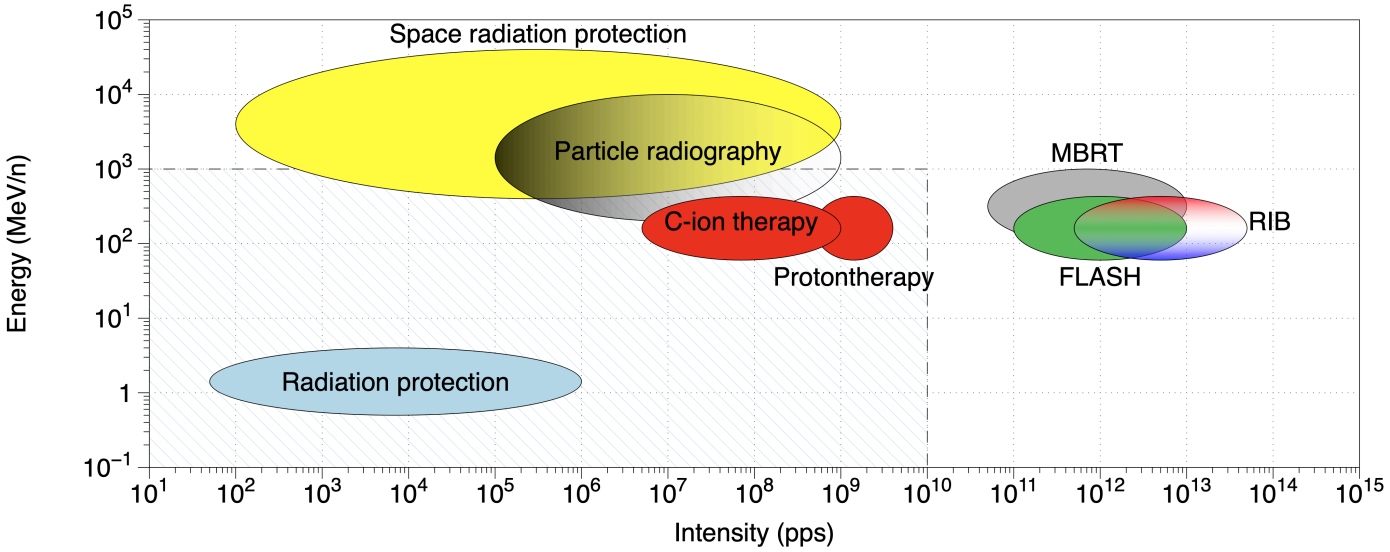


Figure 1: Radiation research at accelerators. The shaded region includes values of energy and intensities covered by the present accelerators. MBRT=minibeam radiotherapy; RIB=radioactive ion beams, FLASH= high dose-rate radiotherapy

The opportunities of the new accelerators can lead to breakthrough advances in space radiation research (where high energy is necessary) and medical physics (including particle radiography, minibeam radiotherapy, very high dose rate therapy, use of radioactive ion beam) and production of new radionuclides for medicine [4]. These new ideas will be discussed in this volume, and will form the basis for the collaboration.

[1] NuPECC, *Long Range Plan*. ESF, Strasbourg. 2017. http://www.nupecc.org.

[2] M. Durante *et al.*, All the fun of the FAIR: fundamental physics at the facility for antiproton and ion research. *Phys. Scr.* 2019 DOI: 10.1088/1402-4896/aaf93f

[3] T. Stöhlker *et al.*, APPA at FAIR: From fundamental to applied research. *Nucl. Instr. Meth*. **B365** (2015) 680-685.

[4] M Durante *et al.*, Applied nuclear physics at the new high-energy particle accelerator facilities. *Phys. Rep.* 2019. DOI: 10.1016/j.physrep.2019.01.004

Space Radiation Research at Accelerators

Radiation biology for space research at GSI: a review

G.Kraft[1]
[1]GSI, Darmstadt, Germany

Biophysical research at GSI started with experiments for space research in 1976 in the very beginning of beam acceleration and in parallel with the atomic physics experiments. The choice of the rather exotic space experiments had technical and scientific reasons: The technical possibilities of exposing biological objects were limited to *in vacuo* conditions because at the only available very low beam energy of 1.4 MeV/n we could not produce a technical stable external beam due to limitations for a beam exit window to atmospheric pressure. This problem was solved later when more users became interested in heavy ion exposure and a biological exposure. Then a chamber for the exposure of large amounts of normal cells under atmospheric conditions, the BIBA was constructed. But at this very beginning, scientist from Universities of Frankfurt, Giessen and Siegen collaborating with NASA became interested in ion exposure especially with iron or other ions of similar atomic numbers as ground based calibration. In their pioneering "Bio- stack" experiments at satellites, they exposed dry biological objects like bacteria spores, yeast and the necessary CR39 dosimeters directly to space environment. At the new GSI accelerators, we could do calibration for these experiments using the standard equipment from atomic physics experiment and introducing simultaneously up to 10 dry samples over an air lock system into the atomic physics target chambers.

These exposures were done at low particle fluencies and most of the dosimetry was performed using CR39 track detectors. The inactivation of our objects were measured as function of the fluence and given as inactivation cross sections σ. For each biological object, the cross sections formed a universal curve for all ions for low LET´s having supra-linear increase with increasing energy loss. But at higher LET values, individual σ-curves separated from the common line forming individual hooks for each atomic number reflecting the decrease in track diameter towards the end of range forming σ-LET hooks. These individual "Darmstadt-hooks" or the equivalent separation of RBE into individual maxima produced a large controversy with the standard opinion in radiation biology where a universal RBE maximum at LET=100 keV/ µm was postulated. However, the splitting into individual maxima for each atomic number could be confirmed later on, when large amounts of very different normal cells could be exposed in the BIBA under atmospheric conditions. With this new exposure setup, the biophysics program for space research increased and included also the measurements of DNA damage and chromosomal disintegrations.

Later on when the focus in GSI biophysics program shifted to tumour therapy and its technical and scientific preparation, space related experiments at GSI were still continued also in that time. Then the space activity was mainly carried by external users, but there were many synergisms between both areas: the detailed fragmentation measurements including the neutron production and a deeper understanding of particle RBE. Both fields were necessary for treatment planning but also of interest for space research. In addition, space research could directly profit from the therapy installation: for therapy, we developed the novel 3-D raster scanning technique in order to reach the ultimate precision. In this technique, the target volume is dissected in a grid of small voxels and the beam is guided voxel by voxel over the target volume. This technique could be also used to test electronic devices like the compartments of the AMS Alpha Magnetic Spectrometer by scanning a beam over sensitive areas and correlating the electronic failures with the actual beam positions. In this way, critical areas could be identified efficiently and eliminated in a very rational way.

A similar technique was used to further localize the origins of the famous light flashes produced by high LET exposure like cosmic rays. When tumours were treated in patients close to the optical system, the same light flashes were produced. The patient could indicate with an electrical signal whenever they observed a flash. From the beam positions of the scanner and the reaction of the patient, the origin of the phosphene phenomena could be localized with greater precision. These two examples show synergisms between therapy and space related problems.

More recently, another interesting example of cross correlation might become of relevance for space research: in the GREWIS project we found a significant biological response to extremely low doses of a few µGy total body exposure to a mixed radiation field suggesting that the permanent exposure in extra-terrestric condition might influence the human immune system maybe more than microgravity. By simulating such low doses, the action to the immune system could be studied already in the FAIR 0 experimental phase.

Is there a Safe Haven in Space?

R. Ewald[1]

[1]Institute of Space Systems, University of Stuttgart, Germany

Ever since the year 2000 humans have continuously worked and researched in Space. This has been made possible by the construction of the International Space Station ISS, to which five international partners contributed as a first such collaboration in Space. Russia, the US, Canada, Japan, and Europe represented by the European Space Agency ESA have each contributed hardware elements, logistic flights, and – up to today – operate the respective space station modules and elements in a combined intercontinental network of space centers. This international peaceful cooperation has in the past not only mastered critical shortcomings of logistics and means of regular crew transportation, it has also provided a blueprint of projects on the Global Exploration Roadmap [1] towards deep space explorations.

The US Space Transportation System – better known as the Space Shuttle – has significantly contributed to the build-up of the ISS complex, which – including the Russian modules – approaches a mass of 450 metric tons in Space. Its lasting heritage is the Space Launch System SLS, which together with the European built Service Module derived from the ISS cargo ship Autonomous Transport Vehicle ATV, will propel the US Orion spacecraft beyond Earth orbit to return to the Moon and go beyond.

Research on ISS is focusing on beneficial use of the space environment – namely microgravity - to improve methods and processes in many disciplines on Earth. But it also is directed to increase TRL for systems critical to future deep space exploration. Life support systems need to become independent of Earth supplies, the need to be reliable and as cyclic as possible. The inclusion of biological elements into the traditional physico-chemical air revitalisation systems also is a step towards increasing food supplies on journeys that last two and a half years, such as to Mars. The propulsion system must guarantee safe arrival and departure of the deep space target, while maybe drawing from in-situ resources found on the surfaces of the celestial bodies visited in the course of those Roadmap missions.

Finally, human beings and biological systems leaving the safe magnetic shield of Earth are exposed to galactic and solar radiation to an extent, where current shielding concepts are not allowing a safe prognosis. To achieve technological breakthroughs, the modelling of materials shielding future astronauts during their journey needs to be improved by being able to access a radiation source representing with high fidelity the conditions in interplanetary space. Future radiation shielding not only has to withstand aggressive contact with atomic radicals, radiation, temperature differences, and exposure to vacuum, it also needs to be light weighed, and free of secondary products, that might deposit a higher dose than the original high energy impactor.

Ethical considerations dictate that a credible answer is given to all questions concerning crew safety and crew health on prolonged deep space missions. Only then they can find a safe haven in Space while exploring the immense wonders that lie out there [Figure 1].

Figure 1: Expedition 57 with CDR Alexander Gerst calling ISS their home.

[1] https://www.nasa.gov/sites/default/files/atoms/files/ger_2018_small_mobile.pdf

Investigating the Effects of Galactic Cosmic Rays on Space Electronics

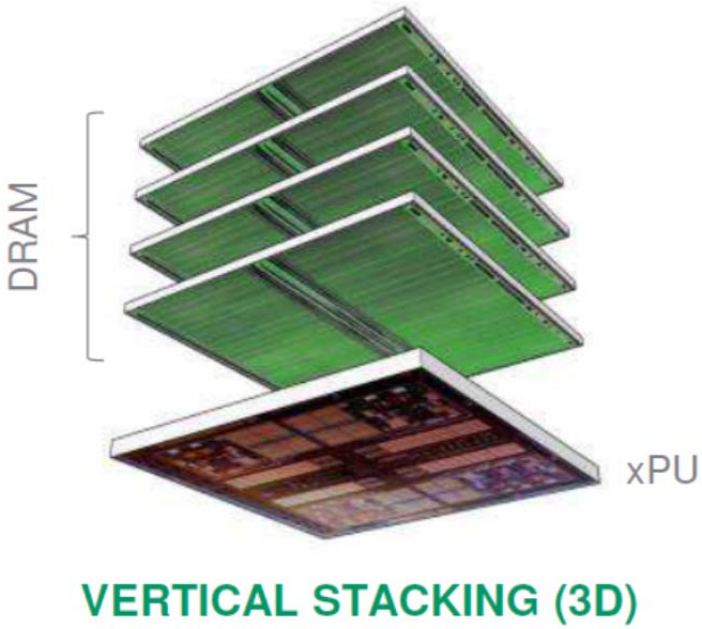
Stefan K. Höffgen, Stefan Metzger
Fraunhofer INT, Euskirchen, Germany.

The radiation environment in space has severely adverse effects on electronic systems. To evaluate radiation sensitivity, electronics are tested on earth with different types of irradiation sources. Galactic Cosmic Rays (GCR) are the most difficult to simulate on earth, because GCR can have energies up to 10^{20} eV, with a flux maximum around 1 GeV/nucleon. Traditionally, single-event effects of these particles were simulated with heavy ions having energies of only a few MeV/nucleon because for "large" devices only the energy loss (often referred to as LET) had to be matched.

Heavy ions of such high energies can produce secondary particles through nuclear interactions which can induce additional ionization that leads to adverse effects. The need to investigate these effects has grown since electronic devices incorporate more and more heavier elements (Cu, W,..) close to sensitive elements which can have significantly larger nuclear cross sections in the 1 to 10 GeV/nucleon energy regime [1].

At the moment there is a large trend in the space community to increasingly use commercial of the shelf (COTS) electronic devices. One of the reasons is that many challenging space applications can only be met with COTS devices because there are simply no HiRel devices available with the necessary performance. However these devices pose additional experimental challenges to investigate their sensitivity to GCR.

High performance digital devices have high requirements on cooling. Without a heat spreader made out of copper of several hundreds of µm thickness, the device will be damaged during operation because of excessive heat. Thus tests at all at low energy accelerators are not feasible and an accelerator with high penetration is needed.



A current trend in the evolution of Si-based microelectronic integrated circuits is to create 3-dimensional structures. There are already commercial available 3D NAND-Flash devices with several tens of active layers stacked on top of each other. These structures cannot be tested with low energy ions, due to the large depths of the sensitive volumes alone. For radiation tests ion beams are needed that provide constant LET over the whole stack (> 64 layers). Because of their commercial availability, 3D NAND-Flash devices could serve as representative components to develop general Radiation Hardness Assurance methods for 3D technologies including new failure mechanisms. Another trend is to stack several dies on top of each other to get a system in a package. To investigate these, the beam has to be able to penetrate through all the dies.

Figure 1: Example of chip with stacked dies (source AMD)

It might be commercially more interesting to test whole boards or systems, than to qualify every part separately. Because of the high penetration depth of the beams it would be feasible to make a campaign, where a large number of devices are tested simultaneously by stacking several boards in a row.

Extending the previous point, whole systems or even small satellites could be tested at FAIR with the 10 GeV/n beam to e.g. investigate the effectiveness of mitigation techniques on system level.

[1] S.K. Höffgen et. al., "Application of the FAIR Facility to Space Radiation Research – Final Report", ESA Contract RFP-D/IPL-PTS/MV/2013.723, 2016.

Joint research; GSI a major continued supporter to ESA's Space Radiation Research Programme

M. Dieckmann, T.J. Ngo-Anh
ESTEC/ESA European Space Agency P.O. Box 299, 2200 AG Noordwijk, The Netherlands

Chronic exposure to galactic cosmic radiation (consisting of heavy ions and protons) and occasional solar particle events (consisting mainly of protons) are predominant features of the space environment and forming the main health hazard for human exploration and colonization of the solar system. For example, vehicles with Moon-destination would cross electron and proton belts entirely for one mission leg, just to address unavoidable location bound particle environments. High-energy particles interfere with electronics, reduce immune response, increase cancer risk, threatening life quality and individual survivability, and thereby endangering mission success. Knowledge gaps remain, in particular regarding the effects of mixed radiation (protons and galactic cosmic radiation components) and the biological effects of very low-dose and low dose-rate chronic exposure to high-energy radiation, as well as the lack of simple countermeasures. This creates a need for investigations into biological effects of space radiation, in order to allow more accurate risk assessments, which in turn leads to more accurate planning of countermeasures (cf. EUB/W31-05). As mixed space radiation describes radiation fields, consisting of particles with stochastic properties also for example in terms of flux, energy, mass, frequency of occurrence and charge, progress focuses to simulate comparable exposures to space radiation with mono-energetic sources at ground-based accelerometers. With this, space radiation is simulated well in ground-based laboratories and forms a vital part of planning for future spaceflight, allowing testing of different organic materials, equipment and technologies to verify that a mission can deal with exposure to the different levels of cosmic radiation in orbit. Accelerators at e.g. the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany produce both high-energy protons and the energetic nuclei of heavier elements, allowing focused, mechanistic studies of the biological consequences for mammalian cells and other relevant model systems (plants, microbes, etc.) of exposure to radiation. Continued availability of space radiation facilities to investigators is critical, as is broad access provided in a timely fashion to meet agency needs. Challenging are scientific demands to objectify exposure data beyond mere indication of Sievert-values for an exposed sample. Alternative research avenues to document e.g. effective dose equivalence, and how space radiation interacts with e.g. DNA or RNA molecules, vulnerable at most diminutive dimensions, are in discussion on e.g. radio sensitive biomarkers to close knowledge gaps on determining short and long-term effects for the organism.

To address these issues, ESA has been cooperating with GSI since 2007 within the so-called IBER programme (Investigations into the Biological Effects of Space Radiation). GSI recently put in place a new concept for the transitional period (c.f. Facility for Antiproton and Ion Research and called "FAIR" in phase 0 covering the period 2019-2022, during which beamtime from the existing accelerator is provided for selected research programmes, such as ESA's IBER programme) until the new-generation accelerator facility will become operational. FAIR will provide the production of conditions that are prevailing, when huge stars explode and enable experimental simulation of interactions of all kinds of matter at extreme temperatures, pressures and densities of unique and critical relevance to the merit of IBER as well.

SciSpacE programme period 1 saw the successful implementation of 11 proposals stemming from AO-2016-IBER during "FAIR phase 0", to continue to make best use of the available beamtime, ESA will release dedicated Announcements of Opportunity soliciting for experiment proposals investigating the biological effects of space radiation covering the SciSpacE programme period 2. To complement and expand on the above activities, it is proposed to continue with a new element introduced in 2016: beamtimes from 5 state-of-the-art facilities will be offered within ESA's continuously open IBER programme to which individual scientists will be able to apply continuously with experiment proposals. This new element will therefore follow the ongoing and very successful ESA Ground–Based Facilities programme (see below) approach, but will be dedicated to radiation facilities and radiation research: peer-reviewed selected experiments shall be awarded with budget which shall cover experiment and travel expenses of the respective science teams. Finally, ESA will continue to actively study the opportunities that the new FAIR facility will offer, namely through the inter-directorate activity "Application of the FAIR Facility to Space Radiation Research" (ESA RFP-D/IPL-PTS/ MV/2013.723), such that the new facility can be fully exploited once operational.

In summary, outside the Earth's magnetic field, crew and electronics are exposed to high-energy particles, ESA's SciSpacE programme will contribute to developing methods and technologies to protect, mitigate, and treat the effects of radiation on the crew and their exploration systems.

Space radiation environment and effects activities

G. Santin[1,2], P. Nieminen[1], V. Ferlet Cavrois[1]
[1]ESA/ESTEC, Noordwijk, Netherlands; [2]RHEA System, Noordwijk, Netherlands

Severe constraints are posed to mission feasibility by the space radiation environment, through effects on astronaut health and reliability of space systems. The various aspects of this domain are addressed at ESA with a very active research and development (R&D) programme, covering environment modelling and in-situ measurements, shielding and other countermeasures, and assessment and modelling of effects.

New models are being developed for solar energetic particles (see e.g. the SAPPHIRE model), addressing the challenges from higher particle energies and the impact of extreme events on cumulative mission fluence. The SEPEM platform (http://sepem.eu) offers tools for statistical modelling of the solar energetic particle environment. New capabilities for now-casting and forecasting of Solar activity are being developed in Space Weather (SW) activities (e.g. SW Helioviewer, and Virtual SW Modelling Centre). An extensive validation is also ongoing to assess the status of new local and global models for trapped radiation in the Van Allen belts.

An extensive in-situ monitoring programme is in place, with development of low-mass, low-power instruments for measurement of the mixed radiation field in space. Following the successful deployment of a series of Standard Radiation Environment Monitor (SREM) units on board platforms in near-Earth orbits and in exploration missions in the Solar system, current efforts aim at development of smaller and ultimately miniaturised instruments (see e.g. NGRM, MIRAM) or specialised detectors for specific mission requirements (e.g. RADEM for the JUICE Jupiter mission). Special attention is also paid at R&D on technology for area and personal active dosimeters for human missions (e.g. MIDAS, and TEC3D).

The shielding effectiveness of planetary magnetospheres and atmospheres is being studied through a series of model developments, covering in particular the near Earth environment and Mars exploration scenarios, but also extending to other planets. Radiation effect reduction through efficient passive shielding design is the subject of a number of studies (see e.g. the ESA ROSSINI, MUSRAS projects) on materials for EVAs, deep space vehicles and planetary and Moon habitats, covering innovative materials sample manufacturing, modelling and experimental tests at high energy (ion) accelerators (including GSI). Radiation tests include dose reduction, beam fragmentation, lateral scattering, microdosimetry, and are used to validate and improve simulation predictions.

Simulation tools are also being improved. The GRAS tool, a general purpose Geant4-based tool for space radiation transport in generic geometries, is being enhanced in terms of (CAD) geometry and physics capabilities, computational speed (e.g. via Reverse or “adjoint” Monte Carlo), magnetic field manager for shielding assessments, (biological) effect modelling and also in ease of use through the CIRSOS framework.

The IPRAM developments developed response functions for exploration scenarios, including dose and biological dose, and an upcoming activity will adapt the SEPEM capabilities to end users in Human Spaceflight.

The Geant4-DNA project (http://geant4-dna.org/) aims at improving the understanding of the detailed interaction of ionizing radiation with the human body at DNA and cellular level, complementing higher level macroscopic damage models. Recent extensions include radiation-induced DNA damage through physico-chemical and chemical processes.

Development and validation efforts are executed in coordination and collaboration with partners in the wider community: the requirements imposed by radiation effects on humans and electronic systems are shared with entities working in space, through the atmosphere, and at ground level, including at natural and man-made radiation environments. Synergies are also fostered through formal cooperation, with the notable examples of the ESA-CERN (2014), and ESA-FAIR (2018) agreements.

Space Radiation Cross Section Measurements at FAIR

John W. Norbury
NASA Langley Research Center, Hampton, VA, USA

Various transport codes show large differences for light ion* production when galactic cosmic ray (GCR) ions are incident on realistic spacecraft shielding materials. Spacecraft measurements and laboratory thick shield measurements also show significant differences compared to model transport calculations. These differences are most likely due to inaccurate nuclear physics models used for light ion production and, in fact, light ion production cross sections represent the largest physics uncertainty in space radiation. Can cross section models be improved by more rigorous comparisons to laboratory measurements? Unfortunately, of all the many and various fragments produced in heavy ion reactions, it is light ion production cross section measurements that represent the largest gap in the cross section database. Thus, the biggest uncertainty in space radiation physics overlaps with minimal data! Actually, the largest gaps in the cross section measurement database are in the GeV/n energy region, which is near the upper energy limit of the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), where the highest available energy is 1.5 GeV/n. The Facility for Antiproton and Ion Research (FAIR) at the GSI (Gesellschaft für Schwerionenforschung) Helmholtz Center for Heavy Ion Research in Darmstadt, Germany, will be able to accelerate ions up to Uranium (U) up to an energy of 10 GeV/n. Therefore, FAIR is ideally suited to close the high energy light ion cross section measurement gap.

*Light ions are defined to be isotopes of Hydrogen (H) and Helium (He), with the most important being ^{1}H (proton), ^{2}H (deuteron), ^{3}H (triton), ^{3}He (helion), and ^{4}He (alpha).

A hybrid active-passive galactic cosmic simulator for FAIR

C. Schuy[1], M. Durante[1, 2] and U.Weber[1]
[1]GSI, Darmstadt, Germany; [2]TU Darmstadt, Darmstadt, Germany.

The radiation environment in space is one of the major obstacles for the human colonization of the solar system [1]. To estimate the deleterious effects of the space radiation environment high-energy accelerator facilities are often used. Typically, a single high-energy heavy, such as 1GeV/u ^{56}Fe, is used as proxy of the complex galactic cosmic ray (GCR) spectrum. Even if this approach is simple and can provide useful information, it is generally recognized that a simulation of the GCR spectrum is necessary to quantify the biological effects of space radiation and to test shielding materials. In fact, the NASA Space Radiation Laboratory (NSRL) at the Brookhaven National Laboratory (BNL) recently commissioned a GCR simulator based on fast sequential delivery of a limited number of light and heavy ions at different energies, to reproduce the LET spectrum of the GCR [2]. The GCR spectrum can also be mimicked at accelerators using a thick passive modulator exposed to a single monoenergetic heavy ion beam and exploiting the fragmentation spectrum behind the shield [3]. FAIR will reach higher energies [4] than BNL, and can therefore provide more accurate GCR simulations especially in the hard portion of the spectrum. Here we propose a hybrid approach for GCR simulation at FAIR combining multiple complex passive beam modulators and fast energy changes of a single heavy ion species (^{56}Fe).

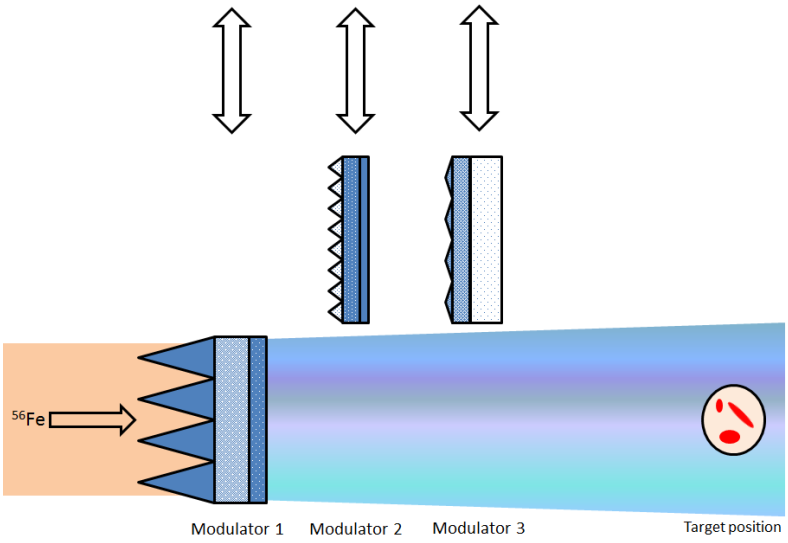


Figure 1: Mono energetic beams of ^{56}Fe interact with multiple complex beam modulators to shape the LET-distribution at the target position

As shown in Figure 1, a mono energetic heavy ion beam interacts with a complex, multi material beam modulator optimized to produce a specific LET-spectrum. After a precalculated amount of primary particles, both the modulator and the energy of the primary particles are changed. This protocol is repeated for a predetermined set of different energy and modulator combinations until the superposition of all LET-spectra lead to a representation of the LET-spectrum as seen in space behind different shielding. Varying the material composition and the geometry of the periodic modulation structures for each modulator allow the adaption of energy loss, nuclear fragmentation and scattering, while active energy variation is mainly used to shape the kinetic energy distributions, especially for the light fragments. Therefore, the proposed hybrid system permits not only the optimization of an LET-distribution, but will also maintain a good approximation of the particle abundance and energies found in space. Due to the high complexity of the multi-layered modulators and the high numbers of free design parameters the development of a fast analytical optimization tool based on the computational code ATIMA and a set of pre-calculated base data, following a simplified physical beam model for pencil beams [5], is foreseen.

[1] M. Durante, F.A. Cucinotta, “Physical basis of radiation protection in space travel”, Rev Mod Phys 2011, doi:10.1103/RevModPhys.83.1245

[2] J.W. Norbury, W. Schimmerling, T.C. Slaba, et al., “Calactic cosmic ray simulation at the NASA Space Radiation Laboratory”, Life Sci Sp Res 2016, doi:10.1016/j.lssr.2016.02.001.Galactic

[3] J.C. Chancellor, S. Guetersloh, K. Cengel, et al., “Emulation of the space radiation environment for materials testing and radiobiological experiments“, http://arxiv.org/abs/1706.02727, 2017

[4] M. Durante, P. Indelicato, B. Jonson, et al., “All the fun of the FAIR: fudamental physics at the facility for antiproton and ion research“, Phys Scr 2019, doi:10.1088/1402-4896/aaf93f

[5] M. Kraemer, E. Scifoni, F. Schmitz, et al., “Overview of recent advances in treatment planning for ion beam radiotherapy“, Eur Phys J D 2014, doi: 10.1140/epjd/e2014-40843-x

Study of high energy particle interaction with thick targets and secondary neutron production for radiation protection on long duration space missions

D. Boscolo[1], M. Durante[1,3], F. Horst[1,2], F. Luoni[1,3], C.A.Reidel[1,4], C. Schuy[1], U. Weber[1]
[1]GSI, Darmstadt, Germany; [2]THM, Gießen, Germany;[3]TU Darmstadt, Darmstadt, Germany; [4]Université de Strasbourg, Strasbourg, France.

Space radiation protection represents a severe problem for guaranteeing the success of a long-duration mission and it has to be taken into account when considering building moon or Martian space habitats. One of the main health risks for the crew is the exposure to galactic cosmic rays (GCR), composed by high-energy protons and heavier ions with energies going far beyond the GeV/u. A possible strategy to minimise the radiation exposure inside the habitat limiting the costs would be exploiting the abundance of in-situ materials to build very thick shielding [1].

Up to now, most of the accelerator experiments on shielding materials for space exploration focused on the dose attenuation of GCR with energies lower than 500MeV/u performed with targets below 20 g/cm^2. Most of the GCR models for human spaceflight risk assessments are developed and validated for this energy region. However, discrepancies between different models have been observed for thicker targets and very high energies where limited information is available [2]. Recent studies demonstrated that the main contribution to the effective dose after thick shielding (> 20 g/cm^2) comes from the more energetic fraction of the GCR spectra (E>1 GeV/u) and, in particular, the contribution of high energetic protons grows when increasing the shielding thickness (Figure 1). This trend is associated to the secondary fragments and neutron production generated by nuclear collisions of protons with the target material [2]. Because of their high biological effect coupled with their low interaction rate, this increased neutron production represents a complication in the definition of optimal shielding approaches. In this direction ESA founded the ROSSINI and the IBER projects, both in cooperation with GSI. Among other objectives, these projects focus on the evaluation of the shielding properties of moon and mars soil simulants (in terms of dose attenuation and production of secondary fragments) and on the characterisation of the secondary neutron field generated by the interaction of radiation with thick shielding materials for ion radiation up to 1 GeV/u.

However, measurements at higher energies are required and could be performed at the SIS100/300 facility where ^{1}H - ^{238}U ion beams with energies up to 10 GeV/u will be available. The secondary neutron field will be measured with neutron specialised detectors including standard devices used for radiation protection like Neutron Multisphere Spectrometer (NEMUS) or GSI Ball and active detectors more common in high energy physics like ΔE/E telescope. Microdosimetry devices such as the Tissue Equivalent Proportional Counters TEPC will be used as well. This will allow fully characterising the effect of GCR after thick shielding materials and providing data to benchmark Monte Carlo simulation codes and models for spaceflight risk assessments.

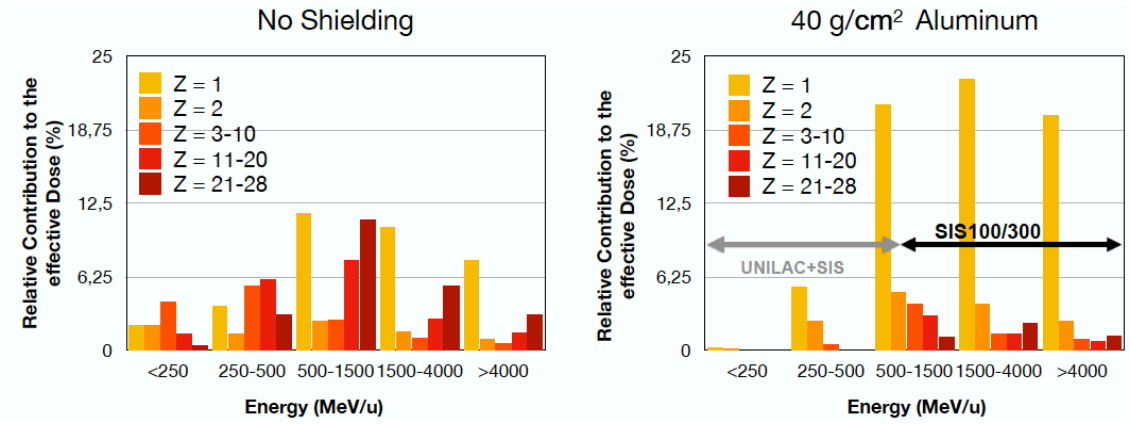


Figure 1: Relative contribution of GCR of different energy and charge to the effective dose in a habitat with No shielding (left panel) and 40 g/cm^2 Aluminium (right panel). Adapted from [2].

[1] M. Durante, “Space radiation protection: Destination Mars”, Life Sciences in Space Research 1 (2014) 2-9.

[2] T.C. Slaba, and S.R. Blattnig. "GCR environmental models I: Sensitivity analysis for GCR environments." *Space Weather* 12.4 (2014): 217-224.

European Radiation Facilities Network (ERFNet)

L. Narici[1,2], C. La Tessa[3], C. Lobascio[4], U. Weber[5]
[1]University of Rome Tor Vergata, Department of Physics & NAST center; [2]INFN Roma2, Rome, Italy;
[3]University of Trento, Trento, Italy & TIFPA-INFN [4]Thales Alenia Space, Turin, Italy; [5]GSI, Darmstadt, Germany;

The European Radiation Facilities Network (ERFNet) is a distributed infrastructure for which it is undergoing a feasibility study, funded by ESA.

ERFNet aim is to support studies relevant for radiation risk mitigation in exploration class space missions.

In the first stage, ERFNet goal will be to help studies on radiation shielding, including works targeted at optimizing the design and development of space habitats. Future upgrades will likely include also radiobiology studies.

The infrastructure is based on three main pillars: irradiation facilities, habitation facilities, and smart knowledgebase and managing system.

ERFNet will provide a single access point (Web-interface) to the system, developed for an easy and complete access to most of the relevant information in the field, to operate on this information (i.e. perform new simulations to characterize and use new materials for shielding purposes), to provide suggestions for design optimization, to facilitate the use of the linked facilities.

To achieve these tasks, an ERFNet Knowledge Base (EKB) is under development. The EKB will link to existent databases (DBs) holding relevant data, aiming at providing standardized and simple access to these data. Whenever needed the EKB will also store in its own repository relevant data and tools. Tools to search for information in literature DBs will be provided as well as strategies to suggest optimal configurations/materials/etc. for the crew radiation risk minimization. To accomplish this goal, ERFNet will link to the most up-to-date risk model. Finally, all the results obtained will be stored in the EKB to increase the amount of information for the successive users.

To provide flexibility and upgrade easiness, the EKB will be modular. As an example, the reference risk model will be easily updated whenever needed. This will be achieved developing specific interfaces between the different moduli.

A number of European irradiation and habitat facilities are being chosen to be the “Core” facilities in ERFNet to be used to support and experimentally validate novel radiation shielding design solutions. It is understood that the irradiation key facility is GSI (FAIR phase 0). GSI is already the only accelerator in Europe able to provide all the charged GCR components. When FAIR will be fully functional, it will provide ion beams up to 10 GeV/u. This feature will enable measurements for scenarios involving thick shielding (> 20 g/cm^2) when the main contribution to the effective dose comes from the more energetic fraction of the GCR spectra (E>1 GeV/u) [1].

Upgrades to exploit the irradiation facilities for space radiation shielding work are foreseen within ERFNet. This would include, for example, simulators for Galactic Cosmic Rays and for Solar Particle Events, tools and strategies to increase the usability for research works of the facility, focused agreements to exploit and optimize the use of the facilities for space exploration studies. An expansion of ERFNet covering also radiobiology studies is foreseen in the future.

For the habitat facilities, prototyping and material laboratories as well as virtual/augmented reality tools for improving users support in developing their novel ideas, are also included in the suggested upgrades.

ERFNet feasibility review is due in July 2019.

In this talk the status of the project and its major aims will be presented.

[1] T.C. Slaba, and S.R. Blattnig. "GCR environmental models I: Sensitivity analysis for GCR environments." Space Weather 12.4 (2014): 217-224.

Dosimetry concepts for space radiation research with high-energy ion beams

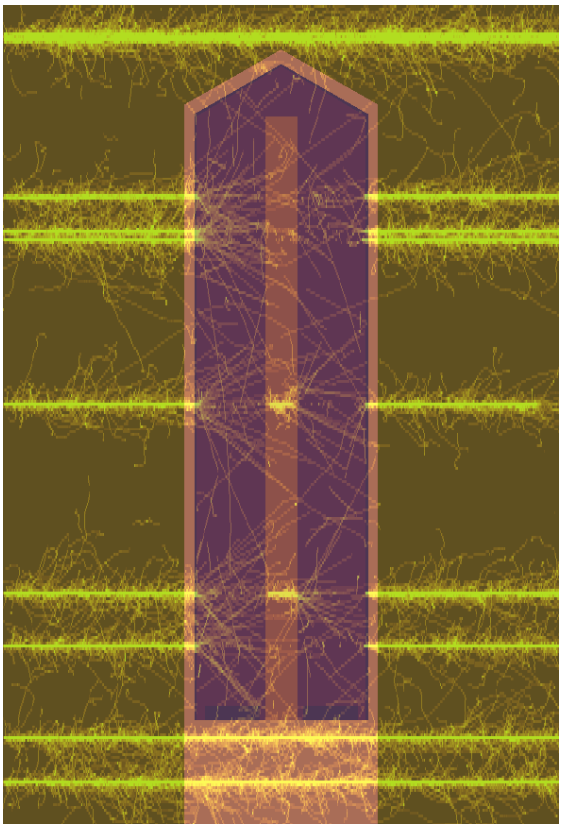
F. Horst[1,2], K. Baumann[2,3], D. Boscolo[1], M. Durante[1,4], F. Luoni[1,4], C. Schuy[1], U. Weber[1], K. Zink[2,3,5]
[1]GSI, Darmstadt, Germany; [2]THM, Gießen, Germany; [3]UKGM, Marburg, Germany; [4]TU Darmstadt, Germany; [5]FIAS, Frankfurt, Germany

A large part of the experiments that will be performed at the BIOMAT facility in the APPA cave at FAIR (e.g. radiobiology or shielding studies) will rely on a precise dosimetric characterization of its radiation fields, preferably in terms of absorbed dose to water. A variety of different beams (^{1}H-^{238}U ions with energies up to 10 GeV/u, intensities up to 5 x 10^{10} ions per spill) will be available from the SIS100 synchrotron and even the production of mixed radiation fields, e.g. simulated galactic cosmic radiation (GCR) fields, is intended. Under these conditions precise dosimetry is anything but an easy task.

Several aspects of the ionization chamber (IC) dosimetry concepts that were originally developed for scanned proton and ion-beam radiotherapy can be taken over, however, there might be the need to adapt and modify them to fit the conditions at BIOMAT.

The contribution will address different issues concerning dosimetry at BIOMAT whose investigation may improve the experimental conditions significantly.

Prior to an ion beam experiment the beam monitor (e.g. a parallel plate large area IC) needs to be calibrated: According to clinical dosimetry protocols [1] this should be done by measuring the absorbed dose to water at a low reference depth in the entrance plateau of the depth dose profile. However, the depth dose profiles of high-energy ion-beams as available at BIOMAT typically do not show such an entrance plateau due to electronic build-up and nuclear attenuation effects which makes a precise calibration quite challenging.



Also, the saturation characteristics of ICs at the very high beam intensities of the SIS100 should be studied.

Another important parameter for precise absorbed dose to water determination is the beam quality correction factor k_Q. This parameter corrects the dose reading for the different response of the IC in the operational radiation quality (e.g. heavy ions) compared to the calibration quality (typically ^{60}Co photons). Such beam quality correction factors are not well-known for heavy ions and in [1] the k_Q is considered to be identical for all ions with Z>2. However, preliminary results from Monte Carlo calculations using the FLUKA code [2] (see Figure 1) show a deviation of a few percent between the k_Q for 430 MeV/u ^{12}C ions and the k_Q for 1 GeV/u ^{56}Fe ions. If such effects are not considered when performing heavy ion experiments they might directly translate into dosimetric errors. Therefore it is worth to investigate in detail theoretically and experimentally how typical ionization chamber models behave in the exotic beam qualities that will be available at BIOMAT.

On the basis of detailed investigations into these topics, flexible and robust measurement concepts as well as a dosimetry workflow for high-energy ion beam experiments can be worked out.

Figure 1: Monte Carlo simulation of delta electron tracks produced by 1 GeV/u ^{56}Fe ions penetrating through a PTW Farmer 30013 ionization chamber placed in a monitor calibration phantom made of water equivalent plastic.

[1] "Absorbed Dose Determination in External Beam Radiotherapy: An International Code of Practice for Dosimetry based on Standards of Absorbed Dose to Water" IAEA TRS-398 (2000).

[2] "FLUKA: a multi-particle transport code" A. Ferrari et al. CERN-2005-10 (2005).

Space-TRiP: From Ion Beam Radiotherapy to Space Radiation Research

A. Topi[1], M. Durante[1,2] and M. Krämer [1]
[1] GSI, Darmstadt, Germany;
[2] TU Darmstadt, Darmstadt, Germany;

The increased interest in space exploration raises the need for extensive studies of health risks from space radiation. In contrast to the radiation experienced on earth where the main contributors to equivalent dose are γ rays and α particles. Space radiation is dominated by particles of high energy and charge [1]. For this kind of radiation serious uncertainties of radiation health risk estimation exist and difficulties in finding good strategies for shielding. This state of affairs is not uncommon to the situation before the start of the ^{12}C radiotherapy pilot project at GSI. Therefore, we are in the process of transforming the calculation energies of the TRiP98 treatment planning system (TPS) to space radiation applications. We think this will enable fast prototyping for dose reduction calculations, complementary to the usual MC methods.

The first study will be performed for energies in the range of ion beam radiotherapy. Previous experiments with space shielding material [2] have shown that the TRiP98 transport model can successfully be used for this kind of evaluation. The comparisons showed, however, that improvements in the yields of light fragments are necessary to model the measured dose reduction. Therefore, we are planning to perform two different approaches: collection of experimental cross section data from existing literature and the implementation of empirical correction in the current model [3] of the code for the energy and fragments of interest.

A second study will be performed for primary energies in the interval from 1 to 10 GeV/u. At this point the simulation will be tested against MC approaches and possible experiments. After evaluation of the nuclear models and the empirical correction, our focus will be the adaptation of the voxel computed tomography (CT) image to the voxelization of space vessels for dose calculation.

Lastly, the ability to predict biological endpoints will be another design point. This is natural, since the TRiP98 code was designed as an ion beam TPS including biological effects. A built-in estimation of the risk will be added in the Space-TRiP code to allow the calculation of interest in space radiation.

[1] M. Durante and F. A. Cucinota, Rev. Mod. Phys. 83, 2011, p. 1245.

[2] M. Krämer, E. Scifoni, M. Giraudo, and M. Durante, GSI-FAIR Scientific report, 2017, p.189.

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FAIR for Space Radiation Research

C.E. Hellweg[1], C. Baumstark-Khan[1], T. Berger[1], R. Hemmersbach[2], C. Liemersdorf[2] and R. Möller[1]
[1]Division of Radiation Biology, Institute of Aerospace Medicine, German Aerospace Center (DLR), Linder Höhe, 51147 Köln, Germany, christine.hellweg@dlr.de; [2]Division of Gravitational Biology, Institute of Aerospace Medicine, DLR, Linder Höhe, 51147 Köln, Germany

The exposure to the space radiation environment remains a major limiting factor for human long-duration space missions due to its high biological effectiveness and the difficulties to effectively shield the radiation. The next decade in human spaceflight will be characterized by a continuous presence of human beings in Low Earth Orbit (LEO), by their return to the Moon and by longer stays in a Moon orbit on the Lunar Orbital Platform - Gateway (LOP-G). These endeavours are also performed to prepare for a human Mars mission.

To support and enable these missions, ongoing improvement of radiation dosimetry for accurate and continuous monitoring and the development of shielding approaches including personal shielding equipment are necessary. Such equipment should be tested using very high energy heavy ions. An ideal setting would be the combination of several beams, e.g. protons, alpha-particles and one or more heavy ions. Furthermore, experiments with human phantoms can contribute to risk assessment.

In the last decades, the cancer risk induced by exposure to galactic cosmic rays was in the focus of attention. Numerous animal experiments and mechanistic studies were performed to derive the relative biological effectiveness of heavy ions to induce cancer and to elucidate the mechanisms and patterns specific to heavy ions. Radiation quality factors and dose-rate modifying factors based on these results were integrated into a model to estimate space radiation cancer risk (NASA Space Cancer Risk (NSCR) model) [1].

Now, target organs for degenerative effects induced by galactic cosmic rays, especially the brain, the cardiovascular system and the eye lens, are in the focus of the radiobiological research. A suspected cognitive decline by chronic exposure to galactic cosmic rays has achieved some celebrity as “Space Brain”. The role of neurons, glia cells including astrocytes, oligodendrocytes and microglia remain to be elucidated – even sex-specific differences in the involvement of microglia have to be considered [2]. Experiments with accelerated heavy ions will help to elucidate the mechanisms of the degenerative effects of space radiation and will set the foundation to develop countermeasures. Here, besides the combination of beams to simulate better the radiation field in space, low dose rate experiments are of high interest.

Besides the chronic space radiation exposure, astronauts experience a quite unique combination of possibly health-deteriorating environmental factors such as microgravity, noise, smell, disturbed circadian rhythm, increased carbon dioxide concentrations and decreased sleep quality. The interaction of radiation exposure with these space environmental factors such as microgravity or changes in the atmospheric conditions might influence the cells’ capability to cope with radiation damage. Therefore, settings at FAIR allowing simultaneous exposure to simulated microgravity on a clinostat or control of atmospheric conditions will enable the investigation of combined effects.

Finally, it has to be considered that humans are not only composed of their body cells that can be affected by heavy ion hits, but they also carry a microbiome inside and at the surface that quickly colonizes the surroundings, also spacecraft. The knowledge on how the human-microbiome and microbiome-environment interactions change under chronic space radiation exposure is very scarce and interesting model systems could be investigated at FAIR.

In conclusion, FAIR can smooth the way to Mars.

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Astrobiology studies with the ESA detailed Mars Energetic Radiation Environment Model and GSI data

Patrícia Gonçalves[1]
[1]LIP, Lisboa, Portugal

In the past 15 years, an area of research and development focused on the study of the radiation environment in space and its effects was created and consolidated in Portugal, in line with the ESA roadmap for this area [1]. The competences developed in this field encompass all the technologies identified by ESA on its Harmonised roadmap in this area are grouped under four major themes, listed below, within all of which several activities have been developed in Portugal, with LIP being a national academic reference in these areas.

1. Environment analysis & Modelling;
2. Radiation Effects Analysis tools;
3. Radiation measurement;
4. Radiation Hardness Assurance.

LIP has worked in all these areas being an international reference in the simulation of detectors and radiation monitors for space using GEANT4 and in the modelling of the radiation environment on Mars.

LIP developed the detailed Mars Energetic Radiation Environment Model, dMEREM, [2] [3] is a model for the ionizing radiation environment characterization models based on Geant4 [4] Monte Carlo applications that have been developed for the European Space Agency. These models enable the interface between the Monte Carlo radiation transport applications and Martian surface composition, atmospheric databases (European Mars Climate database and MarsGRAM). dMEREM is interfaced with a soil composition database based on Gamma Ray Spectrometer Mars Odyssey data (https://grs.lpl.arizona.edu/home.jsp) . Additionally, dMEREM allows the consideration of magnetic field models. Results have shown that the most important parameters that contribute to different dose levels at the surface or in soil depth profiles are: the presence of water in the form of surface oceans or sub-surface lakes or hydrated mineral; the weight percentage of Fe, and dry ice [2] [3].

The study of Mars' radiation environment and exploitation of the possibility of life under such conditions can be a direct application of the detailed Martian Environment Model, especially if complemented with data from experiments with microbiological species when exposed to different radiation fields corresponding to varying radiation of low and high LET radiation, and using shielding materials matching a set of chosen Martian soil composition scenarios.

We propose to use GSI test data to build an effective model for the biological effects of the Martian radiation environment at locations on the surface and subsurface of Mars, based on the dMEREM model framework.

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Radiation for Space Experiment IceCold

E. Rabbow[1], P. Rettberg[1], and the FAIR@GSI division[2]
[1]DLR, Institute of Aerospace Medicine, D-51061 Cologne, Germany. [2]1st International Biophysics Collaboration Meeting (IBCM-1) Marko Durante, GSI, Darmstadt, Germany;

Recently, evidence of the presence of liquid water in the outer Solar System, in particular in form subsurface cold oceans of Europa and Enceladus, increases the expectation of potentially habitable environments outside Earth. The ESA ILSRA-2014 selected space experiment IceCold planned to be implemented on the EXPO platform on Bartolomeo outside ISS investigates the effect of the space environment as available in LEO on organisms that are derived from environments on Earth that are in some aspects analogue to the icy moon environments. Representatives of the three domains of life adapted to low temperature and high salt media will be grown in LEO, exposed to extraterrestrial solar UV radiation and GCR. The candidate organisms are:

- the archaea *Halorubrum lacusprofundi* isolated from Deep Lake, Antarctica,
- the bacterium *Rhodococcus* JG-3, isolated from the McMurdo Dry Valley
- the eukaryote *Rhodotorula* JG-1b, isolated from the McMurdo Dry Valley

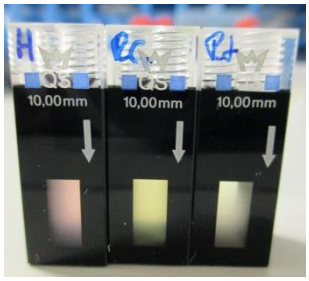
completed by the three reference organisms *Bacillus subtilis*, *Deinococcus radiodurans* or *geothermalis* and *Halobacterium salinarum*.

The microorganisms will be cultured for up to 6 months in LEO in high salt growth media (except for B. subtilis and Deinococcus) simulating the subsurface Icy moon ocean.

LEO GCR is expected to be too low to inactivate microorganisms in this timeframe, but the growth behavior of active may be altered. Proliferation of the cultures will be monitored by regularly repeated automated measurements of the optical density of each culture. In addition, the effect on cultures irradiated with LEO short wavelength UV will be monitored.

At the end of the exposure experiment, the cultures will be returned to ground fixed and/or cooled for further analysis.

Mission parallel ground experiments utilizing x-ray to simulate the GCR will be performed.



Additional experiments performed on ground before, during and after the space experiment will be performed to investigate the individual effect of temperature oscillation, the UV irradiation and the x-ray irradiation on the growth behavior.

The opportunity to perform complementing experiments at the GSI utilizing the cosmic ray simulations, in particular when more than one ion will be available, with the same samples as those exposed in the space experiment, will be extremely beneficial for our understanding of the radiation effect on microorganisms and strongly increase the scientific output in general.

F*igure 1: Cultures of H. lacusprofundi, Rhodococcus and Rhodotorula (left to right)*

Unlike in the space experiment, these ground control experiments allow investigation of a higher number of samples of growing cultures, but also of metabolically inactive states of the microorganisms as additional references.

Active experiments with in situ analysis methods like IceCold as well as passive vacuum and radiation exposure experiments are also currently proposed for the new LOP lunar Gateway missions to investigate the effect of the complex radiation environment in the vicinity of the Moon. Here, complementing radiation exposure experiments utilizing radiation sources like those available at GSI will become even more important for understanding radiation effects as measured in space and for radiation risk assessment.

Space radiation and immune system – a FAIR connection

A. Maier[1], C.Schuy[1], Ulrich Weber[1], C. Fournier[1], G. Kraft[1]
[1]GSI, Darmstadt, Germany

During and after space flights, dysregulations of the immune system may represent a serious health risk, which is most relevant for future long-duration missions to the Moon or the Mars [1]. Recent results from the GREWIS project suggest that total body exposure to low dose irradiation of a few µGy has a significant impact on the immune system [2]. These studies are focused on the influence of radon exposure, where sparsely ionizing radiation as well as densely ionizing radiation occur in a mixed radiation field, which might be comparable in its complexity to the radiation fields of cosmic exposure.

In space, the main contribution of the radiation exposure comes from galactic cosmic rays, which originate outside the Solar System and impinge isotropically on Earth. This so-called galactic cosmic radiation (GCR) consists mainly of high-energy particles from protons up to iron. Additionally, for the scenario of manned spaceflight, secondary radiation is produced in nuclear interactions between impinging particles and the hull of the spacecraft or the human body. Combined, the different radiation qualities of high and low energy and different particle species sum up to a dose of typically 1 mSv/day in low earth orbit (LEO) [3]. For shielding material, additionally to the hull of the spacecraft, polyethylene was preferably selected for use aboard the ISS and is used especially in the crew quarters of the astronauts [4].

In our proposed experiments, we want to investigate the influence of low dose irradiation by a mixed radiation field and broad energy spectrum on the immune system of biological samples. In a first step of this very ambitious experiments we want to focus on the installation of the set up and the modulation of the radiation field For this purpose, we intend to use a heavy ion beam (e.g ^{56}Fe) of high energy (or several successively different energies) in combination with special passive energy modulators in order to simulate a GCR radiation field as seen inside a spacecraft behind different shielding materials [5]. After this beam modulator, the actual samples including biological material can be placed.

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Combined Effect of Space Radiation and Microgravity on Human Body

D. Leonhäuser[1], K. Shreder[1], J. Hauslage[2], M. Durante[1], R. Hemmersbach[2], C. Fournier[1]
[1]GSI, Darmstadt, Germany; [2]DLR, Institut für Luft- und Raumfahrtmedizin, Köln, Germany

Manned human space flight implies a lot of complex challenges, especially for the long-term missions to Moon and Mars. Therefore, investigations of major risks for astronauts, i.e. radiation and gravity loss, are necessary to overcome the uncertainties of risk estimation.

Space radiation, i.e. high energy particles (HZE particles), is expected to cause biological damage on the level of DNA, potentially leading to increased cancer risk, injury of the central nervous system and malfunctions of the immune system [1]. Furthermore, the change of gravity induces loss of bone and muscle substance leading to the known long-term effects osteoporosis and -related fractures, swelling and high blood pressure [2]. With increasing duration of stay in the orbit, malignancies like cancer, and leukemia in particular, could occur with a higher incidence compared to the population. Therefore it is useful to understand the impact of combined exposure to HZE particles and microgravity, especially in cells of the bones and the bone marrow, which is the niche of hematopoietic cells. This could be based on our long standing experience in investigating DNA and chromosomal rearrangements as well as the underlying mechanisms of repair with influence on the genetic stability of the hematopoietic precursor cells for leukemia (HSPC [3,4]).

The use of ground-based simulators of microgravity enables space flight experiments in the lab. In a collaborative work, we have established the use of a 2D clinostat for HZE exposure of hematopoietic cells to simulated microgravity. Finally, the GSI-FAIR accelerator offers ideal conditions concerning the simulation of cosmic radiation and in particular the galactic cosmic radiation (GCR) [5]. First experiments with hematopoietic cells at the GSI accelerator in combination with a clinostat are undergoing.

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New Therapy Approaches

Therapy with different Ions: Clinical perspectives

J. Debus[1,2], A. Jensen[1,2], S. Adeberg[1,2], S. Harrabi[1,2], L. König[1,2], M. Uhl[1,2], A. Mairani[1,2] and K. Herfarth[1,2]

[1]Dept. of Radiation Oncology and Heidelberg Ionbeam Therapy Center (HIT), Heidelberg University Hospital, Germany

[2]Heidelberg Institute of RadioOncology (HIRO), Heidelberg University Hospital, Germany

Heidelberg University has treated 440 patients with carbon ions from 1997 to 2008 in Darmstadt at the German Society of heavy Ions (GSI) which led to the foundation of the Heidelberg Ion-Beam Therapy Center (HIT). Since HIT started its operation in 2009 over 5000 patients have been treated at HIT with carbon ions and protons and nineteen clinical trials have been started since.

Long-term data on effect of carbon ion beam therapy has been published for skull-base chordoma, chondrosarcoma and adenoid cystic carcinoma of the salivary gland (ACC). 10-years follow-up data of patients with ACC treated with carbon ion boost revealed high local control (LC) rates translating into improved overall survival (OS) with favorable acute and late toxicity profile (Schulz-Ertner et al. IJROB 2007 and Jensen et al. Cancer 2015). These data established a basis for definitive carbon ion / IMRT concepts in ACC. Given that in-field recurrences remain the major pattern of therapy failure in this disease, to further improve outcome, a randomized prospective dose-escalation trial with carbon ions only (ACCO trial) has been initiated. In area of skull-base chordoma and chondrosarcomas, 10-year follow-up data of two comprehensive studies were published demonstrating excellent LC rates an OS after carbon ion radiotherapy (Uhl et al. Radiat Oncol, 2014 and Uhl et al. Cancer, 2014). It could be emphasized that so far, no secondary malignancies were observed after carbon ion therapy in patients with craniofacial tumours. Currently, two phase III prospective randomized trials compare protons and carbon ions for chordoma and chondrosarcoma of the skull-base.

Results from plan comparisons in patients with mediastinal lymphoma showed remarkable reduction of OAR doses e.g. heart and breast (55%and 93%) of proton therapy compared to photon IMRT. In both high grade and low grade gliomas plan comparisons showed essential dose reduction, in particular for contralaterally located critical neuronal structures, areas of neurogenesis, and structures of neurocognitive functions while maintaining equal target volume coverage using protons.

Other ongoing trials address the possible different effect of the RBEs of protons and carbon ions will be briefly discussed, but will take years for final conclusions. Studies comparing different beam modalities include clinical trials and plan comparisons. The latter that showed e.g. superiority in OAR sparing of protons over photos in lymphoma, high grade and low grade glioma thus demonstrating the potential of this technique for minimizing long-term sequelae (e.g. secondary malignancies). These findings were confirmed by our preliminary clinical results suggesting a further broadening of indications for ions.

The emerging evidence from Monte Carlo based plan comparison studies suggest that Helium ion beams may provide a similar PTV coverage as protons but more favourable OAR sparing, which has been investigated in meningioma patients (Tessonnier, Mairani et al. 2018). More studies to investigate the clinical potential of helium ions for different tumour entities are needed and currently ongoing at HIT.

Future trials at HIT will include neo-adjuvant irradiation of retroperitoneal soft tissue sarcoma with ions (RETRO-ION) and neoadjuvant irradiation of extremity soft tissue sarcoma with ions (EXTREM-ION). Furthermore, long term effects of particle therapy will be systematically investigated.

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Minibeam Therapy with Protons and Light Ions

J. Eley[1], C. Haga[2], D. Leiser[2], J. Waddell[2], A. Keller[2], A. Zodda[2], A. Rusek[3], C. La Tessa[4], S. Mossahebi[2], J. Snider[2], P. Poulsen[5], C. Raver[2], I. Jackson[2], Z. Vujaskovic[2], A. Dilmanian[6] and S.Krishnan[7]

[1]Vanderbilt University School of Medicine, Nashville, TN
[2]University of Maryland School of Medicine, Baltimore, MD
[3]Brookhaven National Laboratory, Upton, NY
[4]Università degli Studi di Trento, Trento, Italy
[5]Aarhus University Hospital, Aarhus, Denmark
[6]Health Sciences Center, Stony Brook University, Stony Brook, NY
[7]MD Anderson Cancer Center, Houston, TX

Minibeam therapy with protons and light-ions offers the theoretical potential to reduce neurologic side effects of particle therapy for brain cancer patients. The arrays of submillimeter beams include unirradiated gaps, which may spare endothelial and glial progenitors that are able to repair the patterned radiation damage. In this work, we compared neurologic toxicity in Long Evans rats after minibeam therapy using 100 MeV protons and 120 MeV/u lithium-7 ions against that of solid-beam therapy, using single-fraction, partial-brain exposures of 20 Gy and 40 Gy (integral doses). Planar-parallel minibeams were produced using a tungsten collimator having 300-micron planar slits spaced 1-mm apart on center. At 2 weeks after irradiation, skin damage was significantly lower for rats exposed to minibeams compared to those exposed to solid beams. Behavioral testing indicated cognitive impairment for both minibeam and solid-beam treatment groups. Immunohistochemistry stains revealed patterned bands of GFAP labeling in minibeam rats versus diffuse regions of GFAP labeling in solid-beam rats. NeuN staining suggested a decreased density of neurons confined within the minibeam irradiated regions. Our histologic findings point to consistent differences between minibeam therapy and solid-beam therapy, in line with a glial-sparing hypothesis for minibeam therapy; however, cognitive impairments were apparent after both types of radiation, and it remains unclear which radiation method provides less damage to functional neural circuits.

High energy ion beams for spatially fractionated radiation therapy (SFRT)

C. Guardiola[1] and Y. Prezado[1]
[1]IMNC, CNRS, Campus d'Orsay, France.

Spatially fractionation of the dose, such as in minibeam radiation therapy (MBRT), has already proven its capacity to preserve normal tissues [1,2]. SFRT has been mainly explored using photons, such at LINAC-based Grid therapy [3] or synchrotron micro and minibeam radiation therapy [1,2,4].

However, SFRT may be further improved by partnering its benefits with the advantages of charged particles for therapy [5-9]. Recently, proton minibeam radiation therapy (clinical beams) has demonstrated a net gain in normal tissue sparing [6] while leading to equivalent or superior tumour control than standard seamless irradiations [10,11]. Those results were obtained even in cases where highly heterogeneous dose distributions were delivered. Concerning heavier ions, Monte Carlo simulations have shown favourable dose distributions for normal tissue sparing in SFRT, with very high peak-to-valley dose ratios (PVDR) and minimal contribution of high LET nuclear fragments to the valley regions, responsibles of normal tissue sparing [8,9]. A step further in charged particle SFRT could be to increase the beam energy up to 1 GeV/A [5], possibility that will be available at FAIR. That would reduce multiple coulomb scattering, allowing the use of narrower beams, while keeping a good ratio between dose deposited in the trajectory of the primary beam and scattered dose. In addition, it would enable a theragnostics use, as the exiting beam could be employed for imaging purposes.

Our recent Monte Carlo calculations have shown favourable dose distributions for high energy (1 GeV/A) protons, carbon and neon ions. Extremely high PVDR (>100), very low valley doses and favourable entrance to peak dose ratio were obtained. In addition, this allows the use micrometric beams (< 100 µm), contrary to clinical beams. The combination of high energy and intense beams at FAIR might allow to exploit the synergies between SFRT and FLASH therapy [12].

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A Preclinical Small Animal Irradiation Facility for Proton Minibeam Therapy

G. Dollinger, G. Datzmann, M. Sammer, M. Mayerhofer, R. Berti, J. Reindl

Universität der Bundeswehr München, Neubiberg, Germany

Proton minibeam radiotherapy using sub-millimeter beams in a spot scanning approach allows to enhance tissue sparing in the entrance channel by spatial fractionation compared to conventional proton therapy. The advantage of enhanced tissue sparing when applying 20 MeV proton minibeams has already been shown experimentally in a mouse ear model [1]. Dose simulations of proton minibeam therapy utilizing higher energies show that tumor control can be maintained via homogeneous irradiation of the tumor as in conventional proton therapy. The homogeneous dose distribution is obtained due to lateral beam straggling when optimizing the minibeam distances [2] (see fig. 1).

Higher energy proton beams coming from existing proton therapy facilities (cyclotrons or synchrotrons) are not well suited to generate pencil minibeams with beam diameters of about 0.1 mm providing sufficient beam currents (nA) to the isocenter due to low beam brightness. Recently developed RF Linear accelerators (Linac) dedicated to serve protons for therapy purposes show much lower transversal phase space and thus have the potential to generate focused pencil proton minibeams.

In order to further validate the potential of proton minibeam therapy it is planned to build a dedicated preclinical facility and to investigate the technical and clinical challenges of proton minibeam therapy in detail. We suggest to install a post-accelerator based on 3 GHz LINAC technology at a large tandem accelerator. This combination provides a high brightness proton beam that can be focused to a 0.1 mm spot size for preclinical experiments. In a first stage, LINAC structures will deliver a proton beam of up to 70 MeV for small animal experiments that can be extended in future upgrades to 150 MeV or even more.

We propose to integrate this system into a new center of competence for ion beams in materials research and medicine (KIMM). KIMM features unique instruments for research in the fields of radiotherapy, radiation protection and biology, materials science, astro- and environmental physics as well as for applications in industry. The small animal irradiation platform will be a flagship project of KIMM.

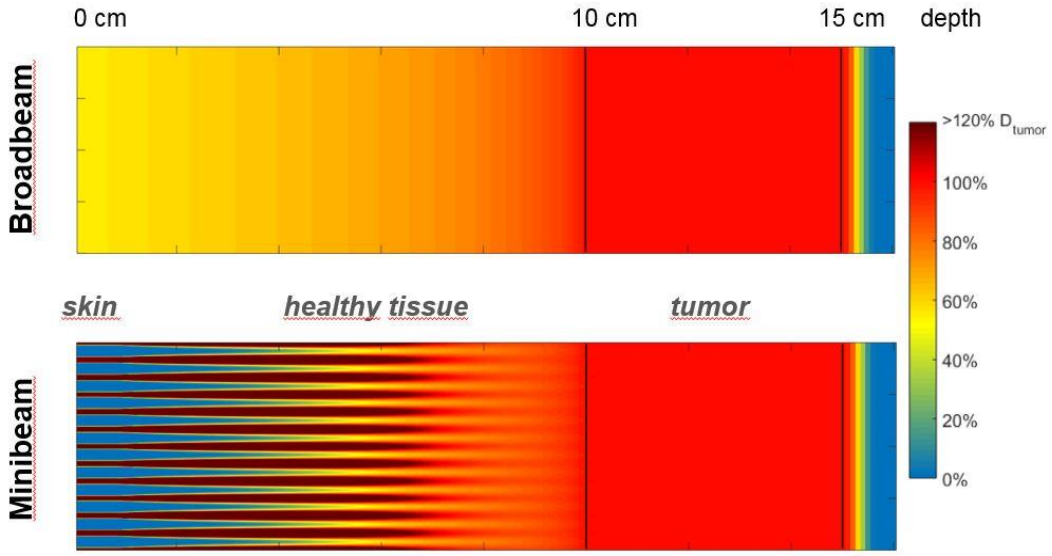

Fig. 1: Comparison of dose distributions simulated for proton broad beam (upper part) and proton minibeam (lower part) irradiation of a 5 cm thick tumor located 10 cm underneath the skin.

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Back to the Future of Antiproton Dosimetry and Radiobiology

N. Bassler[1,2,3]
[1]Medical Radiation Physics, Dept. of Physics, Stockholm University, Stockholm, Sweden
[2]Department of Oncology and Pathology, Medical Radiation Physics, Karolinska Institutet, Stockholm, Sweden
[3]Dept. of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

During 2003 - 2013 the AD-4/ACE experiment at CERN investigated the radiobiological properties of antiproton beams in order to elucidate its potential for cancer therapy.

Compared to proton beams, antiproton beams offer an increased physical dose deposition at the Bragg-peak due to the annihilation products. Also, the anticipated increase in the relative biological effectiveness was experimentally quantified in vitro using V79 cell lines [1,2].

The experiments were complicated by several dosimetric and radiobiological challenges. The secondary particle spectrum in the antiproton beam is a broad mixture of mostly secondary protons, pions and neutrons. Solid state and chemical dosimeters exhibit quenching in the mixed particle beams, and the validity of cavity theory for ionization chambers can be questioned. Various types of thermoluminescent detectors, Alanine [3] and film dosimeters have been applied in the antiproton beam as well as air- and liquid filled ionization chambers.

The RBE estimations for antiproton beams may be improved when a more intense antiproton beam becomes available, possibly at FAIR. Here, an overview of the dosimetry work of the AD-4/ACE collaboration will be given and the pro's and con's of the antiproton therapy idea will be discussed. In particular, thoughts on how antiproton research still can provide new insight in dosimetry and radiobiology relevant for ion therapy will be emphasized.

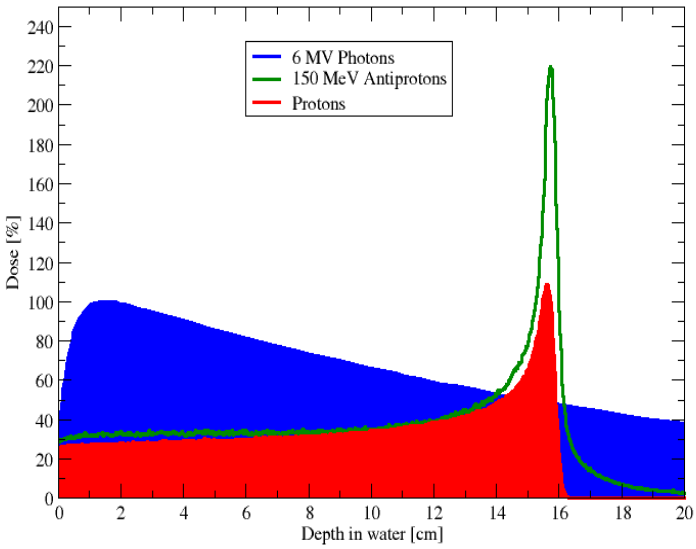

Figure 1: Simulated antiproton depth-dose curve in water, compared to proton and photon beams.

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A Simulated Investigation on the Comparison of Proton, Antiproton and Carbon Ion in Radiotherapy

D. Liu[1,2], and J.-K. Woo[3]

[1]BK21plus Clean Energy Convergence and Integration Center for Human Resources Training and Education, Jeju National University, Jeju 63243, South Korea

[2]Beam Irradiation System (BIS)/Rare Isotope Accelerator complex for ON-line experiments (RAON) of Rare Isotope Science Project (RISP), Institute for Basic Science (IBS), South Korea

[3]Physics Department, Jeju National University, Jeju 63243, South Korea

Proton and carbon ion therapy are the two main particle therapy methods that have been widely used. In addition, the antiproton beam is proposed as a kind of radiotherapy methods. In this investigation, based on the Monte Carlo method, the physical dose distributions in target volume and surrounding interested volumes for proton beam, antiproton beam and carbon ion beam are calculated and evaluated. For simulation, the various beams are assigned to pristine beam, single field beam and two opposite field beams. The calculation results showed that the antiproton beam has the potential advantage to reduce the dose deposition in the proximal region. However, carbon ion still shows a most ideal dose distribution in general. In the future, in addition to physical dose, the biological dose of various beams and the analysis of induced secondary particles of three beams will be considered beside of physical dose.

Towards Proton-Boron Capture Therapy

L. Manti[1], G.A.P Cirrone[2], D. Margarone[3], P. Blaha[1], F.P. Cammarata[4], C. Feoli[1],G.I. Forte[4], G. Petringa[2], G. Russo[3] and G. Cuttone[2]

[1]Physics Dept., University of Naples Federico II & INFN, Naples Section, Naples, Italy; [2]INFN-LNS, Catania, Italy;[3] ELI-Beamline Project, Inst. Physics, ASCR, PALS Center, Prague, Czech Republic; [4]CNR, Institute of Molecular Bioimaging and Physiology, Cefalù (Palermo) & INFN-LNS, Catania, Italy.

We provided the first experimental proof of the idea proposed by Yoon et al. [1] to use the nuclear fusion reaction $^{11}B(p,\alpha)2\alpha$ to enhance clinical proton biological effectiveness. Irradiation of prostate DU145 cancer cells at mid-SOBP of the 62 MeV CATANA (Centro di AdroTerapia ed Applicazioni Nucleari Avanzate) in the presence of sodium borocaptate or BSH ($NA_2B_{12}H_{11}SH$) resulted in an increase of clonogenic cell death, with a dose-modifying factor of over 1.4 at 10% survival level [2]. Moreover, chromosome aberration analysis showed a greater proportion of complex-type aberrations in proton-irradiated normal human MCF-10A cells treated with BSH, thus pointing to a role of high-LET radiation in mediating the observed radiosensitizing effect. Proton-Boron Capture Therapy (PBCT) may therefore represent an innovative, physics-driven approach to increase the ability by protontherapy to locally control hitherto untreated radioresistant cancers, while maintaining its advantageous sparing of normal tissue and organs at risk.

In fact, FLASH radiotherapy (FLASH-RT) modalities, where ultrahigh dose-rate low-LET radiation appears to increase the therapeutic window by a greater-than-usual differential effect between normal tissue and tumour [3], are attracting increasing attention [4], with recent in-vivo data corroborating initial findings [5]; the possibility of using proton beams has also been put forward in this context [6].

Here we propose to exploit the unprecedented physical proprieties of the beams accelerated conventionally at facilities such as FAIR [7] or by laser-matter interaction at the ELIMAIA beamline [8] to combine the promising results by FLASH-RT with those from the PBCT: such highly pulsed, ultrahigh dose-rate proton beams may grant normal tissue an even greater sparing effect than that currently reported while, if previous results were confirmed under these unparalleled regimes, the proton-boron fusion reaction may elicit a significant increase in cancer radiotoxicity, paving the way to novel, clinically sound hypofractionated protontherapy scenarios. Preliminary in-vitro studies will be performed using normal cells and pancreatic cancer cells [9]. A number of radiobiologically suitable endpoints, encompassing cell death, premature cellular senescence, DNA damage, secreted cytokine profiling and gene expression, are envisaged prior to clinical translation studies.

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Radiosensitizating effect of Gadolinium oxide-based nanoparticles on NSCLC cells under low and high LET irradiation

W. Chen
Institute of Modern Physics, Lanzhou, China

Gadolinium oxide-based nanoparticles (GBNPs) have been used as theranostic sensitizers in clinical radiotherapy study. In this study, folic acid-conjugated albumin encapsulated GBNPs were employed to investigate their radiosensitizing effect in NSCLC cells. GBNPs caused hydroxyl radical production and oxidative stress in a dose- and concentration- dependent manner in NSCLC cells after low- and high- LET irradiation. The radiation enhancements of GBNPs reached 26.3% for the NSCLC cells under investigation at 10% survival level compared with irradiation alone. This study unraveled the biomechanisms underlying the radiosensitizing effect of GBNPs on NSCLC cells and presented the first evidence for GBNPs radiosensitization via activating the cytostatic autophagy pathway after low-LET irradiation.

High Z nanoparticles as radioenhancers for different radiation qualities

M.Fuß[1], D. Boscolo[1], M. Durante[1], E. Scifoni[2] and M. Krämer[1]
[1]GSI, Darmstadt, Germany; [2]TIFPA, Trento, Italy

A large interest has been recently attracted by the possibility of using high-Z nanoparticles (NPs) for localized radiation enhancement in radiotherapeutic applications. The basic physical advantage of those heavy atom materials is due to in the much higher interaction probability and thus an increased emission of secondary radiation that deposits an additional dose locally. Depending on the primary radiation type and energy range, different mechanisms prevail, leading to different spectra of secondaries and therefore different direct enhancement effects. These are subsequently expected to translate into distinct radiation chemistry and biological endpoints in living cells and organisms.

The GSI Monte Carlo code TRAX has been used for extensive calculations of the physical dose enhancement [1] and chemical enhancement (radical production) [2] which charactarize the local effect produced by ion irradiation of gold NPs in an aqueous environment. In addition, experimental evidence on the OH· radical production in presence of Au NPs will be provided by a FAIR-phase-0 experiment to explore the existence of additional chemical enhancement effects, as suggested in [3], which are currently not understood and not included in state-of-the-art radiation chemistry models.

Since the radioenhancement with nanoparticles in ion beams has the disadvantage of a relatively low direct interaction probability between ions and NP for physiologically reasonable NP concentrations due to the low fluences required, other primary radiation types such as photons [4] and electrons are still to be considered as interesting alternatives. Other than heavy ions, electrons suffer a much larger relative energy loss when traversing a metal nanoparticle. This can lead to a very interesting change in beam quality, including an enhancement in interaction cross section and in radical production, which are both expected to significantly affect biological endpoints such as cell survival.

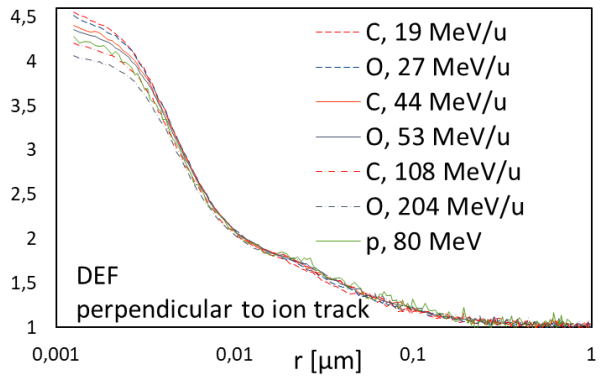

Figure 1: Radial dose enhancement factor (DEF) profile for a 1.2nm Au NP irradiated with different ions

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Research Programs

TREASURE (**T**raining **R**esearchers of south-**EAS**t e**UR**ope with **E**nlight for the Future)

Manjit Dosanjh, ENLIGHT and SEEIIST Collaboration, CERN, Switzerland

Cancer is a major societal issue worldwide and specifically in Europe, where over 3.7 million new cases per year were diagnosed for the EU in 2012. Currently about half of the patients diagnosed with cancer undergo radiation therapy (RT), and about 50% of all cured tumour patients have RT as part of their treatment. Consequently, improvements in RT could have a dramatic impact on patient survival, quality of life and economic costs. To achieve this goal, in recent years RT has considerably progressed with the development of new technologies and methodologies able to increase the conformity of the dose delivered to deep-seated tumours. There is a rapidly growing interest in use of heavy charged particles, i.e., protons and heavier ions such as carbon. This so called particle therapy (PT) as it can offer superior tumour-dose conformality with a reduced number of treatment fields compared to conventional radiation.

With this increasing interest in PT, training and capacitance building is a major focus in the coming years, as the growing number of facilities require more and more trained personnel. Hence the European Training Network **TREASURE** (**T**raining **R**esearchers of south-**EAS**t e**UR**ope with **E**nlight for the Future) will provide training for 15 Early-Stage Researchers (ESR) in the multidisciplinary field of PT by bringing together academic institutes, research centres, clinical facilities and European SMEs from 17 countries in Western and South Eastern Europe (SEE).

This multidisciplinary consortium TREASURE unites for the first time EU experts in the field of PT with scientists from the South Eastern Europe (SEE) countries to support them in their engagement to establish the first PT centre in SEE with the mission of high-level research and clinical treatment. To this end, the interdisciplinary research programme will address current challenges and foster innovative approaches in several key areas of PT, spanning from novel treatment planning, delivery through advanced dosimetry and image guidance up to optimization of therapeutic approaches and clinical trials. This will be pursued in several cutting-edge individual projects in the synergistic fields of medical physics, engineering, radiation biology and oncology.

The breadth of the multi-disciplinary research programme and diverse composition of the consortium will offer an ideal framework to facilitate sharing of knowledge for high-level training of the next generation of physicists, biologists, medical physicists, IT experts and software developers and clinicians for PT.

TREASURE is created in collaboration with ENLIGHT and it will be instrumental in creating a multidisciplinary community in SEE necessary for the foreseen South East European International Institute for Sustainable Technologies' (SEEIIST), a large-scale international facility with a state-of-the-art '*Facility for Tumour Therapy and Biomedical Research with Protons and Heavier Ions'.*

TREASURE has the following main objectives:

Objective 1: Training of 15 ESRs – the future generation of leading scientists who will comprise the substantial human potential for the emerging PT treatment/research centre for the SEE countries from highly prominent science and education EU institutions in innovative research projects in PT related topics (accelerators, radiobiology, detectors, dosimetry, simulations, big data management, etc.) The 15 dedicated research projects will be elaborated in detail in the Sections that follow.

Objective 2: Allow fast transfer of the advancements and innovations from the ESRs research in the PT to the clinical practice for the benefit of the patients, aiming at fostering the personalized therapy approach. The research efforts will be complemented by innovative pre-clinical research and in vivo translation of novel means of modulated energy particle beams with the so far unexplored molecules and cytostatic inhibitors.

Objective 3: Fostering the economic development of the SEE countries through the joint technological development and transfer of the innovative outcome to the industrial partners from the SEE.

Objective 4: Creating a durable and sustainable research network for the merits of the future research projects within the integral European Research Area.

Opportunities for Life-science research at the Dalton Cumbrian Facility (DCF)

F. Currell
University of Manchester, Manchester, UK

Whilst the accelerators at DCF can not achieve the energies typically associated with the delivery of particle therapy, they offer valuable opportunities for underpinning research, in terms of high beam currents, mixed ion beams and the opportunity for planned, longitudinal studies. Funding has been secured to procure the equipment relevant to performing biological assays. This talk will highlight these opportunities with a view to opening a dialog regarding the rote DCF can play in supporting the international biophysics community.

High-resolution dosimetry R&D at LIP for medical and space applications

J. M. Sampaio[1], A. L. Casimiro[1], J. Gentil[1], L. Peralta[1], P. Gonçalves[1]
[1]LIP – Laboratório de Instrumentação e Física Experimental de Partículas
Av. Prof. Gama Pinto 2, 1649-003 Lisboa, Portugal

LIP is the reference institution for experimental particle physics and associated technologies in Portugal. It was created in May 1986 to exploit the unique opportunities created by the country's accession to CERN. Currently the scientific activities of the LIP are very diverse and include a line of research and development of instrumentation and methods for the biomedical applications.

In this presentation, we will make a brief summary of the LIP projects related to dosimetry in medical applications and space radiation effects. These projects are:

Study of high-resolution dosimetry with scintillating fibres: Optical scintillating fibers exist with very small diameter, down to 125 μm. This project aims at developing a system based on 2D and 3D arrays of optical fibers coupled with a fast readout system that allows the characterization of radiation fields with sub-millimeter resolutions. To construct the response function of such system we are now starting to characterize the optical fibers in terms of light yields response, quenching and cross talk effects for protons in the Bragg peak energy region. In the future we would like to develop a system able to perform high-resolution dosimetry for ion therapy [1].

Development of a micro-dosimeter based on 3D silicon diodes: This project is being develop within a collaboration with the University of Santiago de Compostela, Spain. The goal is to produce and demonstrate a small portable radiation detector system, based in silicon 3D diodes [2], with radiation hard embedded electronics for readout and analysis, capable of determining in real time the relevant dosimetric and micro-dosimetric quantities needed to assess radiation induced biological effects of measured radiation.

Physics inputs for enhance ion therapy with nanoparticles: The addition of nanoparticles (NPs) to the tumor cells has been proposed as strategy to combine external ion beam and internal targeted radiotherapy to reduce the total dose to the patient. The effectiveness of NPs to improve the performance of ion therapy has been shown in several experiments [3]. However, current dosimetric studies using Monte Carlo simulations do not explain this enhancement [4]. This project uses new models to improve the physics and reduce the uncertainties underlying the response with NPs in particle therapy.

Radiation hazard assessment in manned missions in the solar system: This project aims at validating the Martian radiation environment model developed at LIP [5] using the RAD/MSL data [6]; establishing the ADE values for different scenarios of a manned mission to Mars taking into account the radiation sources at various stages of the voyage [7]; including the exposure to SEP events; determination of the organ equivalent doses and effective dose according to sex; and analysis of the radiation exposure minimization for different mission trajectories and shielding configurations [8].

Potential synergies with the Biophysics collaboration at the GSI/FAIR will be discussed.

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CNAO facilities for radiobiological experiments

A. Facoetti[1], *M.M. Necchi*[1], *M. Pullia*[1], *M. Donetti*[1], *S. Rossi*[1]
[1]Fondazione CNAO, Pavia, Italy

The National Centre for Oncological Hadrontherapy (CNAO) of Pavia has treated more than 2000 patients so far, two thirds of them with active scanning carbon beams.

Besides the clinical activity, CNAO mission is also addressed to research and in the last 3 years almost 500 hours of beam have been devoted to research in the fields of radiobiology, in the development of new detectors, in bioengineering, in dosimetry and in activities of interest to industries such as the study of the resistance of materials to radiation.

For scientists interested in gaining deeper insights into the radiobiological mechanisms of hadrontherapy, CNAO offers the opportunity to external researchers to use its proton and heavier ion beams to perform basic and pre-clinical studies and to take advantage of the cell culture lab for sample preparation and processing, together with its staff expertise to help them in planning, preparing and carrying out their experiments. In addition, there is also the possibility to exploit the experience and equipment of the labs present at the University of Pavia with which a strong collaboration is ongoing.

In the second half of 2019 a dedicated experimental room where research can be carried out without hindering the clinical activity will be accessible. In a second stage a third ion source will be added to the present two in order to carry on experiments with additional ion species besides the two used presently for treatments and the radiobiology facilities will be implemented.

Thanks to mentioned collaboration with the University, users wishing to carry out *in vivo* irradiations with small rodents can take advantage of the nearby animal house facility, after technical evaluation and approval by the local ethical committee.

Finally, highly motivated international MSc and PhD students can be tutored by qualified physicists, biologists and engineers for their thesis project.

Figure 1: CNAO cell culture Lab accessible to external users; in vitro and in vivo examples of irradiation set ups in CNAO.

Radiation biophysics research at iThemba LABS

C. Vandevoorde[1], S. Cairncross[1,2]; C. Cunningham[1,3], , E. de Kock[1], P. du Plessis[1], M. Engelbrecht[1,3], S. Nair[1,4], R. Ndimba[1], J. Nieto-Camero[1], X. Miles[1], N. Muller[1]

[1]NRF iThemba LABS, Nuclear Medicine Department, Somerset West, 7131, South Africa; [2]University of the Western Cape, Faculty of Natural Sciences, Bellville, 7535, South Africa; [3]Stellenbosh University, Faculty of Medical and Health Sciences, Cape Town, 7505, South Africa; [4]NECSA, Radiochemistry, Madibeng, 0240, South Africa

iThemba Laboratory for Accelerator Based Sciences (LABS) in South Africa is a multidisciplinary research facility that is based on the development, operation and use of particle accelerators and related research equipment. It is the leading facility for accelerator-based sciences on the African continent and the only facility of its kind in the southern hemisphere. Besides the production of radioisotopes, iThemba LABS provides the opportunity to perform research by using particle beams. One of these research areas is closely linked to medical applications and situated in the radiation biophysics division. By combining the expertise of the medical physics and radiation biology research groups, the overall goal of this research division is to explore the physical and biological interactions of different radiation qualities on a variety of biological systems. In addition, the division has a close collaboration with local universities in South Africa in order to train the new generation of researchers in critical skills areas such as radiation biology.

The multidisciplinary research in the division covers many different topics which can be summarized in the following categories:

- Particle therapy
- Targeted radionuclides
- Radiation protection
- Space research

The medical research directions tie in with state-of-the-art radiation therapy where personalised medicine is becoming a reality. Both charged particles and targeted radionuclides will play an important role in the future of precision radiation therapy. Since major breakthroughs in this field are expected from radiobiology research, the division is investigating complex functional end points to elicit the biological response signature of charged particles across the molecular and tissue level and the impact of combined treatment regimens. This research is also aligned with national research priorities by investigating the impact of HIV infection and ethnicity on the radiosensitivity of radiation therapy patients.

The division serves the broader community by offering a biodosimetry service and is continuously upgrading and improving its capacities as part of the radiation protection research projects. The unique neutron radiation modalities at iThemba LABS play an important role in these projects, since large uncertainties remain on the relative biological effectiveness of neutrons, particularly for low-dose an protracted exposures.

Recently, the division started the INVEST project, which aims to optimize and validate a unique ground-based in vitro model to study space health effects. The implementation of this ground-based model over the next three years will result in the first space laboratory for life sciences in Africa, which will form a basis for future collaborations and innovative research projects.

Radiobiological Research at Joint Institute for Nuclear Research

A.N. Bugai
Laboratory of Radiation Biology, Joint Institute for Nuclear Research, Dubna, Russia

Joint Institute for Nuclear Research (JINR) accelerators provide extensive capacity for multifaceted radiobiological research concerning basic problems of radiation genetics, molecular radiobiology, and radiation physiology, as well as a wide spectrum of practical issues.

Most of studies conducted at the Laboratory of Radiation Biology of the JINR are connected with the space radiobiology with special reference to manned interplanetary missions and the use of charged particles for the treatment of malignant tumors. Possible acute and delayed risks to the central nervous system are accepted now as the most concerning in these fields.

The action of heavy charged particles on the brain structures even with low doses causes marked disorders of spatial orientation and cognitive functions. Studying the neurophysiological effects of heavy particle radiations requires the conduction of multistage research ranging from genetic structure damage to higher behavioral functions. The first steps in this direction were already taken at the Laboratory of Radiation Biology, when rats and rhesus monkeys were irradiated by different sources at JINR accelerators: 170 MeV proton therapy beam of the Phasotron (the Laboratory of Nuclear Problems), 500 MeV/nucleon ^{12}C and 2.5 GeV/nucleon ^{87}Kr ion beams of the Nuclotron (the Laboratory of High Energy Physics). Before the experiment, the animals were trained to solve test problems at a computer. The aim of the experiments was to evaluate the disorders of the acquired skills caused by brain exposure to heavy charged particles.

Huge amount of experimental work has to be done at accelerators since there are a lot of unresolved issues concerning the understanding how heavy charged particles disturb the performance of the central nervous system after the cancer therapy or during the space flights. Certainly there is strong need of broad international collaboration in this field.

New Accelerators

The FAIR Accelerator

U. Weinrich
GSI, Darmstadt, Germany

The GSI accelerator complex

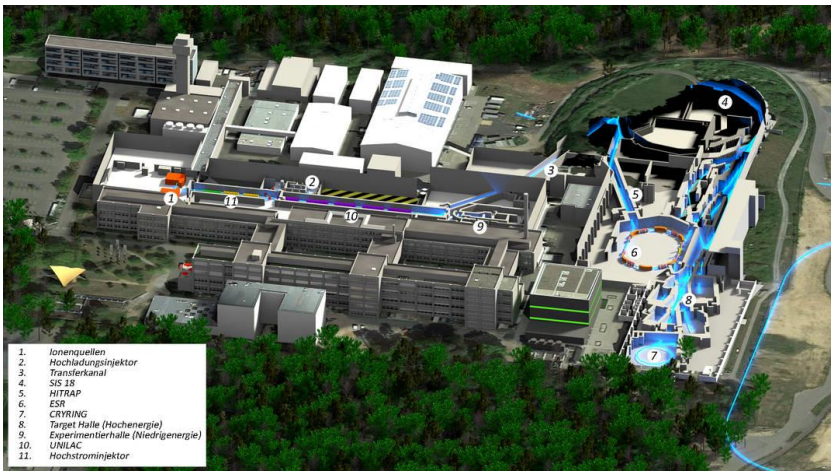

Figure 1: The GSI accelerator and experimental facility

The GSI accelerator and experimental facility is known for its capacity to provide a worldwide unmatched variety of different ion species for fixed target, fragment separation and storage ring experiments at different energy levels and with different timing structures. During the current FAIR Phase 0 the accelerator complex is regularly serving its user community. In addition refurbishment and upgrade measures take place in order to improve the operational reliability and availability and its beam performance for the service as FAIR injector.

The FAIR accelerator complex

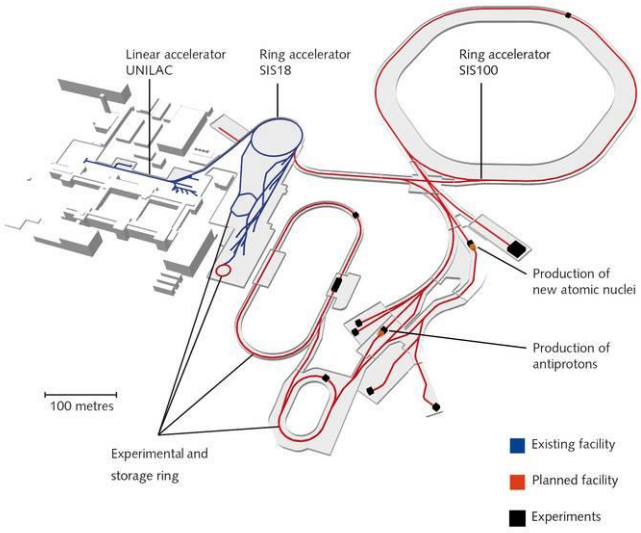

Figure 2: The modularised start version of FAIR

The new FAIR accelerators will essentially extend the potential of the accelerator complex to higher energies. In addition high intensity and high energy operation of protons will be added and used for antiproton generation, cooling and storage for storage ring experiments. The establishment of a reliable, flexible, high beam performance, high duty factor and parallel operation for two linacs, two synchrotrons, two fragment separators, four storage rings and a large amount of fixed target stations will be the major challenge for this facility.

On behalf of the GSI and FAIR accelerator team the actual and upcoming potential of the GSI/FAIR accelerator complex for providing ions and antiprotons will be described.

Status and Perspectives of Medical Accelerators

Th. Haberer[1,2],
[1]Heidelberg Ionbeam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital, Germany; [2]Institute of Applied Physics, Goethe-University, Frankfurt am Main, Germany

Today more than 70 proton therapy centres and 12 ionbeam therapy centers are in clinical operation [1, 2]. Proton systems typically are based on normal as well as superconducting cyclotrons or synchro-cyclotrons. The existing ionbeam therapy centers are solely synchroton-based. Some use carbon beams only, others offer proton as well as carbon beams for clinical use. Whereas about half of the proton centers are located in Northern America two ionbeam therapy clusters can be found: Central Europe and the Far East.

Dose delivery using passive beamspreading methods or active pencil beam scanning is implemented. A clear trend to using active beam scanning can be observed. Obviously this leads to more demanding requirements on the accelerator technology. One example for a clinical center based on active beam delivery only is the Heidelberg Ionbeam Therapy Center, HIT [3].

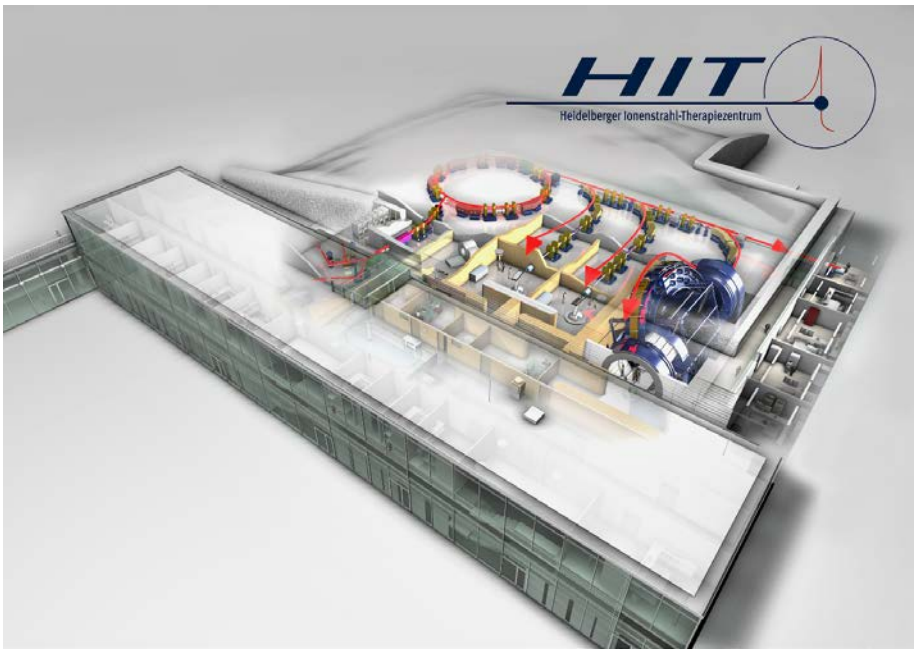

Figure 1: The Heidelberg Ionbeam Therapy Center.

Recently new accelerator concepts like linacs or superconducting synchrotrons aiming at smaller footprints, fast energy modulation and high intensities are under development. Clinically multi-ion treatments including the use of helium and oxygen ions, ultra-fast and/or high-dose delivery are requested.

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Applied nuclear physics experiments at new accelerators

V. Patera[1,2]
[1]Universita' „Sapienza", Rome, Italy; [2]INFN, Roma 1, Italy

Nuclear physics has countless application in modern society. Fields like industry, cultural heritage or homeland security largely profit for such applications. In particular many techniques have been developed based on nuclear physics in medicine, spanning from diagnosis to therapy. A far too easy examples of this reality is the particle therapy [1], that exploit light ion beams to treat deep solid cancers. Another important connection between the human health and the nuclear physics stems from an issue that has been lately a real concern for humanity: the space exploration.

However the use of the nuclear physics in medicine, or in other highly technologic application, frequently asked for several effort to refine theory and to improve the accuracy of the related measurements. Many experiment campaign have been carried out at this aim, with size and complexity of the experimental setup ranging from a table top experiment carried out in treatment room of hospital treatment room to large dedicate detectors built by large research collaboration and carried out in international physics laboratory

Focusing on particle therapy measurement, several features of the nuclear interactions of ions beams in the patient tissue that have impact on the treatment quality. In particular the nuclear fragmentation of the ion beam along its path in the patient is of relevance for the accuracy of the dose delivery, while the production of de-excitation photons, of β^+ emitters and of protons emitted at large angle with respect to the beam can be exploited to monitor the dose profile.

The FOOT experiment [2] (FragmentatiOn Of Target), designed by an international collaboration (France, Germany, Japan, Italy) will be presented as modern example of such a nuclear physics experiment. Target (^{16}O and ^{12}C nuclei) fragmentation induced by 150-250 MeV proton beams will be studied via an inverse kinematic approach. Increasing the beam energy to 300-400 MeV/nucleon also the projectile fragmentation of these beams will be explored. Such a detector will also study the interaction of ^{4}He, ^{12}C and ^{16}O with kinetic energy of 800 MeV/nucleon with graphite and hydrocarbon targets, of interest for radioprotection in space.

Starting from this example we will review the ongoing research activities in the field, including foreseen nuclear physics measurements, the proposed monitoring techniques and the related developments of Monte Carlo models. The possible evolution of these ongoing experiments at future ion beams will also be discussed.

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JINR Particle Accelerators for Radiation Biology

B. Sharkov

JINR, Joliot-Curie 6, Dubna 141980, Russian Federation

Overview of the rapid progress in development of heavy ion accelerator facilities in JINR is presented. Dubna accelerators are capable of generating high-brightness intense beams of heavy ions and protons for various applications including radiation biology. Construction of new generation of heavy ion accelerator facilities is progressing well and forefront accelerator technologies are under development in JINR for low energy as well as for relativistic heavy ion and proton beams..

South East European International Institute for Sustainable Technologies (SEEIIST, http://seeiist.eu)

S. Damjanovic[1,2,3] on behalf of the Intergovernmental SEEIIST Steering Committee[4]
[1]Ministry of Science of Montenegro, [2]GSI Darmstadt, Germany, [3]Chairperson of the SEEIIST Steering Committee, [4]http://seeiist.eu/members/

The states in South East Europe are joining forces to set up a large-scale competitive research infrastructure – the South East European International Institute for Sustainable Technologies (SEEIIST). The objective of this project is to foster regional cooperation in the fields of science, technology and industry in the spirit of the CERN and SESAME models 'Science for Peace'. This would greatly help to address common challenges and needs in SEE, helping in particular to develop sustainable economy and social cohesion. Capacity building and the slowing down if not reversal of the brain drain would become immediate benefits. At the same time, the SEEIIST project has also the potential to become one of the EU's future flagship projects within the framework of the European Neighbourhood Policy.

About two years ago the Government of Montenegro initiated the establishment of the SEEIIST Project, originally proposed by Prof. Herwig Schopper, a former Director General of CERN. This Initiative was formalized as a Regional project after signing a **Declaration of Intent** on 25 October 2017 at a Ministerial meeting at CERN, Geneva. **The Signatory Parties were Albania, Bosnia and Herzegovina, Bulgaria, Kosovo[1], Montenegro, Serbia, Slovenia and North Macedonia. Croatia agreed 'ad referendum', while Greece took an observer status.**

The core of the Project is ***a 'Facility for Tumour Therapy and Biomedical Research with Protons and Heavier Ions'.*** Beyond the treatment of patients, it is planned to dedicate 50% of the beam time to research with multi-ion sources (beyond presently used protons and carbon ions), making the SEEIIST project unique in the world. A particle therapy center does not exist in the SEE Region, where a perpetually growing number of tumours have been registered in recent years. With its double task to treat patients and to perform research, the SEEIIST project would present one of the best examples of '*Science for Society*' projects.

The creation of the Facility will offer numerous opportunities for technology transfer to the SEE-states. In particular, this will be a great benefit for the SEE local industry since the procurement of the different components for the machine and beam lines (magnets, vacuum system, girders, beam lines, power supplies, control system, etc.) can be preferentially assigned to local industry. Moreover, the initiative will give rise to spin-offs not directly linked to the facility, but also trigger complementary technologies.

Thanks to the first financial support by the European Commission – Directorate General for Research and Innovation (EC DG RTD) the SEEIIST project is now entering into a Design Study Phase which, thanks to their generous support, will be hosted in the renown research centers CERN and GSI. The preparatory groups have just been set up. The central goal would be to push a next generation facility for tumour therapy and biomedical research with multi-ion sources, which would even be a benefit for Europe as a whole.

[1]This designation is without prejudice to positions on status and is in line with UNSC 1244/1999 and the ICJ opinion on the Kosovo Declaration of Independence

Plans for heavy ion therapy in The United States

A. Pompos Ph.D.[1], H. Choy M.D.[1]
[1]UT Southwestern Medical Center, Dallas, TX 75390, U.S.A.

Heavy ion therapy is a unique form of radiation therapy for the treatment of cancer. It deposits ionizing radiation to cancer cells via accelerated charged particles that are heavier than protons. First, a narrow beam of heavy ions is accelerated in a particle accelerator to achieve the energy needed to reach shallow but also deeply (30cm) located tumor (70-430MeV/u for $^{12}C^{6+}$ ions). After the ions reached the desired energy, they are extracted from the accelerator and are magnetically guided to patient treatment rooms. The ions leave the magnetic transport system and are focused on the tumor. The ions enter through the patient's skin and travel to the tumor to deposit via their Bragg peak the therapeutic dose of ionizing radiation to a typically 5mm wide and couple of mm deep "spot". Then the beam is aimed at another "spot" at the tumor and the process is repeated till the whole tumor volume is "scanned" with therapeutic dose. Heavy ions exhibit differential relative biological effectiveness (RBE) due to a large difference in linear energy transfer (LET) alongside their tissue path. At tissue entrance (depending on tissue type), typically LET is low resulting in low RBE, but at the Bragg peak the LET is high leading to high RBE which further magnifies their physical dose advantage in comparison to conventional (Xray) or proton radiation.

Heavy ion therapy started in the U.S. in 1973 at Lawrence Berkeley National Accelerator Laboratory (LBNL) where patients were treated with helium ion beams neon ion beams. Heavy ion therapy stopped in the U.S. in 1993 due to ailing accelerator. The therapy migrated outside of the U.S. to Japan (5 centers), China (2), Italy (1), Austria (1), Germany (first center at GSI, then 2 centers), where more than 20,000 patients have already received treatment with heavy ions resulting to encouraging preliminary clinical outcome data. Despite its lack of a therapeutic heavy ion center, the U.S. has significantly contributed towards improving heavy ion technology for medical use. The US government's Department of Energy and National Cancer Institute (NCI) both supported numerous accelerator science, technology and medical use projects aimed at heavy ion therapy. All of these projects need heavy ion beam, sometimes of therapeutic quality which does not exist in the US. It is not convenient, nor cheap to conduct experiments at foreign institutions nor conduct US led clinical trials at foreign heavy ion centers confirming the need of at least a few initial such centers to be built in the US. The U.S. scientific and medical communities are anxious to re- establish heavy ion therapy in the U.S. In 2015, the NCI awarded two exploratory planning grants entitled "Planning for a National Center for Particle Beam Radiation Therapy Research" [1]. These grants were aimed to assist U.S. institutions that have been actively working to establish heavy ion therapy centers in planning. UT Southwestern Medical center received one of the grants and the North American Particle Therapy Alliance lead by University of California San Francisco received the other award.

Since then, these and multiple other major US academic institutions are working on establishing the first hospital based heavy ion centers in the US. This effort is envisioned to be different than the historical approach taken by proton therapy. The heavy ion effort is aimed to be almost exclusively clinical trial based. Initially a small number of small centers to be constructed, yet with large enough capacity to allow enough patients to be treated to conduct enough clinical trials to uncover the full benefit of heavy ions for cancer (and potentially non cancer) patients. While this is happening, appropriate reimbursement models are envisioned to be developed to support the novel usage of heavy ions in the realm of hypofractionation.

Once the full benefit of heavy ions have been uncovered and the technology reaches a more economic size, then we theorize is the proper time to proliferate and build the remaining missing US centers to provide the large scale needed heavy ion therapy cancer care.

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New infrastructure for image guided preclinical research in particle therapy

S. Brandenburg[1], L. Barazzuol[2], S. Both[2], R.P. Coppes[2] M.-J. van Goethem[1,2], B.N. Jones[1], P. van Luijk[2]
[1]KVI-CART, Groningen, the Netherlands;[2]Radiation Oncology UMCG, Groningen, the Netherlands

Introduction
Next generation animal experiments to further develop clinical (particle) radiotherapy cannot be carried out without modern image-guidance. Novel animal models, such as orthotopic tumour models, display anatomical variation that requires not only image-guided irradiation planning of individual animals but also pencil beam scanning to have the necessary flexibility to create the required high conformity and accuracy dose distributions. Therefore, we will upgrade our current particle therapy research infrastructure with imaging equipment and additional dose delivery modalities. Image-guided irradiation planning reduces dose variation between animals and will therefore increase the significance of the response of individual animals. This will reduce the number of animals needed to detect significant differences, and lead to more accurate answers on the research questions to be addressed.

Materials and methods
The cyclotron at KVI-CART has delivered beams of protons (range in water up to 230 mm) for small animal radiation biology research since more then twenty years. At the new infrastructure also helium (range up to 60 mm) and carbon (range up to 20 mm) beam will become available for irradiations of small animals. A wide range of irradiation modalities based on both scattering and pencil beam scanning will be available, including shoot-through with high energy protonsand (spread-out) Bragg peaks for protons, helium and carbon. Scattering and pencil beam scanning will be available for both shoot-through with protons and (spread-out) Bragg peak irradiations with protons, helium and carbon. Additionally, spatial fractionation (GRID) and high dose rates in excess of 300 Gy/s (FLASH) will be developed.
Image guidance will be provided by 3D X-ray and bioluminescence imaging at the irradiation position. State-of-the art image-based Monte Carlo irradiation planning extending the capabilities of existing tools for photon irradiations will be developed. In collaboration with the Central Animal Facility and the Small Animal Imaging Center at the UMCG a comprehensive service from obtaining the necessary authorisations to performing the post-irradiation testing of the irradiated animals, including advanced data storage capabilities will be offered to users. The infrastructure will provide open access through a peer review process of project proposals.

Research plans
The new infrastructure will offer the possibilities to address various research questions such as

- Studies of radiosensitivity variations within normal tissue and tumor.
- Mechanistic studies using tumour and normal tissue models to investigate interaction between radiation and systemic treatments, such as chemotherapy, immunotherapy and DNA damage response (DDR) modulators and radiation.
- LET and RBE studies for biological treatment planning.
- Therapeutic window optimization and translation to the clinic.

Conclusion
Building upon the expertise obtained over twenty year of small animal irradiations with protons we will provide the radiation biology and physics community with a state of the art, open access research infrastructure for small animal research. The upgrades to the infrastructure will become available from the end of 2021.

Acknowledgement
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The ELIMED/ELIMAIA Open Users Beamline for Laser-Driven Ion Beams and First Planned Irradiation Activities

G.A. Pablo Cirrone[1,2], F. Cammarata[3], R. Catalano, G. Cuttone[1], M. Guarrera, G. Korn[2], G. Larosa[1], L. Manti[4], G. Petringa[1], A. Russo[1], G. Russo[3], F. Schillaci[2], V. Scuderi[2] and D. Margarone[2]

[1]INFN-LNS, Istituto Nazionale di Fisica Nucleare, Catania, Italy;

[2]Institute of Physics Czech Academy of Science ELI-Beamlines, Dolní Břežany, Czech Republic

[3]Institute of Molecular Bioimaging and Physiology - National Research Council - (IBFM-CNR), Cefalù, Italy

[4]Physics Department, University of Naples Federico II, Naples, Italy and INFN Section of Naples, Naples, Italy

The main direction proposed by the community of experts in the field of laser-driven ion acceleration is to improve particle beam features (maximum energy, charge, emittance, divergence, monochromaticity, shot-to-shot stability) in order to demonstrate reliable and compact approaches to be used for multidisciplinary applications, thus, in principle, reducing the overall cost of a laser-based facility compared to a conventional accelerator one and, at the same time, demonstrating innovative and more effective sample irradiation geometries.

The mission of the laser-driven ion target area at ELI-Beamlines (Extreme Light Infrastructure) in Dolní Břežany, Czech Republic, called ELI Multidisciplinary Applications of laser-Ion Acceleration (ELIMAIA) [1], is to provide stable, fully characterized and tunable beams of particles accelerated by Petawatt-class lasers and to offer them to the user community for multidisciplinary applications. The ELIMAIA beamline has been designed and developed at the Institute of Physics of the Academy of Science of the Czech Republic (IoP-ASCR) in Prague and at the National Laboratories of Southern Italy of the National Institute for Nuclear Physics (LNS-INFN) in Catania (Italy). The key section of the beamline, which includes the beam focusing, the energy selection, the beam transport, the dosimetric and sample irradiation elements, is called ELIMED (ELI MEDical and multidisciplinary applications) [2] portion.

At ELIMED, controlled proton and light ion (included carbon) beams up to 300 MeV and 70 AMeV respectively, will be transported up to the in-air section where absolute dosimetry will be carried out with dose-rate independent devices. A transmission, dual-gap air ionisation chamber will provide the on-line measurement of dose at the irradiation point simultaneously allowing for corrections coming from ion recombination effects. The maximum expected error in the final dose released to the sample is less then 5%. The ELIMED first irradiation experiment is scheduled for 2020 when the first radiobiological campaign for in-vitro irradiation is expected.

In this work the status of the ELIMED/ELIMAIA beamline will be reported along with a complete description of the main dosimetric systems and of the first preliminary calibrations. The expected final beam characteristics, in terms of dose per pulse, dose-rate and beam spot size (directly derived by Monte Carlo simulations), will also be ported. Moreover, the first planned biological irradiation experiment will be briefly discussed

Figure 1: Photo of the ELIMAIA/ELIMED beamline installed at the ELI-Beamlines facility in Dolní Břežany, Pragu e(CZ).

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From CERN technologies to medical applications

M. Cirilli[1]
[1]CERN, Geneva, Switzerland.

CERN is the world's largest particle-physics laboratory, located at the border between France and Switzerland. Its core mission is fundamental research in particle physics. Since its beginnings, CERN has also acted as a trailblazer in the technologies related to accelerators, detectors and computing. As a laboratory with a long-term research plan, it is continuously innovating, and it is part of its mission to ensure that these innovations bring practical benefits to society as a whole: the most known example is certainly the invention of the World Wide Web by CERN scientist Tim Berners-Lee in 1989, but the laboratory has contributed to applications in many other fields, from medical and biomedical technologies to aerospace applications, safety, "industry 4.0", cultural heritage and emerging technologies [1].

CERN's expertise builds broadly on three technical fields: accelerators, detectors and computing. Behind these three pillars of technology, lies a great number of areas of expertise: from cryogenics to ultra-high vacuums, from particle tracking to superconductivity and many more. Applications to the health domain represent one of the most relevant knowledge transfer opportunities in terms of potential impact on society, and in 2017 the CERN Council has approved a strategy document to set the framework for these specific activities [2]. Some recent examples of transfer to medical applications are:

- an innovative radio-frequency quadrupole (RFQ) designed to be compact, modular, low-cost and suitable for medical applications, now licensed to a company as an injector for the next-generation linear proton therapy systems;
- a novel gantry design [3] based on a toroidal magnet concept, which bends the treatment beam without the need to rotate the structure and could greatly reduce the size of ion gantries;
- the Medipix family of read-out chips [4], now used for various applications including spectral X-ray imaging and radiation monitoring in space.

CERN operates testing facilities and develops qualification technologies for high-energy physics, which are useful for ground testing and qualification of flight equipment. This opportunity is particularly attractive for miniaturised satellites called CubeSats that typically use commercial off-the-shelf components for their electronics, since radiation qualification according to standard procedures is expensive and time-consuming.

Accelerators are also increasingly needed for the production of radioisotopes, which are used in nuclear medicine imaging and therapy. Artificially-made radioisotopes are still mostly produced by research reactors, but new accelerator-based technologies are being explored for next-generation facilities that would replace the wobbly reactors. The ISOLDE accelerator facility at CERN has constantly been developing the so-called Isotope Separation Online (ISOL) technique, which is now being taken one step further by the CERN-MEDICIS installation [5], dedicated to the production of a wide range of innovative radioisotopes for medical research.

Computing tools, infrastructures and services developed at CERN have also great potential for applications in the medical field, and these activities are becoming more and more relevant with the growing interest in machine learning and data analytics tools.

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INFN-LNS Hadrontherapy facility: clinical outcome, radiobiological studies and preclinical molecular imaging approaches

G. Cuttone[1], V. Bravatà[1,2], F.P. Cammarata[1,2], G.A.P. Cirrone[1,3], G.I. Forte[1,2], M. Ippolito[4], L. Minafra[1,2], R. Parenti[3], G. Petringa[1], I. Petrovic[5], A. Ristic-Fira[5], G. Russo[1,2], G. Sabini, A. Stefano[1,2], L.M. Valastro

[1]National Institute for Nuclear Physics, Laboratori Nazionali del Sud, INFN-LNS, Catania, Italy
[2]Institute of Molecular Bioimaging and Physiology, IBFM-CNR, Cefalù, Italy
[3]Institute of Physics Czech Academy of Science ELI-Beamlines, Dolní Břežany, Czech Republic
[4]Nuclear Medicine Department „S Cannizzaro" Hospital, Catania, Italy
[5]Vinča Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia
[6] Medical Physics Department „S Cannizzaro" Hospital, Catania, Italy

Hadrontherapy is currently recognised as an important strategy in the specific case of tumour treatments localized close to sensitive anatomical sites. Moreover, the possibility to characterize tumours and their microenvironment, before and after treatments, represents a powerful approach to optimize the efficacy of the treatment, as well as to test innovative drugs for targeted therapies. For more than twenty years researchers of LNS-INFN are involved in the field of in-vitro and in-vivo experiments to study and characterize the response of different tumour models exposed to ionizing radiations (protons and light ions). Among these the most recent are ETHICS (pre-clinical Experimental and THeoretical studies to Improve treatment and protection by Charged particleS - INFN Call 2014), dedicated to characterization of the action mechanisms on normal cells by charged particles, MoVeIT (or Modeling and Verification for Ion beam Treatment planning - INFN Call 2017), HADMAC (HADrons on MAlignant Cells) dedicated to studies of the effects of various LET (linear energy transfer) values of ^{1}H, ^{4}He and ^{12}C ions on different human cancer cell lines, MIRTO (MIcrodosImetric study and RBE measurement with 62 clinical prOton beam), NEPTUNE (Nuclear process-driven enhancement of Proton Therapy UNraVeled - INFN Call 2019) and PBCT (Proton Boron Capture Therapy - PRIN 2019). In addition, during the last two years, a network was created by the synergy of equipment and expertise of the LNS-INFN, providing experience in clinical hadrontherapy University of Catania – Center for Advanced Preclinical in vivo Research, (CAPiR), providing animal houses and preclinical imaging platforms including a microPET/CT; Nuclear Medicine department of "Cannizzaro Hospital", providing differently synthesized radiotracers; IBFM- CNR, providing know-how in performing radiobiological in vitro and in vivo studies. At today, this platform represents a unique Radiopharmaceuticals and Hadrontherapy infrastructure in Italy, offering the possibility to perform preclinical studies on hadrontherapy and possible combined treatments with the great support of molecular imaging or testing new radiotracers. Some research projects (INFN CSN5 Calls; Prin 2017-P2) and experimental preclinical studies (PETS, Myelomoveit; Hypoxia), which are inserted on this research platform, are already started [1-3]. The possibility to explore new frontiers of particle irradiation with extremely high-dose-rate beams generated by laser-matter interaction is investigated by the group, as well. INFN-LNS realised, in fact, the first User-addressed transport beam line for laser-driven ions. The beamline [4] (named ELIMED: ELI-Beamlines MEDical and multidisciplinary applications) is nowadays in its installation phase at the ELI-Beamlines facility (Dolni Brezany, CZ) and will start its operative phase within 2019.

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The new CNAO irradiation facility for research applications

M.M. Necchi[1], M. Donetti[1], A. Facoetti[1], M. Pullia[1], S. Rossi [1]
[1]Fondazione CNAO, Pavia, Italy

The CNAO (National Center for Oncological Hadrontherapy) in Pavia is one of the five centres worldwide in which hadrontherapy is administered with both protons and carbon ions**.** The main accelerator is a 25 m diameter synchrotron designed to accelerate ions injected with an energy of 7 MeV/u up to the energy corresponding to the magnetic rigidity of 6.35 T•m. For C^{6+} ions this corresponds to 400 MeV/u; in the case of protons, the maximum energy of 250 MeV corresponds to a magnetic rigidity of 2.43 T•m, well below the technically achievable maximum. For other ions, possibly produced with a dedicated third source, the maximum rigidity would still be 6.35 T•m and the corresponding particle range would be determined by their charge and mass.

Although the Center is mainly dedicated to clinical irradiation, it also provides great opportunities to perform various research for scientific and industrial activities related to radiation biophysics, radiobiology, space research and detector development. For researchers a dedicated experimental irradiation room will be available, using the CNAO beams, in time slots not impacting on patients treatment, but specifically devoted to research purposes (i.e. some night shifts and week-ends, typically) and, if applicable, in a parasitic modality during daily treatments, for the experiments in which the duration is not important and the measurement itself can be “paused” for an indefinite time.

The beam distribution in the experimental room will be performed with the same active scanning system in use in the treatment rooms. In order to make the best use of the available space, the part of beamline inside the experimental room can be assembled in various configurations. In the first case the irradiation point is as downstream as possible in order to get the maximum irradiation field. In the opposite case, the irradiation point is just at the beam entrance into the room, leaving the maximum space downstream for Time Of Flight (TOF) measurements; this configuration requires to remove the whole beam line starting with the scanning magnets. An intermediate irradiation position has been chosen as default leaving almost 2 m free space downstream the irradiation point and still allowing an irradiation field of 135 × 135 mm^2. A fourth configuration allowing beam monitoring in the most upstream position completes the possibilities, as illustrated in Fig. 1 hereafter.

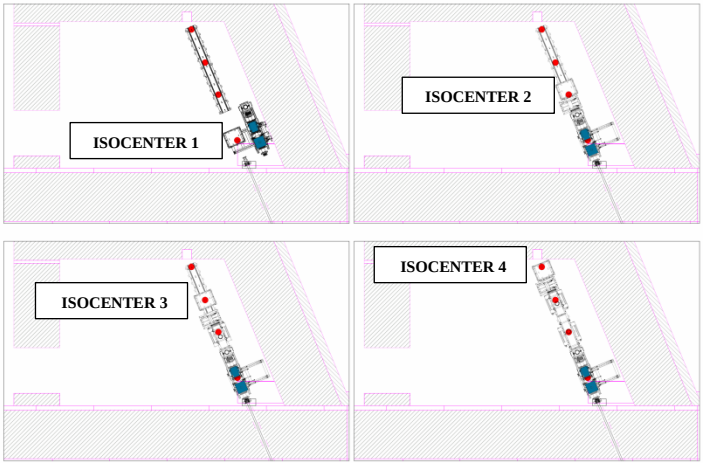

Figure 1: Possible irradiation positions along CNAO experimental beam-line (from isocenter 1 at the beam entrance to isocenter 4 in the most upstream position).

Innovative detectors, both for in-vivo monitoring during hadrontherapy treatment and for TOF measurements, could be developed and tested in the experimental room.

Particle identification plays a fundamental role in radiation risk assessment in space, because different health risks are related to different ions and their ionizing powers. Active detectors are largely used in human space habitat to measure the radiation field characterized by large dynamics in terms of time and kinetic energy. Actually, in the field of space research, the proton and Carbon ion beams available at CNAO represent a tool to simulate space radiation on ground, and will be used to test shielding materials in spacecraft and cosmic radiation damage to microelectronics.

LhARA; the Laser-hybrid Accelerator for Radiobiological Applications

K. Long
Imperial College London/STFC, London, UK

The ‘Laser-hybrid Accelerator for Radiobiological Applications’, LhARA, is conceived as a novel facility dedicated to the study of radiobiology. LhARA is a hybrid accelerator system in which laser interactions drive the creation of a large flux of protons or light ions that are captured using a plasma (Gabor) lens and formed into a beam. The conceptual design of LhARA permits the facility to be built in two stages. In the first stage, a programme of in-vitro experiments will be served with proton beams with energies between 10 MeV and 15 MeV. The beam will be transported and focused using a series of Gabor lenses and dipoles. In stage two, the beam will be accelerated using a fixed-field accelerator with large dynamic aperture. This will allow experiments to be carried out in vitro and in vivo with proton beam energies of ~70 MeV. In addition, ion beams will be provided for in-vitro an in-vivo experiments. The conceptual design of LhARA will be summarised.

The LARAMED project at LNL: Radionuclides from the nuclear physics to medicine

J. Esposito[1], A. Boschi[2], S. Cisternino[1], A. Duatti[1,3], G. Fiorentini[4], G. Keppel[1], P. Martini[1,2], L. Mou[1], M. Pasquali[1], G. Pupillo[1], G. Sciacca[1], H. Skliarova[1], D. Bettoni[1,4]

[1] Legnaro National Laboratories, Italian National Institute for Nuclear Physics (LNL-INFN), Viale dell'Università, 2, 35020 Legnaro (PD), Italy
[2] Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Via L. Borsari, 46, 44121 Ferrara, Italy
[3] Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Via L. Borsari, 46, 44121 Ferrara, Italy
[4] Department of Physic and Earth Science, University of Ferrara, Via Saragat, 1, 44122 Ferrara, Italy

The great advancement of nuclear medicine (NM) held in the last decades mainly relies in the development and use of a wide range of different and more effective radiopharmaceuticals. This goal has been achieved by combining the biological behaviour of new ligand molecules, selective for the specific tumour target, and the main nuclear properties of novel radioisotopes, specific for diagnostic, therapy and theranostic applications. The use and availability of a variety of radionuclides has experienced a great development as a result of the increase of technologies related to their production, even based on cyclotrons.

At INFN-LNL a BEST 70p high performance cyclotron was installed in 2015, to be dedicated not only to the new frontiers of nuclear physics studies with Rib's (SPES project), but also to the interdisciplinary and medical physics investigations, through the LARAMED project [1], acronym for LAboratory of RADionuclides for MEDicine.

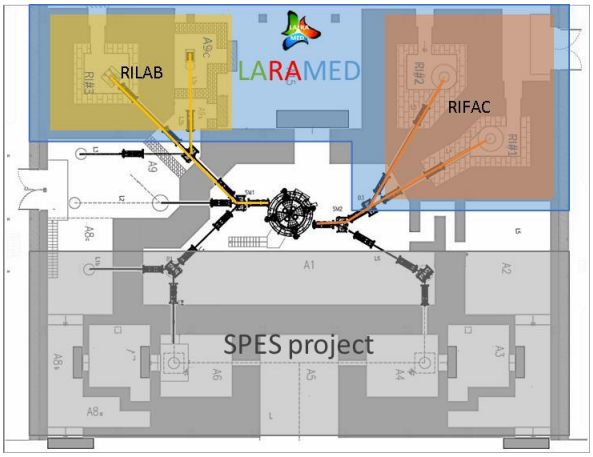

Figure 1: The layout of the SPES building (underground level) showing the cyclotron with outward beam lines. In evidence, the LARAMED section (colored in blue) comprising four bunkers (RI#1, RI#2, RI#3, A9c). This area is divided in two separate sections: The RadIoisotopes LABoratory (RILAB) and the RadioIsotope FACtory laboratory (RIFAC).

Albeit the facility is currently under development (installation of beam-lines, laboratories etc), LARAMED team since 2012 started working on the alternative production of conventional radionuclides, already used in NM such as Tc-99m (TECHN-OSP and APOTEMA projects). The focus is now devoted on studying new emerging radionuclides such as Cu-67 (COME project), Sc-47 (PASTA project) and Mn-52 (METRICS project), as well as on the technical development of high-power target (TERABIO premium-project). The collaboration with NM radiopharmacies holding a PET cyclotron (e.g. Sant'Orsola Hospital, Bologna and Sacro Cuore Don Calabria Hospital, Negrar) as well as with national and international research institutes, such as the University of Ferrara and the ARRONAX facility (Nantes), made all this effort possible.
An overview of radiometals cyclotron production studies, from cross-section measurements to target production, irradiation, target processing, and recovery, carried out by the LARAMED research group is the purpose of this presentation.

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High Intensity Beams

Investigating the mechanism behind FLASH radiation effects

F. Van den Heuvel, F. Fiorini, M. Brooke, J-L Ruan, A Ryan, A.E. Kiltie, M. Hawkins, B. Vojnovic
Dept of Oncology, University of Oxford. Oxford, UK

FLASH radiation therapy is the delivery of radiation therapy doses using much higher dose rates than the clinical norm. A rule of thumb is that the FLASH therapy is delivered with at least a dose rate of 40Gy/s. Traditional dose rate in clinical settings are of the order of 600cGy/min or 0.1Gy/s. Preliminary results from a number of groups, show that an increased therapeutic window exists due to the a lower normal tissue complication response compared to traditional dose rates. The tumour response is identical[1].

The mechanism at the basis of this effect is curently unknown. A possible proposed mechanism is the creation of a transient hypoxic environment, which due to different re-oxygenation dynamics in tumour compared to normal tissue creates a difference in response. Our hypothesis is that: "If the FLASH effect is due to transient oxygen depletion, then the strength of the effect depends on the Oxygen Enhancement Ratio (OER) of the modality used".

In this proposal we wish to test this hypothesis using a Carbon ion beam modified to provide FLASH compatible dose rates. As the effect is only observed in living tissue. We propose to use mice to be irradiated at different OER levels.

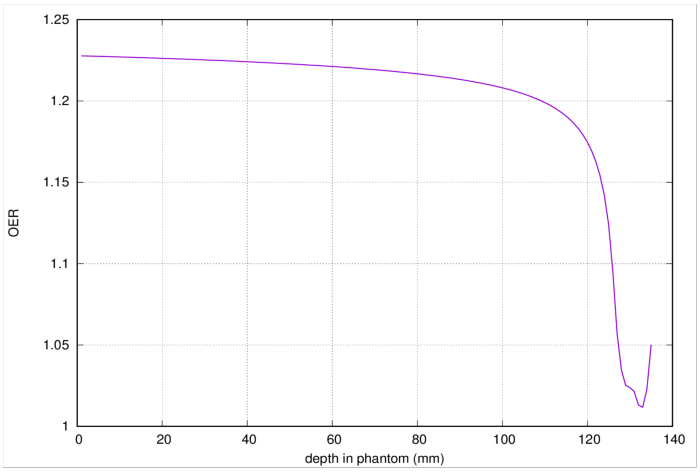

Figure 1: Variation of the OER as a function of depth in water for a Carbon ion beam with energy 250 MeV/nucl.

To show feasibility we adapted previous software which predicts number of double strand breaks introduced depending on modality and energy to incorporate Oxygen effects[2]. This allows to estimate the OER of a modality with a given spectrum. Using FLUKA we calculated the spectrum of charged particles at the centre of a carbon pencil beam and calculated the OER.

This provides the geometrical setup restrictions for our experiment.

The experiment itself involves obtaining a dose-response curve of intestinal crypt survival in mice after FLASH and compare this to conventional treatment. By positioning the mice at different carbon-beam pathlengths different levels of OER are used and the survival curve comparisons should correlate.

[1] M.-C. Vozenin, P. De Fornel, K. Petersson, V. Favaudon, M. Jaccard, J.-F. Germond, B. Petit, M. Burki, G. Ferrand, D. Patin, H. Bouchaab, M. Ozsahin, F. Bochud, C. Bailat, P. Devauchelle, and J. Bourhis, The advantage of flash radiotherapy confirmed in mini-pig and cat-cancer patients., Clinical cancer research, Jun 2018.

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Radiobiology of high dose-rate particle beams

E. Beyreuther[1,2], *L. Karsch*[2,3], *J. Pawelke*[2,3]

[1]Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiation Physics, Dresden, Germany; [2]OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden; Helmholtz-Zentrum Dresden – Rossendorf, Dresden, Germany; [3]Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany

In the past few years, the normal tissue protecting effect of Flash electron irradiation was shown for several endpoints and in different species [1], [2]. Contrary to conventional, clinical beam delivery over minutes, the therapeutic dose is administered within less than 0.5 s by Flash irradiation. Hence, this treatment regime is linked to high mean dose rates of ~100 Gy/s and high pulse dose rates of $\geq 10^5$ Gy/s, clearly exceeding the parameters of a few Gy/min on time average and of ~ 10^2 Gy/s within one pulse of conventional, clinical Linacs. Of note, tumors were cured by electron Flash as efficient as by conventional electron beam treatment over minutes [1]. Moreover, the protecting Flash effect was recently validated for photons [3], which promises a general validity of this effect also for other types of clinically used radiation.

First attempts testing the feasibility of proton Flash were conducted at clinical proton beam facilities in France [4] and at the University Proton Therapy Dresden (UPTD), Germany. At UPTD, a setup was established that allows for the irradiation of zebrafish embryo either with dose rates of 100 Gy/s for Flash or of 5 Gy/min for conventional reference. The zebrafish embryo were treated with graded doses up to 40 Gy and embryonic survival as well as the manifestation of morphological abnormalities were followed for up to four days. However, analysing the different endpoints, a clear dependency on dose but no significant dependence on proton dose rate was revealed.

This unexpected result implies, that more studies are needed to resolve the influence on beam time structure for the induction of a protective Flash effect. Here, research facilities like FAIR with a broader parameter space regarding ion species, particle fluence, LET, pulsing and beam time structure provide the possibility to study the physical limits of Flash in more detail. Therewith also questions on a potential influence or interaction of high dose-rate particle beam, high LET and oxygen level of the irradiated tissue could be investigated systematically. The results obtained therein could help to further develop dedicated clinical accelerators, like superconducting or heavy ion synchrotrons, to make clinical use of the Flash effect.

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[2] P. Montay-Gruel *et al.*, “Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s,” *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, vol. 124, no. 3, pp. 365–369, 2017.
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[4] A. Patriarca *et al.*, “Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System,” *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 102, no. 3, pp. 619–626, Nov. 2018.

Radiobiology of the Laser-accelerated ions at Ultra high dose rates

P. Chaudhary
Centre for Cancer Research and Cell Biology, Belfast, UK

Ion beam therapy has emerged as more effective in the treatment of certain tumors than photon based therapies. However, significant capital and operational costs make proton therapy less accessible. This has stimulated interest in alternative Ions delivery approaches , and in this context the use of laser-based technologies for the generation of ultra-high dose rate ion beams has been proposed as a prospective route. A better understanding of the radiobiological effects at ultra-high dose-rates is important for any future clinical adoption of this technology. In this study, we irradiated human skin fibroblasts-AG01522B cells with laser-accelerated protons at a dose rate of 109 Gy/s, generated using the Gemini laser System at the Rutherford Appleton Laboratory, UK. We studied DNA double strand break (DSB) repair kinetics using the p53 binding protein-1(53BP1) foci formation assay and observed a dose similarity in the 53BP1 foci repair kinetics in the cells irradiated with 225 kVp X-rays and ultra- high dose rate protons for the initial time points. At the microdosimetric scale, foci per cell per track values showed a good correlation between the laser and cyclotron-accelerated protons indicating the similarity in the DNA DSB induction and repair.

The Basic Mechanism behind FLASH Radiotherapy: Measuring DNA Damage and Oxygen Depletion at Ultrahigh Dose Rates

B.Jakob[1], N. Averbeck[1], and M.Durante[1,2]
[1]GSI, Darmstadt, Germany; [2]TUD, Darmstadt, Germany.

Delivering ultra-high dose rates of several tens to hundreds of Gy/s have been reported leading to a remarkable reduction in normal-tissue radiation toxicity [summarised in 1]. This approach is currently pursued to use as "FLASH" irradiation approach in radiotherapy [2]. The underlying mechanism for the observed sparing is still under discussion. One hypothesis is based on local oxygen depletion at very high dose rates when oxygen diffusion is outcompeted by the fast radical production and thus under normoxic conditions, reoxygenation and damage fixation by oxygen is limited. In contrast to well oxygenated normal tissue, a lack of dose rate dependent sparing of tumours was observed, which might be attributed to frequently occurring hypoxic areas. Using charged particle irradiation, single heavy ions with high Z can deliver dose rates exceeding 10^{12} Gy/s during traversal of a cell nucleus. In addition the new FAIR accelerator can deliver bunches of lighter ions with dose rates sufficiently high for FLASH irradiation. Individual ion traversals can be visualised in living cell nuclei by the aid of GFP-tagged repair factors using beamline microscopy revealing a fast accumulation at induced DNA damage along the ion trajectory (Fig. 1) [3]. The recruitment kinetics of some of these repair factors like NBS1 or MDC1 was shown to be dependent on damage complexity [4], thus giving a potential readout for differences in oxygen dependent damage modulation.

To pinpoint the oxygen depletion effect at high dose rate, we propose to conduct live cell microscopy studies at the beamline modulating the oxygen partial pressure to generate different conditions of hypoxia, normoxic or hyperbaric oxygen conditions. Oxygen tension can be measured via modulation of the lifetime of excited triplet states in transition metal complexes, which are quenched by oxygen. This method has been used for measuring intracellular oxygen supply using Phosphorescence Lifetime Imaging Microscopy (PLIM) [5] and will, be applied to measure local oxygen depletion upon irradiation with subcellular precision. In the same time the recruitment of repair factors or the generation of ROS species will be measured.

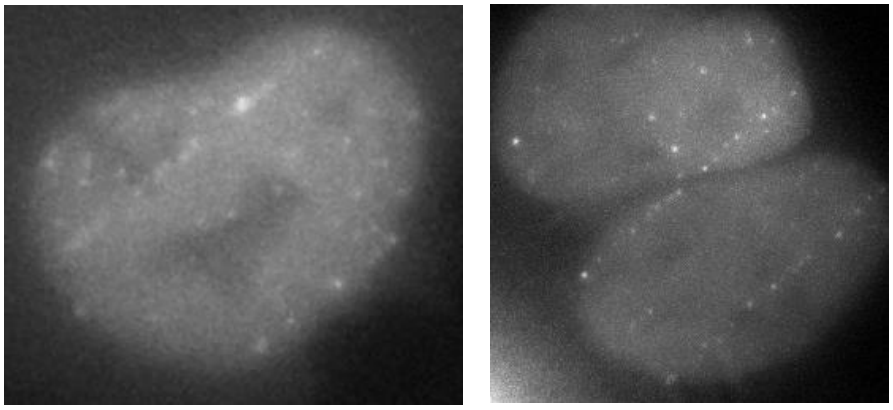

Figure 1: Recruitment of NBS1 (left) or XRCC1 (right) to radiation induced DNA damage after irradiation with 1GeV/u iron ions showing the damage accumulation along the ion trajectories in living human cells.

If local oxygen depletion at high dose rate is the limiting factor in damage generation and fixation, recruitment kinetics of NBS1 or MDC1 should be slower under hypoxic condition and less influenced by dose rate. In addition the amount of recruited factors related to the repair of oxidative damage should be lowered compared to normoxic conditions. In parallel experiments cellular clonogenic survival at different dose rates and, using samples fixed at different times post-irradiation, differences in double–strand break repair will be measured as established radiobiological relevant endpoints.

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FLASH irradiation by tumour conformal beam application with 3D modulators and biological verification

Y. Simeonov[1], M. Durante[2,3], R. Engenhart-Cabillic[4], K. Parodi[5], C. Schuy[2], W. Tinganelli[2], K. Zink[1,4], U. Weber[1,2]

[1]THM, Gießen, Germany; [2]GSI, Biophysics, Darmstadt, Germany; [3]TU Darmstadt, Darmstadt, Germany; [4]University Hospital Gießen-Marburg, Germany; [5]LMU München, Med. Phys. Dept., Germany

Recent in-vivo investigations have shown that short pulses of electrons at very high dose rates (>40 Gy s^{-1}) are less harmful to healthy tissues but just as efficient as conventional dose-rate radiation to inhibit tumour growth, suggesting that these so-called FLASH irradiations can substantially enhance the therapeutic window in radiotherapy [1,2]. However, the mechanism remains unclear [3] and a similar effect has not yet been proven for proton or ion beam irradiation. Whilst with cyclotrons these dose rates can be achieved for protons [4], it is more difficult with the synchrotrons used in heavy ion therapy.

Recently, we demonstreated that 3D printed modulators composed of fine and well-defined pyramid-shaped structures can be used to apply a highly conformal dose distribution of charged particles within a very short irradiation time (typ. 1-2 s; Fig. 1) [5]. We propose the use of this setup for FLASH irradiation with heavy ions. Since 3D modulators allow a beam application with only one scan for single fixed energy, dose rates as high as 40-100 Gy/s can be reached with a sufficiently high beam current. The new FAIR accelerator will be able to deliver ~10^{11} ions/spill into the APPA Cave, achieving dose rates of up to 100 Gy/s or more for realistic tumour sizes. It should be mentioned that scanning of a pencil beam causes an additional increase of the local dose rate by a typical factor of 10 (the sharper the beam the higher the local dose rate).

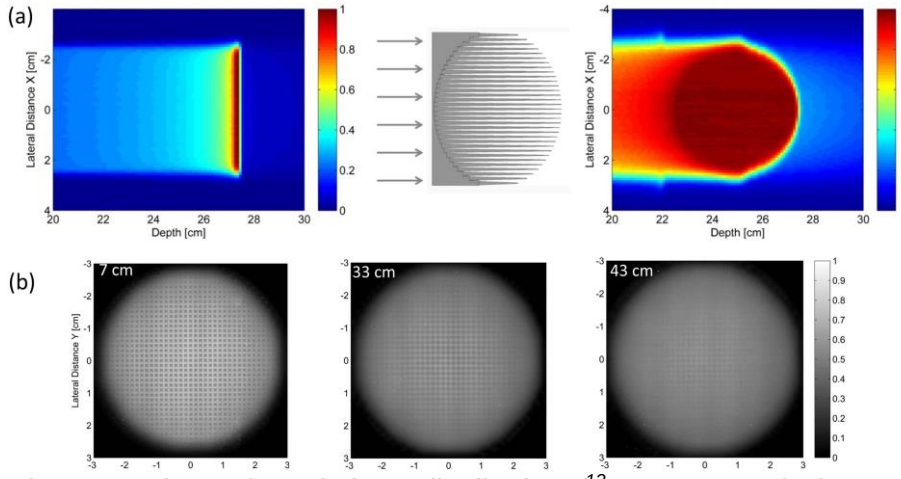

Figure 1: a) Conformal dose distribution (^{12}C, 400 MeV/u beam, sphere Ø= 5cm) produced by a 3D modulator, irradiation time ≈2 s [5]. b) Measured 'Dose grid' effect induced by a 3D modulator at different distances from the patient [5].

We propose to investigate at FAIR the efficiency of FLASH irradiations for proton, carbon and helium beams and medium-sized target volumes in a series of animal experiments with mice using our 3D modulators. Our setup can be used soon in FAIR phase-0 exploiting the increased intensity at SIS18 and directing the beam in Cave M. A radio-resistant xenograft tumour will be injected 7 days before irradiation on the back of mice. After 7 days tumour will be clearly visible. The next step will be to study a treatment plan that through the healthy tissues of the animal, from the belly to the back, can control the tumour both with the FLASH and with the conventional treatment. Tumour growth will be measured, and the damage induced to the healthy tissue will be analysed after sacrificing the animal.

Additionally, the biological effect of the fine dose grid, which can optionally be induced by the 3D modulator, shall be investigated. A dose grid pattern will be applied on the skin and in the near-surface normal tissue if the modulator is positioned close to the target (see Fig. 1b). Normally, a distance of typ. 60 cm is kept in order to avoid dose grid structures. However, the grid pattern structures can be exploited in order to reduce normal tissue side effects, i.e. to perform minibeam particle therapy [6] without passive grids and at the necessary high dose rates.

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Radioactive Beams and Detection

Simultaneous cancer treatment and online imaging with radioactive ion beams at FAIR

T. Steinsberger[1,2], C. Graeff[1], U. Weber[1], K. Parodi[3] and M. Durante[1,2]
[1]GSI Helmholtzzentrum für Schwerionenforschung, Biophysics Department, Darmstadt, Germany;
[2]Technische Universität Darmstadt, Darmstadt, Germany; [3]Ludwig-Maximilians-Universität München, Department of Medical Physics, Germany

Radiotherapy using accelerated heavy ions has the potential to overhaul cancer treatment and replace invasive techniques (surgery, catheter ablation) for selected noncancer diseases. However, particle therapy is hampered by the range uncertainty and requires more precision to fully leverage its physical advantages and expand the applications to noncancer diseases such as heart arrhythmia.

The best way to visualize online the beam in vivo would be the use of β^+ emitters for treatment. Radioactive ion beams (RIB) with positron emitting isotopes can in fact be visualized by PET. Compared to PET monitoring of stable particles [1], RIB improve the count rate by orders of magnitude, eliminate the shift between the peaks of measured activity and dose, and reduce the impact of washout using short-lived isotopes and acquisition times. The use of RIB as a pre-treatment range probe had been already proposed many years ago, but therapeutic use was hampered by the low intensity achievable at conventional accelerators [2]. The RIB intensity will be increased x10,000 at FAIR compared to the current beams [3]. This means that currents around 10^7-10^8 pps will be reached.

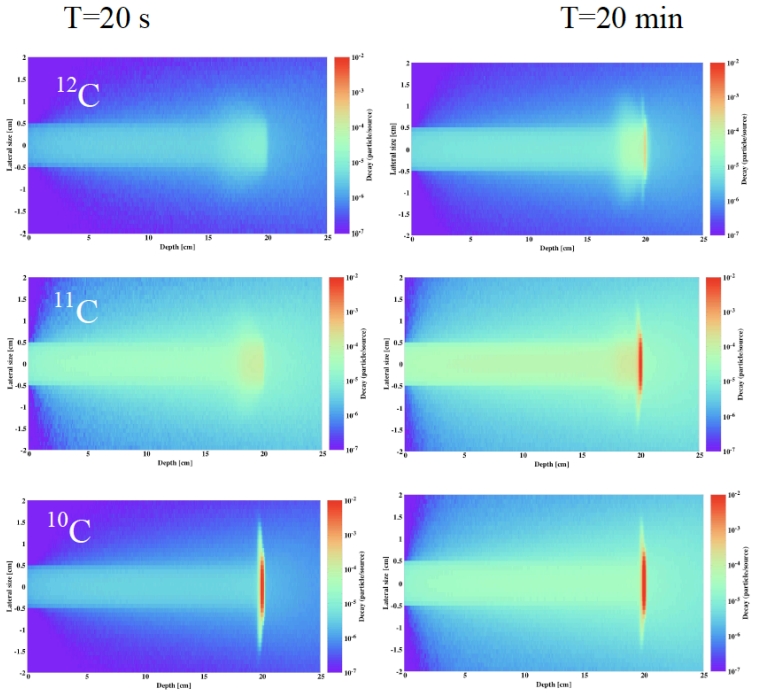

Figure 1: Simulation of stable and radioactive C-ion beams with the same range in water (20 cm). PHITS simulation courtesy of C. La Tessa.

We will concentrate on the production of four β^+ emitters: ^{10}C ($t_{1/2}$=19.29 s), ^{11}C ($t_{1/2}$=20.33 min), ^{14}O ($t_{1/2}$=1.17 min) and ^{15}O ($t_{1/2}$=2.04 min). We will especially concentrate on isotopes with short half-life $t_{1/2}$, such as ^{10}C, which have obviously the greatest potential for online beam monitoring (*Figure 1*). At FAIR, RIB will be produced using the in-flight technique, where the primary beam is not stopped in a thin target. The projectile fragments are all created with almost the same vector momentum as the primary beam and are separated in an electromagnetic separator: the FRS. From SIS18, using the FRS, the beam can be directed to the Cave M, where we can exploit the medical equipment including the online BASTEI PET in the cave and where we will install the new detector under development at LMU [4]. We will then perform physical beam dosimetry in a water phantom and biological dosimetry in a cellular phantom to assess the biological effectiveness of the RIB. Finally, the system will be tested in an animal model. The goal of the project is to achieve a resolution <0.3 mm during the treatment.

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[2] M. Kanazawa *et al.,* Application of an RI-beam for cancer therapy: In-vivo verification of the ion-beam range by means of positron imaging. *Nucl Phys A* (2002) **701**:244–252.

[3] M. Durante *et al*., Applied nuclear physics at the new high-energy particle accelerator facilities. *Phys. Rep.* (2019). DOI: 10.1016/j.physrep.2019.01.004

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Real-time PET imaging for range verification in proton and ion radiotherapy

P. Dendooven[1], I.S. Ozoemelam[1], M. Kapusta[2], N. Zhang[2], E.R. van der Graaf[1], M.-J. van Goethem[1], S. Brandenburg[1]
[1]KVI-Center for Advanced Radiation Technology, University of Groningen, Groningen, the Netherlands;
[2]Molecular Imaging, Siemens Healthineers, Knoxville, TN, U.S.A.

The conformity achievable with proton and ion beams is in practice not yet fully accomplished due to uncertainties in predicting, during treatment planning, the location of the Bragg peak in the patient and the lack of in-vivo dose delivery verification methods during irradiation. These shortcomings have generally been taken into account via conservative treatment planning (e.g. employing relatively large safety margins around the tumor and avoiding beam directions pointing at critical organs), unavoidably leading to non-optimal treatment plans. In state-of-the-art intensity-modulated proton therapy (IMPT), robust optimization treatment planning is being introduced as it is better suited to deal with planning uncertainties [1]. In-vivo dose delivery verification is possible by imaging the positron emitters created by the beam in the patient using positron emission tomography (PET). PET images show where the protons or ions have passed and enable, in an indirect way, to verify whether the irradiation was performed according to plan (for an overview, see e.g. [2]). The present-day use of PET for in-vivo dose delivery verification has a major drawback: information is delayed due to the radioactive half-life (up to 20 minutes) of the positron emitters.

We are investigating the possibility of real-time feedback by PET of the very short-lived ^{12}N nuclide (half-life 11 ms) [3,4]. Recently, experiments at the AGOR cyclotron facility of KVI-CART using two 20x20 cm^2 Siemens Biograph mCT PET scanner panels were performed. These experiments demonstrate feedback of the proton range within 90 ms with an accuracy of about 2.5 mm for 10^8 protons and 1.0 mm for 10^9 protons delivered within 10 ms. Such quick feedback makes real-time error detection and corrective action conceivable.

The status of ^{12}N PET imaging for real-time range verification in proton therapy will be briefly presented. Mainly, the optimization of this method in terms of hardware, software and protocols for clinical application will be discussed. The discussion will consider various types of accelerators, e.g. in terms of their specific beam time structure. Different ion beams (e.g. helium ions) will be considered, including the special case of PET imaging of very short-lived positron emitters being used as therapeutic beams.

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Toward hybrid γ-PET imaging of radioactive ion beams at FAIR

M.J. Safari[1], G. Dedes[1], P.G. Thirolf[1], A. Zoglauer[2], T. Yamaya[3], M. Durante[4], K. Parodi[1]
[1]Ludwig-Maximilians-Universität München, Department of Medical Physics, Germany
[2] University of California, Berkeley, USA
[3]National Institute if Radiological Sciences - QST, Chiba, Japan
[4]GSI Helmholtzzentrum für Schwerionenforschung, Biophysics Department, Darmstadt, Germany

Despite the rapid spread of proton and carbon ion therapy, full clinical exploitation of the benefits of the well-localized Bragg peak remains a challenge, and clinical practice still applies generous safety margins around the tumour and utilizes conservative beam directions to account for treatment uncertainties. To overcome these limitations, several physical secondary emissions are investigated for in-vivo and non-invasive localization of the Bragg peak [1]. To date, the most clinically explored method is Positron-Emission-Tomography (PET), which exploits delayed emissions of 511 keV annihilation photons following the decay of (pure) β^+-emitters like ^{11}C,^{15}O, produced in nuclear interactions of the primary stable therapeutic ions with the irradiated tissue. However, the amount of such radioactive by-products of the irradiation is fairly limited, and not obviously correlated to the stopping position of the primary beam. On the other hand, resorting to the original proposition of using primary β^+-radioactive ion (RI) beams (e.g., ^{11,10}C,^{14,15}O) for treatment would enable direct observation of the β^+-decays primarily generated from the stopping position of the therapeutic beam, enabling both an increase of signal as well as a more straightforward correlation to the Bragg peak [2,3]. Interestingly, isotopes such as ^{10}C and ^{14}O would not only enhance the signal due to their shorter half-life of ca. 20 and 70 s, but also contribute an additional third γ-emission, which could potentially enhance detection sensitivity [4,5]. Such intrinsically delayed PET signals could be complemented by the detection of energetic (~3-8 MeV) γ-radiation promptly (< ns) emitted from excited nuclei during irradiation [1], resulting in an almost instantaneous Bragg peak signature not blurred by physiological 'wash-out' processes. Although therapeutic use of RI beams was not conceivable through fragmentation of conventionally accelerated stable ions, it can become a future reality at facilities like FAIR, which allow for production of light RI beams of sufficiently high intensity and energy for such applications [6]. In this context, we aim at developing a novel hybrid on-line monitoring system able to image all above-mentioned prompt and delayed photon emissions, to support the precision of planned pre-clinical small animal experiments at FAIR [6]. To this end, we have recently upgraded the capabilities of the MEGAlib (Medium Energy Gamma-ray Astronomy library) software to handle simulation, classification and reconstruction of all possible PET, Compton and γ-PET events, and are currently investigating different system designs based on detector technologies under development at LMU and NIRS-QST (figure 1, a) toward a first prototype for eventual installation in CAVE M of FAIR. Initial results show the ability of such a system to detect single γ-rays (Compton scattering) with uncertainty of 2.8 deg FWHM (angular resolution measure) and coincidence annihilation γ-rays (PET) with uncertainty below 1 mm FWHM (width of line of response), yielding a promising spatial resolution of the reconstructed Compton, PET and Compton-PET images of 3.5 mm, 0.9 mm, and 0.7 mm FWHM, respectively (figure1, b-d).

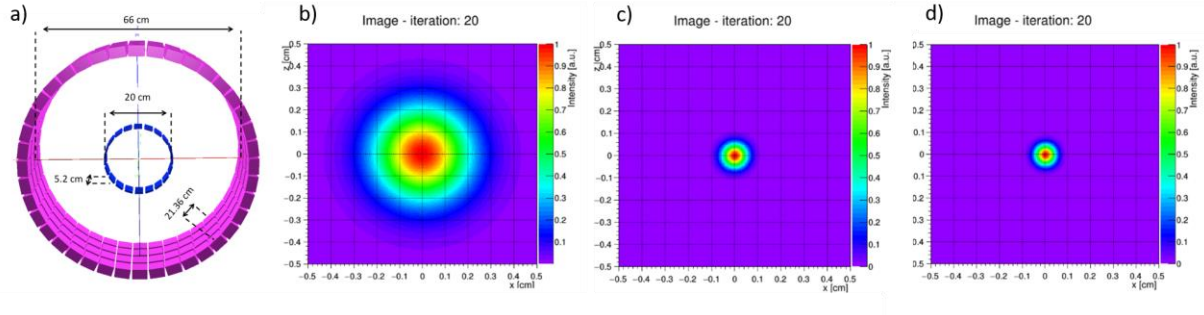

Figure 1. Exemplary hybrid gamma-PET imaging system using NIRS-QST detector technologies (a), resulting in the shown reconstructed images of a central ^{22}Na point source for b) Compton, c) PET, and d) Compton-PET events.

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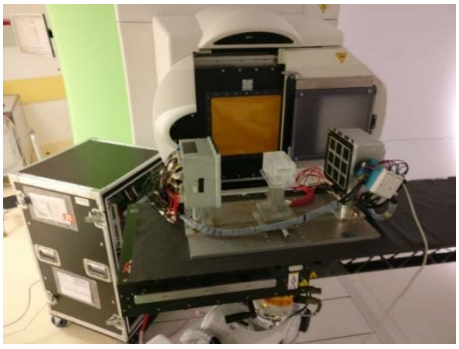
PET Real-Time Imaging of Ion Beams

V. Rosso[1], N. Belcari[1], M.G. Bisogni[1], R. Borgheresi[1], A.K. Kraan[1], M. Morrocchi[1], G. Sportelli[1]
[1] Department of Physics, University of Pisa and INFN, Italy.

Ion beams in radiotherapy have being assessed by researchers in the last decades exploiting their characteristic depth-dose profile. The possibility to deliver a conformal dose to the tumor region, minimizing the dose to the normal tissues located in the beam entry channel, led to the spread of particle therapy around the world. The research still goes further investigating new ions and also antiprotons. Nevertheless, the steep gradient at the end of the depth-dose profile makes these treatments much more sensitive to spatial uncertainties than conventional radiotherapy. These uncertainties will play a still major role thinking to high-dose rate particle therapy. The nuclear reactions of the incident ions and nuclei give rise to the production of beta+ isotopes along the antiprotons [1] and ion beams paths [2] allowing real-time imaging. In this context we propose to extend the usage of the monitoring system based on the detection of beta+ isotopes for the quality assurance in ion beam radiotherapy.

The proposer group have showed that it is possible to base the quality control in proton therapy [3] based on the comparison between expected (calculated via Monte Carlo simulations) and experimental activity distributions, and has developed an in-beam PET system that has operated in several proton therapy centers in Europe: DoPET. DoPET is a PET system based on two stationary planar heads. Each head has an area of 16x16 cm^2: it is based on LYSO crystal matrices (2 mm pitch) coupled to a PMTs (Hamamatsu H8500) and are readout by custom F/E electronics and DAQ. The detection system is very compact, and can be easily installed along the beam line: see Fig. 1. The activity profile along the beam direction is the reference figure, and we have shown that the activity profile width has a power low dependence [4]: thanks to these characteristics it is possible to check the ion beam delivery, detecting variations in the activity range down to 1mm. As the activity signal depends on the production of beta+ isotopes, being the PET measurement linear, also the ions fluence check is possible. Moreover, it is possible to extract information on the composition of the crossed medium: in fact, the activity decay rate is the sum of all the single isotope contributions, and the detection of relative variations in terms of Carbon and Oxygen composition are possible [5]. Thanks to all these features, it is possible to develop an image guidance technique. Using few selected pencil-beams from a high-dose rate treatment plan, as path-checker, it is possible to check if the dose delivery will be successful, and eventually, elaborate adaptive strategies to tune the dose distributions.



In conclusions, PET data are useful for:

- real-time imaging of the ion beam path
- quality control of treatments
- measuring the production cross sections of positron emitters in conjunction with an ion counter.

Figure 1: DoPET at CCB-Krakow (PL). The two stationary heads and the phantom are set on the treatment coach, in front of the beam nozzle. On the left the flying case containing the HV power supply and all the DAQ.

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Journal of Instrumentation, 14, (2019) C02001

A multimodal imaging system for in vivo range verification in particle therapy

M. G. Bisogni[1], the INSIDE collaboration
[1]University and INFN, Pisa, Italy

Particle therapy (PT) is a cancer therapy using ions for the treatment of solid and radioresistant tumors. One of the main issues in PT is the need to know the actual path of the beam in the patient. Prediction of the particles range must be as accurate as possible in the planning and delivery of the treatment. Potentially, safety margins could be reduced if routine *in vivo* range monitoring and verification would be available in PT facilities. Motivated by this request, many different approaches have been proposed in the past years [1]. Among them, the most consolidated is Positron Emission Tomography (PET), which allows to measure the activity of positron (beta+) emitting radionuclides produced by nuclear interactions of the beam with the crossed tissues [2]. Besides the detection of beta+ emitting nuclides produced by target or projectile nuclear fragmentation, the prompt emission of high-energy photons and, for ions heavier than protons, of light secondary charged fragments provide an instantaneous information of the beam range in the patient [3]. Over the last years several demonstrators of the aforementioned techniques have been realized and are now at different stage of readiness level for clinical investigation. It is however recognized that the most innovative approach on range monitoring relies on hybrid detection scheme that offers the unique combination of complementary information from different modalities. The INSIDE collaboration (University of Pisa, University of Rome "Sapienza", INFN of Milan and Turin and Centro Nazionale di Adroterapia Oncologica-CNAO, Pavia), since 2013 pioneered the development of a bimodal imaging system providing a robust range verification and monitoring during PT treatments [4]. The INSIDE bimodal system (figure 1) consists of an in-beam PET scanner and of a charged particle tracking system, called dose profiler (DP). INSIDE was installed at CNAO since 2016 and it has been successfully used in a pilot study to monitor a patient with lacrimal gland tumor [5]. The system is now committed to a clinical trial that includes 40 patients affected by head-neck cancers.

Building on the long-standing experience gained with INSIDE, the collaboration aims to propose a multimodal system based on the combination of an in-beam PET and a charged particle tracking system that is also capable of simultaneously detecting gamma radiation. This combination of techniques would make it possible to increase the sensitivity of the system, for example by implementing detection of simultaneous emissions of beta+ and gamma from isotopes such as 14O or 10C [6]. Furthermore, complementing the real-time information provided by the detection of prompt particles with the volumetric information offered by PET would open to the possibility of performing biological imaging, dynamic studies and tests on radiobiological models. The enormous potential offered by a multimodal system like the one proposed can take full advantage of the characteristics of the beams produced at FAIR. High-energy radioactive ion beams are particularly favorable for increasing the sensitivity of PET and ultra-high dose rates would allow to test monitoring schemes enabling adaptive therapy.

Figure 1: The INSIDE system at CNAO.

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Dosimetry

Radiation Quality of Therapeutic Ion Beam from Unconventional Accelerator Modalities

G. Magrin[1,*]
[1]EBG MedAustron, Wiener Neustadt, Austria

'Unconventional' and innovative ways of accelerating particles and using them for therapy, require also re-thinking of the characteristics of the detectors used for dosimetry and for radiation quality assessments.

For some of the radiation fields and modalities proposed, the delivery may foresee peculiarly high dose-rates in the scale from kilo Grey per second (as for the case of linear ion accelerators) and of the Giga Grey per second (as in the case of laser-driven ion accelerators). For other modalities, the fields show exceptionally high gradient, as in the case of microbeam radiation therapy, where regions of high-dose and low-dose are alternated in sub-millimetric patterns. Finally for other modalities, ionization characteristics show additional complexities (as in the case of antiproton beam therapy) resulting from the collision of matter and antimatter.

The radiation quality, which describes the characteristics of the radiation which are correlated to the biological effectiveness, is based on distributions. The most comprehensive way of describe the radiation quality is through distributions of the energy of the individual projectile particles in the specific site. This is often unachievable also today in the therapeutic proton and carbon-ion beams. The alternative is to perform an indirect characterization of the radiation quality though distributions of linear energy transfer (LET) or lineal- energy spectra. When the experimental conditions are more stringent, radiation quality must be reported using, instead of the whole distributions, their first and second moments: the track and dose averaged LET, L_F and L_D, or the frequency and dose mean lineal energies, $\bar{y}_F$ and $\bar{y}_D$.

The assessment of radiation-quality for unconventional therapeutic ion beams is a topic of increasing interest. The complexities that arise from the radiation-quality characterization should be tackled focusing on the experimental feasibility and proceeding in steps. The first step is to concentrate on high-dose-rate ion beams and provide a specific review of tools and methodologies for the radiation-quality characterization which are available today. The main strategies are the miniaturization of solid-state and tissue-equivalent-proportional- counter microdosimeters and the use of the variance-covariance technique [1,2]. The result will be the assessment the highest beam intensities at which a detectors, appropriately adapted, may operate to specify the radiation quality.

*This topic will be also covered in the framework of MediNet-Task2 collaboration, the network focusing on radiation-quality studies in ion-beam therapy financed as part of the program ENSAR2 by European Union's Horizon 2020 under grant agreement No 654002.

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Microdosimetry as a tool for radiation risk assessment

C. La Tessa[1,2], S. Agosteo[3], P. Cirrone[4], V. Conte[5], G. Cuttone[4,], M. Missiaggia[1], G. Petringa[4], E. Scifoni[2], F. Tommasino[1,2]

[1]University of Trento, Trento, Italy; [2]Trento Institute for Fundamental Physics and Application INFN-TIFPA, Trento, Italy; [3]Politecnico of Milan and INFN Section of Milan, Italy; [4]Laboratori Nazionali del Sud INFN-LNS, Catania, Italy; [5]Laboratori Nazionali di Legnaro INFN-LNL, Legnaro, Italy;

Estimating the overall dose following the exposure to a given, simple or complex radiation field and linking its quality to a biological outcome is one of the primary concerns both in radiotherapy and space radioprotection [1].

Microdosimetry has been recognized as one of the most promising approaches to address this issue as it can also asses the RBE for different endpoints using measurable physics quantities [2]. Currently, two methodologies are applied to link the direct measurements of lineal energy y to biological effects, the weighting function approach (BWF) [3] and the Microdosimetric Kinetic Model (MKM) [4].

Microdosimetry detectors are already used as standard radiation monitors inside the International Space Station (ISS) and have been proposed as potential tools for treatment plan verification and standard quality assurance activities in radiotherapy centers. For these reasons, microdosimetry can find an application in several research programs that are planned at FAIR.

Following the same rationale, dedicated microdosimetry tallies have been implemented in several Monte Carlo transport codes and tested against experimental data [5,6].

Although the microdosimetry approach has already provided results, there are several aspects that can be improved. From a detector point of view, the main progresses focus on improving the spatial resolution for a more precise characterization of the radiation field especially at its edges. Another limiting factor is represented by the maximum sustainable fluence rate. Currently, both these issues are being addressed by developing different types of detectors, including miniaturized TEPCs, silicon and diamond microsensors [7]. Another key improvement in this methodology is the development of a new model for obtaining the RBE, in alternative to the BWF and MKM approaches.

A collaboration between Politecnico of Milan (Italy), Laboratori Nazionali di Legnaro LNL (Italy), Trento Institute for Fundamental Physics and Applications TIFPA (Italy) and Laboratori Nazionali del Sud LNS (Italy) has been established to develop the different aspects of microdosimetry. An overview of the existing techniques will be given in this presentation, showing its applications both in space radioprotection and radiotherapy with ions. Planned and potential updates as well as future measurements will be also discussed in the framework of the new beams available at the FAIR facility.

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Recent development of solid-state microdosimetry for RBE study of ion therapeutic beams and radiation protection for astronauts in space

A. Rozenfeld (on behalf of CMRP Microdosimetry group and collaboration)
Centre for Medical Radiation Physics, University of Wollongong, Australia.

Based on many years of experience in development of silicon-on-insulator (SOI) microdosimeter, the Centre for Medical Radiation Physics (CMRP), University of Wollongong, has successfully developed a microdosimetric probe which is based on a SOI microdosimeter with 3D micron sized sensitive volumes (SVs) mimicking dimensions of cells, known as the "Bridge" and "Mushroom" microdosimeters, to address the shortcomings of the TEPC such as high voltage operation, large size which reduces the spatial resolution and wall effect [1]. Fig 1 shows the MicroPlus probe developed at CMRP connected to the SOI Mushroom microdosimeter.

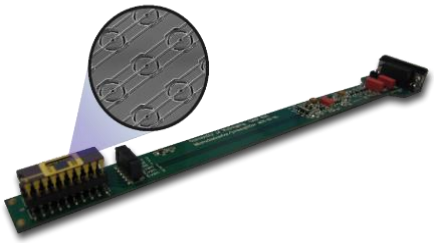

Fig. 1 MicroPlus probe connected to the microdosimeter with SEM image of the mushroom microdosimeter

The silicon microdosimeters provide extremely high spatial resolution and were used to measure the microdosimetry spectra in different heavy ions fields at Heavy Ion Medical Accelerator in Chiba (HIMAC), Japan and in a proton pencil-beam scanning (PBS) and passive scattering system at different accelerator facilities. Measured microdosimetric parameters were used for derivation of RBE_{10} using Microdosimetric Kinetic Model (MKM). Derived RBE_{10} values in response to 290 MeV/u carbon-ions SOBP is presented in Fig. 2. The RBE_{10} values obtained with the SOI microdosimeters match very well with those obtained from the TEPC measurements. Due to the high spatial resolution of the microdosimeter, a more detailed RBE_{10} distribution was obtained at the end of the SOBP compared to the TEPC.

Fig. 3 shows the comparison of the Geant4 simulated and microdosimetric measurement based RBE_{10} for the 400 MeV/u ^{16}O beam in water. Due to submilimetre spatial resolution, it was possible to see that the peak of physical dose does not coincide with the maximum RBE_{10}.

The developed SOI microdosimeters can be very useful for dose equivalent measurements in Solar Particle Events (SPE) and Galactic Cosmic Rays (GCR) mixed radiation fields for radiation protection of astronauts and evaluation of radiation shielding. Recently an experiment with different thicknesses of Al alloy to mimic the ISS wall [2] was carried out in 500 MeV/u Fe ions field at HIMAC to determine the quality factor, $\bar{Q}$ and the dose equivalent, Hp(10) per incident ion cm^{-2} at different depths in a phanotm downstream of the Al wall. Fig 4 shows the microdosimetric spectra and corresponding to them, $\bar{Q}$, for different scenarios.

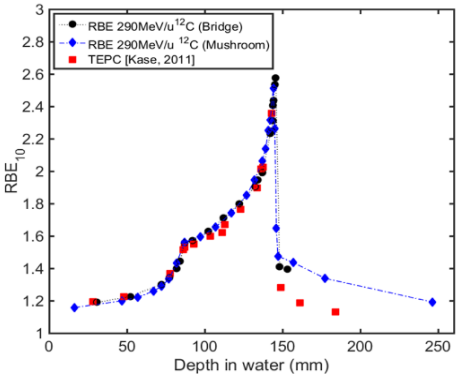

Fig. 2 Derived RBE_{10} along the central axis of the SOBP of ^{12}C ion beam, obtained by SOI bridge and mushroom microdosimeter and TEPC at NIRS.

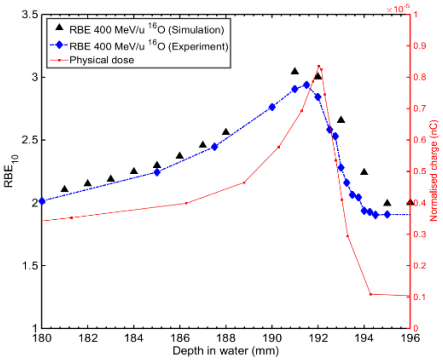

Fig. 3 Detailed view of RBE_{10} distribution obtained with the mushroom microdosimeters (μ^+ probe) as a function of depth in water for the 400 MeV/u ^{16}O pristine BP

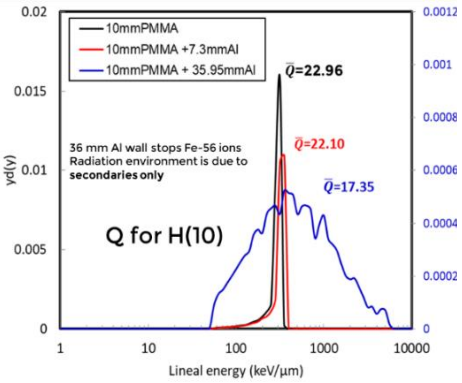

Fig. 4 Microdosimetric spectra obtained during 500MeV/u ^{56}Fe irradiations in free air

This work presented an application of SOI micodosimeters for RBE evaluation in heavy ion therapy and for $\bar{Q}$ and H determination in mimicking GCR radiation environment that can be used for radiation shielding optimization and radiation protection in space.

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Relative Biological Effectiveness (RBE) of a clinical eye proton therapy beam: experiments and Monte Carlo approach

G. Petringa[1], S Agosteo[2], A. Attili[3], A. Bianchi[5], P. Blaha[7], D. Bortot[2], F. P. Cammarata[1,4], V. Conte[5], G. Cuttone[1], C. Feoli[7], C. Gigliuto[1], R. Khanna[1], C. La Tessa[6], L. Manti[7], M. Missiaggia[6], D. Mazzucconi[2], A. Pola[2], S. Puglia[1], A. Rozenfeld[8], G. Russo[1,4], A. Selva[5], L. Tran[8], S. Tudisco[4], G.A.P. Cirrone[1]

[1]INFN-LNS, Catania (I); [2]Politecnico of Milan and INFN Section of Milan (I); [3]INFN Section of Rome III (I); [4]IBFM-CNR, Cefalù (I); [5]INFN-LNL, Legnaro (I); [6]INFN Section of TIFPA (I)

[7]University of Naples and INFN Section of Naples (I); [7]University of Wollongong, Wollongong (Australia)

CATANA (Centro di AdroTerapia ed Applicazioni Nucleari Avanzate) was the first Italian protontherapy facility dedicated to the treatment of ocular neoplastic pathologies. Since 2002, it is in operation at the LNS Laboratories of the Italian Institute for Nuclear Physics (INFN-LNS), to date 400 patients have been successfully treated. Nowadays, a slightly increased biological effectiveness (with respect to reference low-LET radiation) is considered in clinical proton treatment planning by assuming a fixed RBE of 1.1 for the whole radiation field. However, data emerging from various studies suggest and highlight how variations in RBE, which are currently neglected, might actually result in deposition of significant doses in healthy organs. Accurate knowledge of the RBE increase in eye protontherapy is of extreme importance as the distal part of the Spread-Out Bragg Peak (SOBP) often involves critical anatomical regions like optic nerve and the macula for which an excess of biological dose could lead to patient's vision loss. To our knowledge, while comprehensive literature exists on the clinical results of protontherapy treatment of uveal melanoma. In this study, melanoma derived from a metastatic axillary lymph node was used (MP38). In addition, to evaluate damage incurred by typical organ at risk, normal epithelial cells from the retina was used (ARPE19). A collaboration, between INFN-LNS, the University of Wollongong, the University of Naples, IBFM- CNR, INFN-LNL, INFN-MI and INFN-TIFPA is currently ongoing to perform an experimental measure of the RBE value along a typical SOBP for eye protontherapy. RBE will be evaluated from by a twofold approach, i.e. using four different micorodosimetric detectors (silicon detectors and mini-TEPCs) and the MKM model and by radiobiology measurements performed at seven positions along the CATANA 60-MeV SOBP.

Monte Carlo (MC) simulations of the whole experimental set-up, including the physical characteristics of the proton beam, will be implemented using the Geant4 toolkit. The spectra generated by these simulations will be used as the physical input for the radiobiological simulations based on the MKM model, from which an estimation of the RBE along the SOBP will be evaluated and compared with the experimental data.

Investigating ion track structure at FAIR

T. Friedrich[1], M. Durante[1,2], M. Krämer[1], M. Scholz[1]
[1]GSI, Darmstadt, Germany
[1]Institut für Festkörperphysik, TU Darmstadt, Darmstadt, Germany

A hallmark of the dose deposition of charged heavy particles - in contrast to photon radiation - is the emergence of a track structure around the particle's path, which is mainly formed by secondary electrons caused by a cascade of ionization processes. Notably, the properties of track structure depend strongly on particle type and energy. The high ionization density within the track structure implies the enhanced effect of particle radiation in comparison to a reference radiation quality with low LET (typically gamma radiation). The enhanced effect is modelled within biophysical simulations based on mechanistic considerations.

In the prominent class of amorphous track structure models, the ion effectiveness is derived assuming that the smooth 'amorphous' distribution of local dose across the tracks induces damage just as a reference photon radiation of the same dose would do. However, since the majority of radiation damage is induced by secondary electrons released by the primary particles and the damage yield depends on the electron energies, such models are implicitly based on the premise that the underlying secondary electron energy spectra are similar for ions and photons.

Amorphous track structure models like e.g. the local effect model (LEM) have found many applications in therapy and basic research [1]. While the model performs well in predicting the effects of a wide span of particle species and energies, also limitations have been uncovered. They have been detected at high particle energies such as in the entrance channel of therapeutic beams [2], where the effects are slightly underestimated by the model, and for very low energetic soft X rays [3]. Although based on the track structure properties in particular at high energies the effectiveness of ions is expected to converge to that of the low LET reference radiation, the discrepancy between model prediction and experimental data could be explained by potential differences in the secondary electron spectra.

Microdosimetric measurements unveil the microscopic energy deposition distribution which directly reflects the pattern of induced ionizations, and is strongly connected to the underlying secondary electron spectrum. With increasing distance to the track centre, the spectral properties of the secondary electrons and microdosimetric spectra are expected to change considerably. The FAIR facility will allow ideal conditions to experimentally investigate properties of track structure for the following reasons:

- The FAIR facility provides very high energies which lead to large track structures (about a factor 50 broader than with SIS 18), where spectral properties can be probed in any radial distance to the beam.
- The FAIR facility moreover provides large intensities, which will allow performing such measurements even at large distances where the local dose deposition of individual particles is low.

In fact, microdosimetric experiments at FAIR are being suggested [4]. In combination with track structure transport calculations, the spectra as a function of the distance to the track center can be used to analyse the impact of secondary electrons spectral properties on the effect enhancement within the large track structure patterns. This information can be used to check the impact of variable secondary electron spectra vs the amorphous track approach in effect predictions. Presumably, in particular low energetic electrons are expected to give rise to further effect enhancements. The results are therefore crucial for a basic understanding of the transition of physical into biological damage, and can be set in relation to the experience made so far at the current accelerator facilities available at GSI under same circumstances. All together the on-site infrastructure promises the ability to study track structure phenomena for arbitrary ion species and a broad energy range over ~3 orders of magnitude. Beyond therapy, the presentation highlights the relevance of track structure research for applications in space research and radiobiology.

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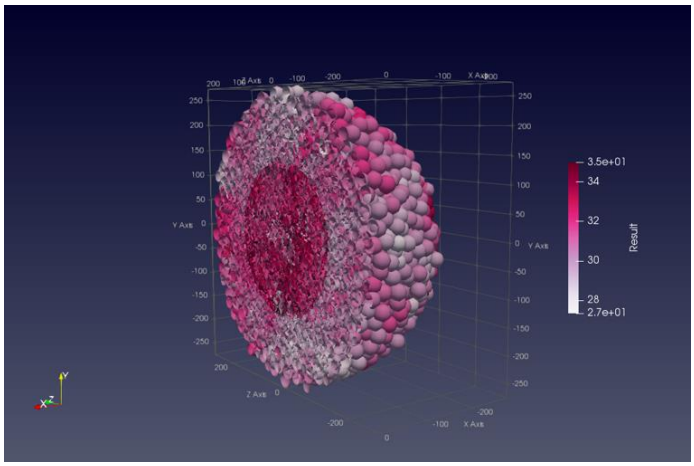
BioDynaMo: A platform for computational modelling and simulation of biophysical dynamics

R. Bauer[1,2] for the BioDynaMo collaboration
[1]School of Computing, Newcastle University, Newcastle upon Tyne, UK; [2]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

Biological systems usually involve highly complex processes, comprising different spatial and temporal scales. Moreover, since biological and physical dynamics are strongly interdependent, one major challenge in systems biology is to find a practical, common ground for their description. Fortunately, the vast technological advances in the last decades have opened up new avenues for experimental observation, collection and analysis. In particular, computational approaches allow to take into account large amounts of highly complex data.

Here, I will present the BioDynaMo (short for "Biology Dynamics Modeller") software platform [1], which is developed by an international consortium including Newcastle University (UK) and CERN (CH). It constitutes an open-source tool [2] for the computational biology community and allows to simulate millions of cells in a detailed 3D physical environment. In particular, BioDynaMo supports the usage of fundamental biological behaviours, including cell proliferation, cell death, migration or growth of cellular elements. Moreover, it accounts for different cell interactions, such as for instance via the secretion of diffusive substances, or mechanical forces. Importantly, an agent-based approach is used, which provides an intuitive way to devise biologically plausible multi-scale models.

I will present examples where BioDynaMo is used to model complex tissue dynamics involving physical mechanisms. As a first example, neuronal tissue development is simulated based on a small number of "gene-type" rules. It is shown that the developing system produces highly complex structures from a simple initial setting. In a second example, I will present simulations of cancer growth, constituting a computational basis for the study of the interaction between tumour and the local tissue environment. Finally, I will present work involving the impact of thermodynamics on cell morphology and integrity, constituting a novel approach to model and optimise the cryopreservation of biological tissues.



Overall, it is demonstrated that BioDynaMo can serve as a hypothesis generator and testing tool for biomedical research, including cancer treatment. Importantly, BioDynaMo is a highly performing [2] platform that promotes collaboration, reproducibility and interdisciplinarity. We anticipate that BioDynaMo will benefit future biomedical applications by providing a framework for detailed biophysical models, informing on treatment design and optimisation.

Figure 1. BioDynaMo simulation of cells in a 3D physical environment. Individual cells can interact with their local neighbourhood, allowing the modeller to simulate complex tissue dynamics. ParaView [4] is used for visualization.

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Preliminary results from a synchrotron dedicated Prompt Gamma Spectroscopy system: experiments with ^{1}p, ^{4}He, ^{12}C, ^{16}O beams

R. Dal Bello[1,2], P. Magalhaes Martins[1,3], G. Hermann[4], T. Kihm[4], M. Seimetz[5], S. Brons[6], J. Seco[1,2]

[1]German Cancer Research Center - DKFZ, Division of Biomedical Physics in Radiation Oncology, Heidelberg, Germany, [2]University of Heidelberg, Department of Physics and Astronomy, Heidelberg, Germany, [3]Instituto de Biofísica e Engenharia Biomédica - IBEB, Faculty of Sciences of the University of Lisbon, Lisbon, Portugal, [4]Max Planck Institute for Nuclear Physics, Heidelberg, Germany, [5]Instituto de Instrumentación para Imagen Molecular (I3M), CSIC-Universitat Politècnica de València, Valencia, Spain, [6]Heidelberg Ion-Beam Therapy Center – HIT, Heidelberg, Germany

Beam monitoring techniques aim to retrieve the position of the Bragg peak in the target in order to mitigate the planning limitations caused by the range uncertainties. This critical issue applies to all the beam species used in ion beam therapy. We propose the use of Prompt Gamma Spectroscopy (PGS) to provide on-line and in-vivo beam tracking for ^{1}p, ^{4}He, ^{12}C and ^{16}O beams accelerated by synchrotrons. We investigated the applicability of $CeBr_3$ scintillators for this purpose. These crystals combine a good energy and time resolution and low intrinsic activity, allowing the detection of the prompt gamma radiation over a wide energy spectrum [1]. We optimized with Monte Carlo simulations our spectroscopic unit based on a primary $CeBr_3$ and a secondary BGO for noise reduction. The combination of these two crystals promised a significant improvement of the signal to noise ratio in the detection of the discrete spectral lines [2]. Moreover, we retrieve the arrival time with a dedicated beam trigger. The data acquisition is based on an advanced FADC/FPGA system for high speed digitalization [3]. The development of the system focusses on the application of PGS in synchrotron based facilities. Such system is applicable not only to the clinical beam species (^{1}p and ^{12}C), but also to the ones in research phase (^{4}He and ^{16}O). The preliminary results show excellent performances in the detection of the gamma radiation over the full energy spectrum (Figure 1). Up to twenty independent spectral lines were identified from E = 511 keV to E = 6.8 MeV for the interaction of ^{1}p, ^{4}He, ^{12}C and ^{16}O beams on ^{16}O, ^{12}C or metal targets. Moreover, we measured a strong correlation of the residual range of the primary ^{12}C particles with the intensities of the discrete reactions. Future work will include a complete characterization of the system and the systematic measurement of the energy dependent cross sections.

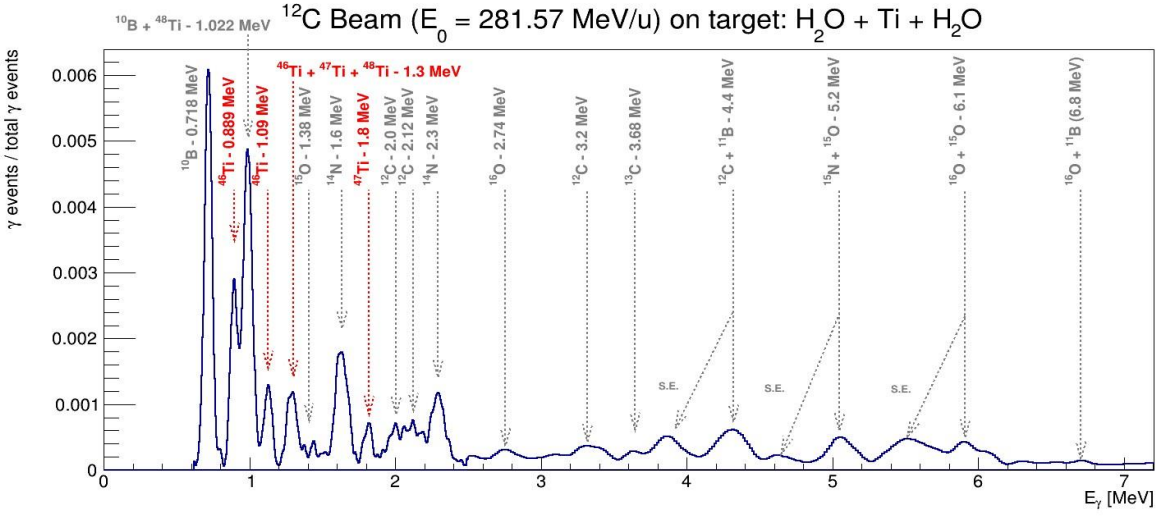

Figure 1. Prompt Gamma radiation detected with the optimized spectroscopic unit in presence of a ^{12}C beam impinging on a water target with a thin titanium insert.

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High-energy neutron field characterization with the Bonner sphere spectrometer NEMUS

M. Zboril[1]
[1]Physikalisch-Technische Bundesanstalt, Braunschweig, Germany

Future particle accelerator facilities like FAIR at GSI will be characterized by new qualities of the primary beam related to an increase in the maximal particle energy and intensity together with a pulsed structure. Consequently, the radiation field of secondary particles will present new challenges for spectrometry and dosimetry, which are needed for calibration or radiation protection purposes. Neutrons, due to their high relative biological effectiveness and special shielding requirements, represent an important part of the secondary radiation.

The energy distribution of secondary neutrons, anticipated at facilities like FAIR, range from the maximal energy of the primary particle (several GeV) down to thermal neutron energies (25 meV), thus spanning up to 12 orders of magnitude. A neutron spectrometer capable of covering such a large neutron energy range is the Extended Range Bonner Sphere Spectrometer (ERBSS) [1]. The ERBSS NEMUS [2] of the Physikalisch-Technische Bundesanstalt (PTB) serves as a secondary standard for the spectrometry and dosimetry of unknown neutron fields, traceable to PTB primary standards of the neutron fluence rate.

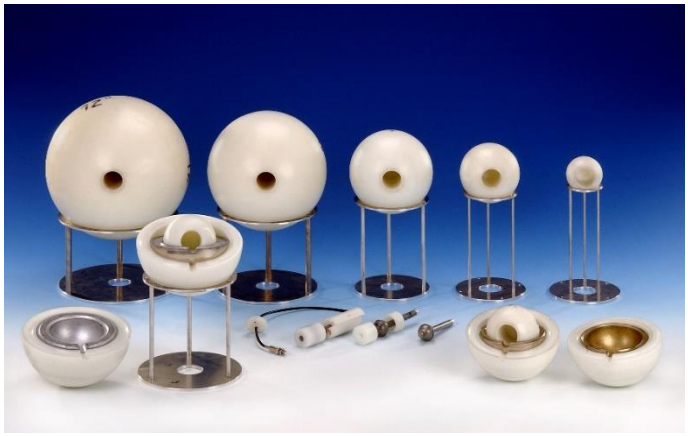

Figure 1: Setup of the ERBSS NEMUS of PTB.

NEMUS has been used to measure high-energy neutron fields at accelerator facilities [3] and proton therapy facilities [4,5]. In 2019/2020, the NEMUS setup (Fig. 1) will be used at GSI within the ESA-IBER-17 (Investigations into Biological Effects of Radiation) biophysics programme, in the scope of the project “Measurements of neutron production in thick passive shielding and assessment of LET distributions for radiobiological effects”. The main objective of the project is to test and optimize a multi-detector experimental setup for investigating the complex charged and uncharged radiation field produced by galactic cosmic ray-like radiation after traversing thick passive shielding. Such an approach will make it possible to benchmark Monte Carlo codes for high-energy neutrons production and transport.

In general, NEMUS has the potential to be used for high-precision spectrometric measurements of secondary neutrons at facilities like FAIR, where future experiments—ranging from space radiation protection to high-dose rate particle therapy—will need a traceable characterization of the radiation fields.

In the talk the NEMUS spectrometer will be briefly introduced and its potential applications in spectrometry of high-energy neutron fields will be outlined.

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Neutron Production in Heavy Ion Therapy

M. Nandy
Saha Institute of Nuclear Physics, 1/AF Bidhannagar, Kolkata 700064. India

In the global scenario of growing incidence of cancer particle therapy has emerged as one of the most preferred treatment procedure due to its high conformity of dose distribution. In spite of the high precision of dose concentration in the target tissue, there is a small risk of second malignancies along the path of the primary beam.

However, there is a second risk of radiation exposure from secondary radiation to the tissues not directly in the path of the radiation field. The secondary radiation can contribute to the total dose in the target tissue, alter the relative biological effectiveness or can deliver dose outside the target volume. In the case of proton therapy this dose arises solely from the neutrons and photons produced through nuclear interaction of the primary beam with the treatment head and the body tissue. A small fraction of the dose may be contributed by the light charged particles that are produced in the reaction. But in the treatment of tumours with carbon or other heavy ions a part of the secondary dose comes from the fragments of primary ion produced from nuclear reaction in the patient.

The neutron yield is dependent on the energy of the primary beam, material and aperture of the collimator and the air gap. Since neutrons have a long attenuation length in tissue these neutrons can produce a significant dose to organs other than and away from the primary target organ.

Though the best choice for all the scientific parameters important for charged particle treatment does not coincide for a single ion species, carbon is the most preferred one for certain tumours. But potential of new ions should be and are being probed. In the present work yield of neutrons and charged particles from carbon and other heavy ion induced reaction has been calculated. The dose distribution due to these particles has been simulated as a function of the penetration depth. It has been observed that for a single straight field the dose due to the secondaries produced in the patient is a few percent at a distance of ~10 cm beyond the Bragg peak. Yield of neutrons due to interaction of the primary beam in the collimator is much higher. These can be shielded off the patient with an optimized arrangement. At the end of the primary ion track the radial energy distribution due to primary ions falls off inversely with the square of the radial distance from the track centre. This is expected as the electrons released in the interaction can have only a very small fraction of the incident energy and are stopped in a small distance. These results will be discussed in the talk.

The exposures from secondary radiation outside the target volume are of concern particularly in paediatric and young patients as they have a long life expectancy. As we probe the possibility of new stable and radioactive ion beams for treatment of malignant tumours, the secondary dose from all possible sources and the risk of secondary malignancies there from needs to be investigated carefully.

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An Integrated System for 3D Energy Deposition Measurements in a Water Phantom for Hadron Therapy

J. Leidner[1], M. Ciocca[2], A. Mairani[2], F. Murtas[1,3], M. Silari[1]
[1]CERN, 1211 Geneva 23, Switzerland; [2]Fondazione CNAO, 27100 Pavia, Italy;
[3]INFN-LNF, 00044 Frascati, Italy

GEMPix [1] is a small gaseous detector obtained by coupling a small triple Gas Electron Multiplier (GEM) detector to a quad Timepix ASIC. It has a sensitive volume of 2.8 x 2.8 x 0.3 cm^3. After preliminary measurements with the GEMPix in the CNAO (National Centre for Oncological Hadrontherapy) water phantom [2], an integrated system for measuring the 3D energy deposition has been developed. It consists of a commercial water phantom with a remote-controlled positioning system, a reference ionization chamber to normalize the acquired data to the beam intensity and the GEMPix. Measurements of the 3D energy deposition represent an important step towards a possible use of the GEMPix for quality assurance or treatment plan verification in hadron therapy. Smooth, reproducible Bragg curves with small statistical uncertainties were obtained with carbon ions at CNAO. After corrections, GEMPix measurements match FLUKA Monte Carlo simulations within 10% for most data points for carbon ions of three different clinical energies. In addition to the Bragg curve also obtained by conventional quality assurance systems (typically arrays of ionization chambers), the GEMPix offers 2D images of the beam and a 3D reconstruction of the deposited energy with a very good spatial resolution due to its 55 µm pixel pitch. As this application requires a larger sensitive area matching the typical maximum radiation field size of 20 x 20 cm^2, other readout solutions based on the Timepix ASIC and on the detection of optical photons produced in the GEMs are currently under investigation.

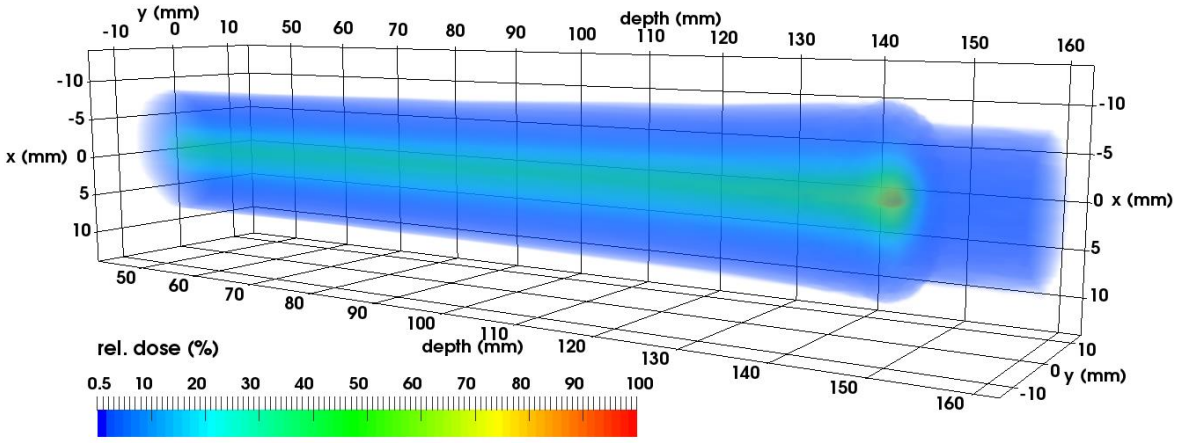

Figure 1: *The 3D energy reconstruction of carbon ions with a range of 150 mm in water: the beam enters the water on the left and spreads out. The Bragg peak and the fragmentation tail are also visible.*

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Electrons @ FAIR

M. Krämer[1], M. Durante[1,2], M. Fuss[1]
[1]GSI, Darmstadt, Germany
[2]Institut für Festkörperphysik, TU Darmstadt, Darmstadt, Germany

Electrons, in particular those with energies below a few keV, play a significant role as mediators of radiation action between primary radiation (ions, electrons, photons) and targets (biological structures, electronic devices [1]).This holds even for fast charged particles at FAIR energies, because the vast majority of secondary electrons is still emitted at energies in the sub-keV range. At the same time, interaction cross sections reach the maximum in the very same energy range, making these electrons the most important ones for direct as well as indirect radiation action (radical production).

For this very reason, we propose both experimental as well as computational investigations of low energy electron actions over the entire range of FAIR projectile energies.

On the experimental side spectrometer devices designed to measure double differential production cross sections of low energy electrons will be necessary. For example, the GSI Toroid [2] could be modernized and equipped so that it can be used with all experimental facilities of the future FAIR accelerator complex (Unilac, SIS, APPA, Cryring). On the computational side we are constantly developing our in-house TRAX simulation code which is capable of describing radiation action of electrons on the micro- and nanometer scale [3,4]. Recently, TRAX has been extended to describe radiation chemistry as well [5].

Investigations will include determination of basic data such as single and double differential production cross sections from solid targets and possibly from liquid targets such as water, which is of particular importance for radiation action in biological systems. These data would fit nicely into radiation chemistry simulations [5].

Complementary experimental setups like that described in ref. [6] may shed some light on the production of biologically active radicals such as OH.

Finally, extensive computational investigations are planned for ion track structure at high energies, and these calculations can lead to improvements in the treatment planning used for heavy ion therapy [7].

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Dry DNA stability after irradiation with swift heavy ions

M.Yu. Karganov[1,2], *I.B. Alchinova*[2], *M.V. Polyakova*[1,2], *V.I. Feldman*[3], *S.A. Gorbunov*[4], *O.M. Ivanov*[5], *R.A. Rymzhanov*[5], *V.A.Skuratov*[5,6,7], *A.E. Volkov*[4,5,8]

[1] The Institute of General Pathology and Pathophysiology, 8, Moscow, Russia
[2] Research Institute for Space Medicine, Federal Biomedical Agency of Russia, Moscow, Russia
[3] Lomonosov Moscow State University, Moscow, Russia
[4] P.N. Lebedev Physical Institute of the Russian Academy of Sciences, Moscow, Russia
[5] Joint Institute for Nuclear Research, Dubna, Moscow Region, Russia
[6] National Research Nuclear University MEPhI, Moscow, Russia
[7] Dubna State University, Dubna, Russia
[8] National Research Center 'Kurchatov Institute', Moscow, Russia

Effects of irradiations of Phage Lambda dry DNA samples at room and cryogenic temperatures with 158 MeV Xe (S_e^{Xe} = 10.8 keV/nm) and 48 MeV Ar (S_e^{Ar} = 3.5 keV/nm) ions at IC-100 cyclotron of Flerov Laboratory of JINR were investigated. Site-specific enzymes restriction endonucleases were applied to indicate DNA damages induced by these ions.

Electrophoresis was applied to analyze the dependencies of the distributions of DNA fragments sizes on the ion fluence ranging from 10^8 cm^{-2} to 10^{10} cm^{-2}.The positions of the bands on the electrophoregramm were compared with those of the standard of DNA fragments of known sizes (ladder mix). Irradiations with the both ions demonstrated that more bands of DNA restriction fragments ranging from 3000 to 500 b.p. appear when the ion fluence increases. Irradiations of DNA with 154 MeV Xe ions realizing the larger electronic stopping resulted in the larger numbers of detected bands at all applied fluences. At the largest fluences (~10^{10} cm^{-2}) a great number of small DNA fragments (less than 100 b.p.) occurs forming a diffuse cloud without any bands.

Electron paramagnetic resonance (EPR) technique was also used to investigate damages of a dry DNA sample irradiated at the cryogenic temperature (140 K) with 158 MeV Xe ions up to the fluence 8.6 x $10^9$$cm^{-2}$. A poorly resolved signal centered at the *g*-factor value for the free electron $g \approx g_e$ was detected, which probably results from a mixture of different-type radicals trapped in the DNA film. The total concentration of paramagnetic species in this sample was estimated to be 1.3 x 10^{19} spin/g.

A number of dry DNA samples were irradiated with carbon and iron ions (10.4 MeV/u, 4.6 MeV/u, 10^8 cm^{-2},10^9 cm^{-2}, 10^{10} cm^{-2}) at UNILAC GSI in the frame of FAIR Phase-0. Preliminary results of these irradiations are also discussed.

Initial damage of dry DNA by swift heavy ions

F.O. Akhmetov[1,2], R.A. Rymzhanov[3], Alexander E.Volkov[2,3,4]

[1] National Research Nuclear Institute MEPhI, Kashirskoe shosse, 31, 115409, Moscow, Russia

[2] National Research Centre 'Kurchatov Institute', Kurchatov Sq. 1,123182 Moscow, Russia

[3] Joint Institute for Nuclear Research, Joliot-Curie 6, 141980 Dubna, Moscow Region, Russia

[4] P.N. Lebedev Physical Institute of the Russian Academy of Sciences, Leninskij pr. 53,119991 Moscow, Russia

The kinetics of initial excitation of dry DNA in tracks of swift heavy ions decelerated in the electronic stopping regime is modeled. We choose dry DNA to separate effects of DNA damage by radicals formed in water.

MC code TREKIS [1] was applied for simulation of excitation of the electron subsystem of the DNA and the kinetics of energy transfer to the ion subsystem of the material in the nanometric vicinities of the projectile trajectories. To take into account the collective response of these subsystems to excitation the dynamic structure factor – complex dielectric function formalism was used when forming cross sections applied in TREKIS.

Spatial distributions of the energy and momentum transferred from relaxing electrons to the DNA ion system were used as initial conditions for a molecular dynamics modeling of further response of this system resulting in additional damage formation.

Finally, spatial distributions of disrupted bonds and defects appeared in the dry DNA at ~10-100 ps after ion impacts were obtained for fast C, Fe and Au ions of various energies.

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Development of an analytical model for the depth dose profile produced by gamma radiation

S. Elj[1], *A. Ben Ismail*[1]

[1]Laboratory for Research on Energy and Matter: Development of Nuclear Sciences / LR16CNSTN02, National Centre for Nuclear Sciences and Technology, Sidi Thabet technopark - 2020 BP 72, Tunisia.

Monte Carlo codes are among the most used tools today for calculations and simulations related to medical physics [1] and particularly for studies of low dose medical applications.

In this work, we have undertaken on the development of an analytical model with the aim of calculating the deposit dose produced by ionizing radiation inside a medical phantom (filled with light water). The CNSTN cobalt 60 source irradiator was used as the experimental validation platform for this study. A Monte-Carlo modeling of the irradiator was thus performed by the Geant4 toolkit [2], with validations of some dose deposition results obtained by referring to previous experimental work. The model was then adapted to our case of study, by developing a more specific configuration, suitable for gamma radiation beam and variable energy beams.

The study of the theoretical behavior of the doses produced by these photons [3] in a phantom filled with water was also carried out. The numerical results obtained demonstrate different behaviors according to the different energies. Digital fitting were then made by the Matlab tool for these different behaviors. The compilation of all this resultats led to the development of an analytical model for the prediction of the behavior of the deposited doses in the case of the studied phantom.

Further studies of these same works, with 2D analytical modeling and the generalization of the study for the cases of other types of radiations, will be established later.

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Radiobiology

Normal tissue biological models to investigate radiation-induced side effects

P. van Luijk[1], L. Barazzuol[1,2], S. Both [1], S. Brandenburg[3], R.P. Coppes[1,2]

[1] Dept. of Radiation Oncology, University Medical Center Groningen, Groningen, The Netherlands,
[2] Dept. of Biomedical Sciences of Cells and Systems, Section Molecular Cell Biology, University Medical Center Groningen, Groningen, The Netherlands
[3] KVI-CART, University of Groningen, Groningen, The Netherlands.

Introduction

During radiation exposure, especial for medical use in diagnostic procedures and therapy, healthy tissues are exposed to radiation, potentially leading to damage and organ dysfunction. This may have severe consequences in terms of feasibility of administering curative treatments and reduction of quality of life of patients. Insight in targets and mechanisms at the cellular, tissue, organ and organism level may allow the development of prevention and treatment strategies to mitigate these issues.

Models and methods

We have developed in vitro and in vivo models of radiation-induced organ dysfunction of salivary gland, thyroid gland, brain, spinal cord and the cardio-pulmonary system. The in vitro models consist of recently developed possibility to culture animal and patient stem cell derived organoids; 3D cell culture systems closely resembling tissues and tumours of which they are derived. For the brain, organoids are generated from human pluripotent stem cells. The consequences of loss of (stem) cells are studied in organoids (salivary gland, thyroid gland and brain) and small animal models (mice and rats). These models allow the investigation of mechanistic and clinical related response of the tissue or cancer stem cells, as well as the parachyme to different radiation qualities, such as DDR, RBE, senescence immune response etc.

The KVI-CART facility currently provides high-precision image-guided proton irradiation, allowing the specific irradiation of defined sub-volumes and the investigation of the role of damage to specific anatomical structures in the response of these organs. This facility is currently being upgraded to also include online image guidance and other radiation qualities.

Excitingly, characteristic responses of the salivary gland and cardio-pulmonary models have been validated in prospective trials (clinicaltrials.gov identifiers NCT01955239 and NCT02377934) in patients receiving radiotherapy for head-and-neck cancer and lung cancer. Specifically, the finding that stem cells are responsible for regeneration of salivary gland tissue after irradiation was confirmed in a prospective randomized controlled trial in which toxicity after stem cells sparing IMRT was compared with toxicity in patients receiving standard treatment. Similarly, characteristic changes in the cardio-pulmonary circulation resembling pulmonary arterial hypertension were confirmed in a prospective cohort study in patients treated for lung cancer. Such inter and intra tissue differences in radiation response needs to be investigated in other organs as well and should also be related to different radiation qualities.

Aim / outlook

Using these models we aim to study various topics relevant to therapeutic use of radiation:

- Spatial variations of radiobiological effectiveness (RBE) of dose deposition in particle therapy
- Variations of RBE with different endpoints and mechanisms
- The influence of radiation quality on tissue microenvironment
- Modulate/Target radiation responses such as senescence and autophagy with different radiation qualities
- Study radiation drug/immune therapy interactions in all of the above
- Normal tissue response to different approaches of delivering radiation (FLASH, minibeam, etc.)

Conclusion

Using the described models in conjunction with the various irradiation facilities will provide unique opportunities to study the aforementioned topics as well biological responses to radiation in general.

The Impact of Lipid Metabolism in Radiation Resistance

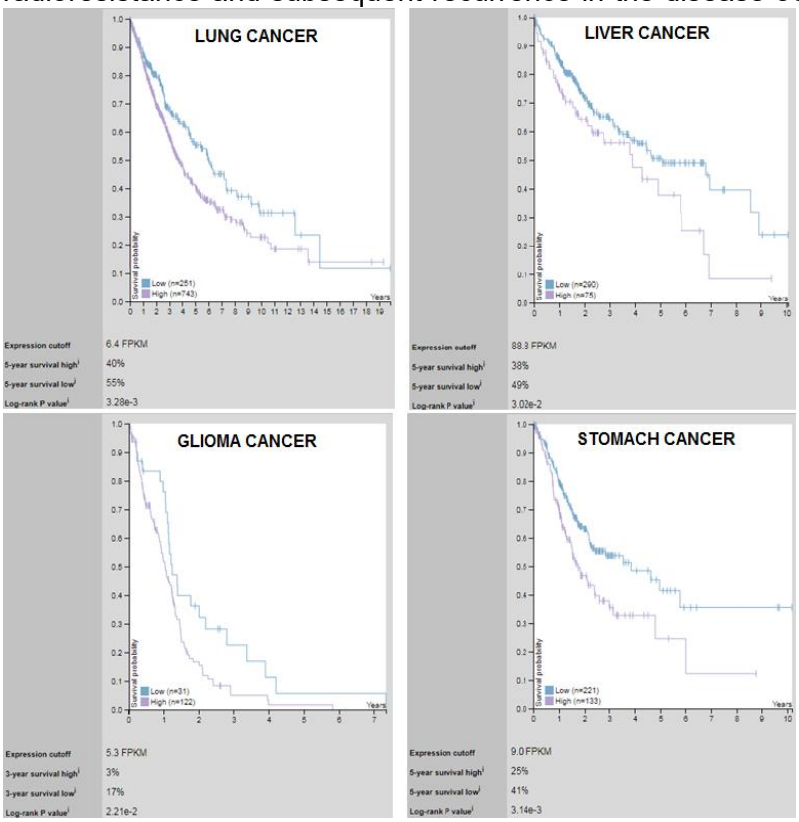
M.G. Marafioti [1, 2], L. Tirinato [1], F. Pagliari [1], J. Jansen [1,3], R. Hanley [1,3], J. Guerreiro [1,4], B. Yao [1], T. Ribeiro [1], F.S. Costanzo [2] , J. Seco [1,3].

Presenting and Corresponding Author: Joao Seco (j.seco@dkfz.de)

[1] Biomedical Physics in Radiation Oncology, Deutsches Krebsforschungszentrum Heidelberg, Germany
[2] Molecular Oncology Lab, Department of Experimental Medicine, Univ. Magna Gaecia of Catanzaro, Italy
[3] Department of Physics and Astronomy, Physics Faculty, Heidelberg University, Germany
[4] Centro de Ciências e Tecnologias Nucleares (C2TN), Instituto Superior Técnico, ULisboa, Portugal

Introduction

Despite all recent advances in the detection and therapy of cancer, it still remains as the 2nd highest cause of deaths all around the world. Radiotherapy (RT) is one of the most important and non-invasive treatment method, commonly used either as primary modality or in conjunction with other treatments. Unfortunately radioresistance and subsequent recurrence in the disease occurs in numerous patients that have received RT. A small population of cancer cells known as Cancer Stem Cells (CSCs) are believed to be responsible for radioresistance in various types of cancer. To date, the mechanism that confers radio-resistance to CSCs is still unclear. In the last years, altered lipid metabolism and lipid droplets (LDs) accumulation have been recognized to have an important role in CSC tumorigenicity. In figure 1, we show 5-year survival for lung, liver, glioma and stomach patients with 1) high and 2) low expression of the perilipin-2 (PLIN2) gene, obtained from the human protein data atlas (https://www.proteinatlas.org/).



The data demonstrates that lipids can play an important role in predicting patient 5-year survival probability. To this regards, our study aims to understand the LD expression and role in radioresistant in MCF-7 (breast), H460 (lung), H4 (neuro-glioma), PC3 (prostate) and T24 (bladder) cancer cells.

Figure 1: Patient 5-year survival as a function of high and low expression of Perilipin-2 ('PLIN2) gene expression in 1) lung, 2) liver, 3) glioma and 4) stomach cancer.

Methods

Radiation clonogenic assays were performed for different cancer cell lines: MCF-7, H460, H4, PC3 and T24. Cells were irradiated with a 6MV linear accelerator (LINAC) with a field size of 20cm by 20cm. Reactive oxygen species (ROS) and LD double staining was performed on the aforementioned cells using CM-H2DCFDA and Nile Red, respectively. Fluorescence activated cell sorting was used to sort cells into two sub-populations (LD^{High} and LD^{Low}), in order to investigate the functional role of LD in cancer cell radiation resistance. Moreover, gene expression analysis was assessed by real-time PCR for irradiated and non-irradiated cells.

Results and Conclusions

Our data show that radioresistant cells present a common lipid alteration, specifically an increase in LD content. Interestingly, the highest clonogenic potential was mainly shown by the LD^{High} sorted subpopulation. This new radioresistant phenotype correlates with a CSC phenotype.

A Pointillist View on Particle Tracks and DNA-Repair in 3D-Conserved Cell Nuclei by means of Super-Resolution Localization Miroscopy

M. Hausmann[1], J.-H. Lee[1,2], E. Maus[1,2], E. Brieger[1], R. Muhtadi[2], E. Wagner[1], E. Bobkova[1], F. Bestvater[3], S. Schumann[2,4], I. Falkova[5], M. Falk[5], G. Pilarczyk[1],G. Hildenbrand[1,6], H. Scherthan[2]

[1]Kirchhoff-Institute for Physics, University of Heidelberg, Heidelberg, Germany; [2] Bundeswehr Institute of Radiobiology, Munich, Germany; [3] German Cancer Research Center (DKFZ), Heidelberg, Germany; [4] Dep. Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany; [5] Czech Academy of Sciences, Institute of Biophysics, Brno, Czech Republic; [6] Dep. Radiation Oncology, Universitätsmedizin Mannheim, Mannheim, Germany

The three-dimensional architecture of genomes on the meso- and nano-scale acts as an important supra-layer of gene regulation and fundamental biological processes such as DNA damage response and repair. In this context, chromatin and protein nano-probing and super-resolution microscopy are powerful methods for topological analyses of genomic targets [1] in native chromatin and repair protein complexes in single cells at resolutions of single antibodies, proteins, histones, short DNA stretches, etc. We use multi-colour nano-probing (specific antibodies and/or specific oligonucleotides) and single molecule localization microscopy (SMLM) [2] to analyse the nano-architecture and -dynamics of DNA damage markers, chromatin markers, and DNA repair protein complexes in 3D-conserved nuclei of different cell types after exposure to various types (low-LET, high-LET; α-, β-particles) and doses of ionizing radiation (e.g. Figure 1 below) [3,4]. Localization microscopy of dispersed genomic *Alu* sequences has also resulted in linear-quadratic dose-effect curves for low to higher dose ranges, which may be related to DNA breakage events preferentially in these regions [5]. In addition, the spatial distribution-changes of anti-H3K9me3 labelled heterochromatin clusters have indicated a dose-independent chromatin relaxation upon radiation exposure [6].

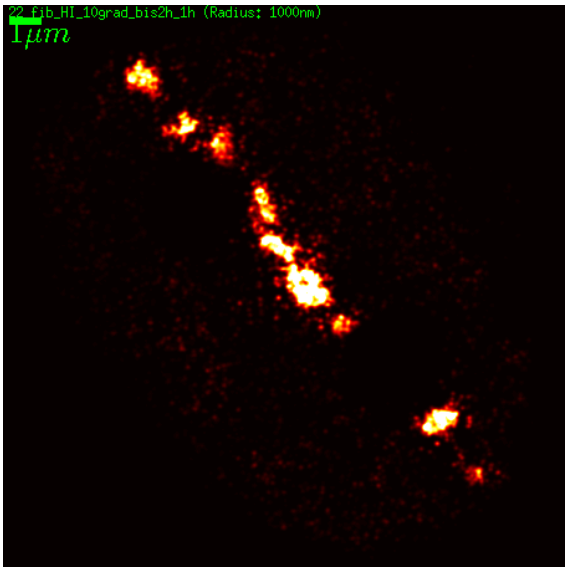


Figure 1: SMLM measurement of 53BP1 labelling 1 hour after N-ion irradiation.

We can show that single molecule localization microscopy could be used to study damages along high LET particle tracks and the associated repair protein recruitment over time. So far, our studies have revealed a cell- and radiation type-specific nano-architecture of DNA damage foci with respect to γH2AX, Mre11 or 53BP1 and their dynamic molecular rearrangements during repair processes. Correlations to radio-sensitivity were identified after N-ion irradiation. Our studies will contribute to the molecular understanding of cellular radiation responses at the sub-light microscopic chromatin levels, thereby showing how chromatin and repair foci nano-architecture contribute to repair pathway decision, laying the basis for improved biological dosimetry and radiotherapies in the future.

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lncRNA-actin cytoskeleton axis regulates cellular response to heavy particles

H. Pei[1], Z. Guo[1], W. Hu[1], A. Wu[1], W. Mao[1], J. Nie[1], B. Li[1], T.K. Hei[1,2], and G. Zhou[1]

[1] State Key Laboratory of Radiation Medicine and Protection, School of Radiation Medicine and Protection, Collaborative Innovation Center of Radiological Medicine of Jiangsu Higher Education Institutions, Medical College of Soochow University, Suzhou 215123, China;

[2] Center for Radiological Research, College of Physician and Surgeons, Columbia University, New York, NY 10032, USA

It is no doubt that heavy particles induce highly lethal effects on tumor cells; nevertheless, the biological mechanisms remain unclear enough. Basing on the classic Target theory, DNA is considered as the target of ionizing radiation. However to heavy ion irradiation, we speculate that actin cytoskeleton is very possibly a target as well because it is a multifunctional subcellular organ and plays an important role in cell migration, division, signaling transduction, transportation, and sensing mechnical variation both inside and outside. We identified a long non-coding RNA, LNC CRYBG3, which is inducible by ionizing radiation, especially heavy particles. We elucidated that it interferes with the assembly of actin cytoskeleton by directly binding to G-actin, which consequently blocks the formation of constriction ring and induces binucleated cells. We further clarified that LNC CRYBG3 also interacts with G-actin and Bub3/APC complex and induces aneuploidy by blocking cell division processing. These findings indicate that LNC CRYBG3 plays an important role in regulating cell division by targeting actin cytoskeleton and its ectopic expression results in the death of tumor cells by disturbing G-actin assembly and consequently blocking both cytokinesis and nuclear division.

Ion beam stimulation therapy for iron-oxide mineral forming neurodegenerative disease

J.-K Kim, Y. Choi, J.-G Jeon*
Biomedical Engineering, School of Medicine, Catholic University of Daegu,

Daegu City 42472 Republic of Korea, *jkkim@cu.ac.kr

Iron oxide magnetite was identified as redox-toxic mineralization in hallmarks of AD from patient or transgenic AD mice brain (1-3). We have discovered therapeutic effect of proton stimulation in AD plaque targeting magnetite. Our prior works (4-5) as proof-of-concept studies of proton stimulation on iron oxide minerals in Aβ fibril or in a plaque-forming transgenic AD mice model demonstrated disruption of Aβ-magnetite complex and removal of Aβ-plaque burden (60-90% in single treatment) and detoxification of ferrous magnetite into soluble ferric magnetite in dose-dependent manner. Proton stimulation was performed in traversing pristine mode without deposition Bragg peak inside tissue with entrance dose of 1-4 Gy. Therefore, this innovative treatment on AD brain did not damage on normal tissue including microvessel, demonstrating no ischemic damage or inflammation, haemorrhage after treatment. We suggest further study with heavy ion beam to take an advantage of higher peak-to-plateau ratio at higher energy and enhanced electron emission from magnetite via nanoradiator effect in 1-5 Gy compared with proton stimulation.

Since iron-oxide mineral is not only in AD dementia but also Parkinson's disease, we want to organize international collaborative research group for these studies under umbrella of GSI in a wide range of investigational subjects.

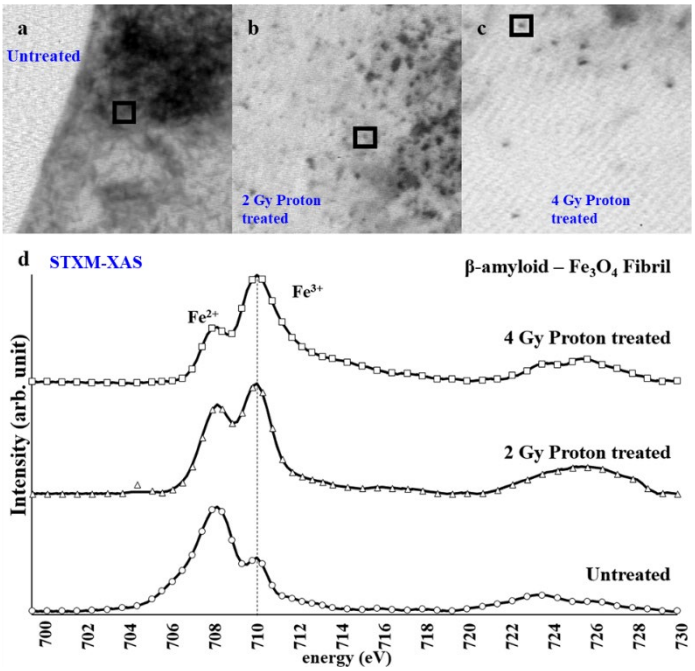

Figure 1: STXM-XAS study shows conversion of ferrous into ferric magnetite.

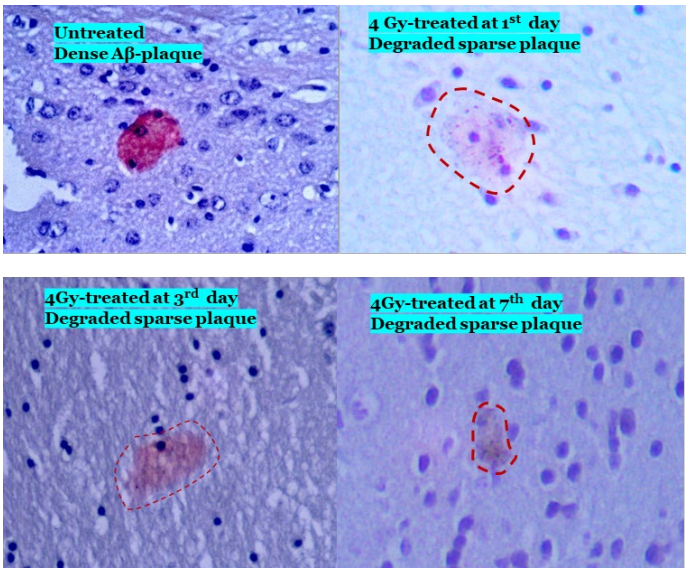

Figure 2. Congo Red staining (plaque) were reduced by more than 78-99 % in a dose-dependent and kinetic manner after single dose treatment.

[1] B. A. Mahera et al., PNAS 113 (2016) 10799.

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Radiobiology data with low energy neutrons

M. Pedrosa-Rivera[1,2], T. Forsyth[1], U. Köster[1], I. Porras[2], J. Praena[2], M.J. Ruiz-Magaña[2], M.C. Ruiz-Ruiz[2]
[1]ILL, Grenoble, France; [2]UGR, Granada, Spain.

Historically most of the radiobiology data for neutrons have been obtained at facilities with a mix of fast neutrons, epithermal neutrons, thermal neutrons, and gamma rays [1, 2]. As the result of the irradiation is a mixed field, it is not possible to directly study the effect of one of the components alone. The radiobiological effect of neutrons alone is therefore obtained from differential measurements which are challenging and intrinsically affected by larger uncertainties from the background deduction.

High flux reactors and spallation neutron sources can be an option to study the effect of low energy neutrons. Equipped with so-called neutron guides, they are sources where neutrons are efficiently transported over large distances by total reflection on a vacuum-matter interface. These neutron guides are slightly bent to prevent a direct view on the source. Only thermal and slower neutrons can follow the curvature by total reflection while faster neutrons and gamma rays go straight and are stopped in the shielding of the neutron guide. Due to larger critical angles cold neutrons can be more efficiently guided than thermal neutrons and higher beam intensities are available for experiments.

One such beam, called PF1b, exists at Institut Laue-Langevin in Grenoble. Experiments that study nuclear reactions induced by neutron capture or the effects thereof are performed there. For nearly all neutron capture reactions the cross-section follows at low energies (thermal and below) a perfect 1/v behaviour, where v is the neutron velocity. Therefore cold neutrons can fully replace thermal neutrons as long as the so-called thermal-equivalent capture flux (or just capture flux) is used.

Different mammalian cell lines grown in one layer were irradiated in such beam, obtaining a survival curve by clonogenicity assays. This survival curve (see figure) shows the effect of the cold beam (plus a small contribution of gamma rays produced locally by interactions in the sample). By a comparison with the effect on the same cell line exposed to a pure gamma ray irradiation, the Relative Biological Effectiveness (RBE) of thermal neutrons can be extracted.

Also, an isotopic substitution of nitrogen was done with one of the cell lines. By comparing the effects on samples with natural isotopic composition (which is dominantly ^{14}N) with samples where the ^{14}N was quantitatively replaced with ^{15}N (which has negligible neutron capture cross-section), the isolated effect of the ^{14}N capture reaction could be determined. This is a pioneering experiment where for the first time the RBE of the $^{14}N(n,p)^{14}C$ reaction could be deduced.

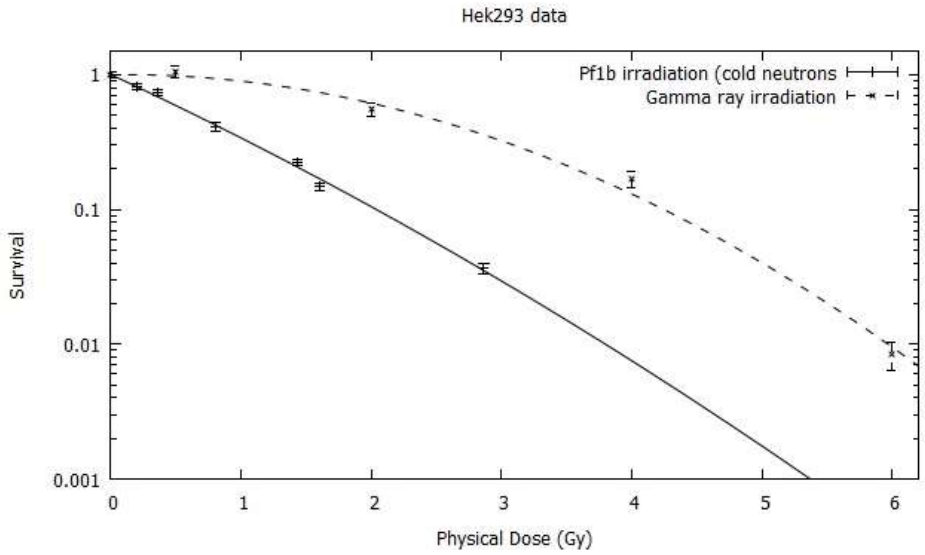

Figure 1: Survival results for embryotic cells (Hek293). The straight line corresponds to the effect of the cold neutron beam irradiation at ILL and the broken line corresponds to the effect of a gamma ray irradiation at a hospital LINAC.

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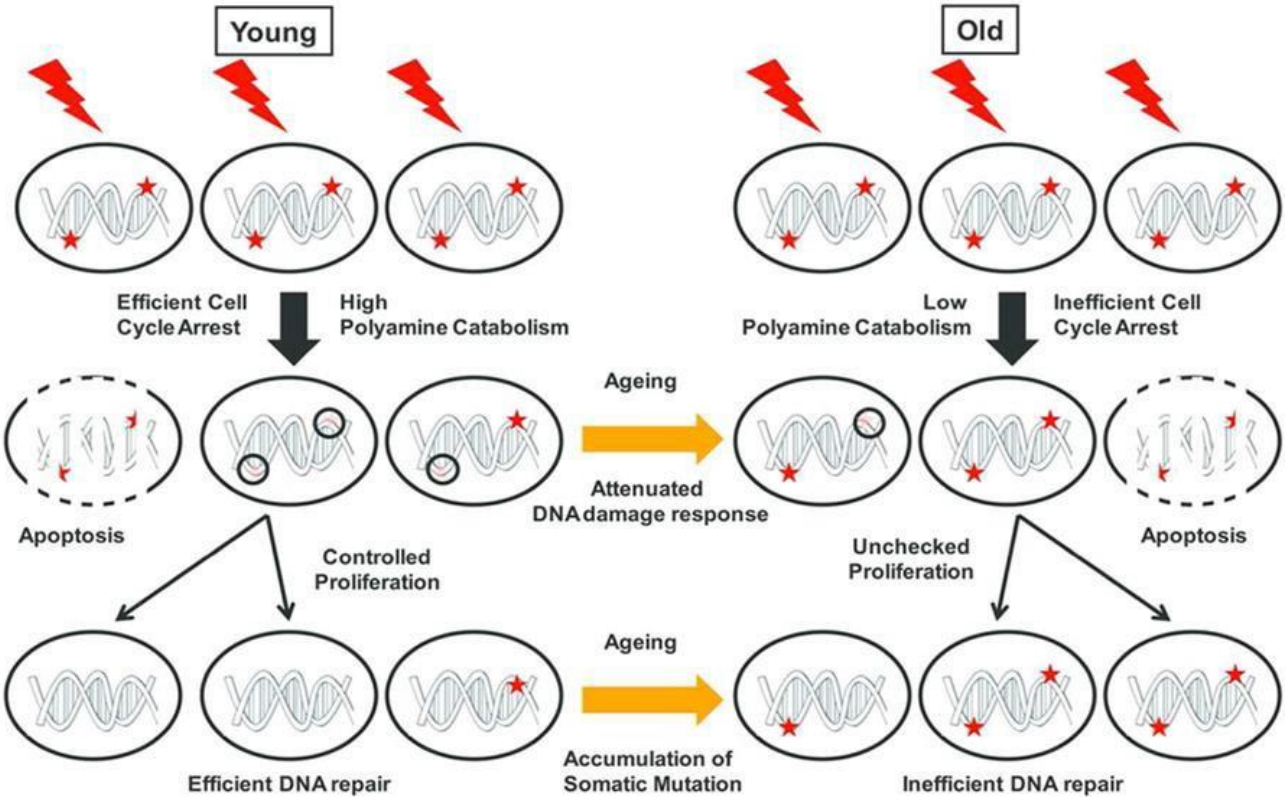
Radiation Metabolomics: Biomarkers and Beyond

S.K. Manna[1], S. Golla[2], K.W. Krausz[2], J.R. Idle[3] and F.J. Gonzalez[2]
[1]Biophysics and Structural Genomics Division, Saha Institute of Nuclear Physics (HBNI), Kolkata 700064, India; [2]Laboratory of Metabolism, National Cancer Institute, National Institute of Health, Bethesda, MD 20892, USA; [3]Department of Clinical Research, University of Bern, Murtenstrasse 35, 3008 Bern, Switzerland.

Exposure to ionizing radiation may take place due to nuclear accidents, sabotage, occupational hazards or therapeutic interventions. A robust, rapid and, preferably, noninvasive as well as field-deployable method is essential for real-time monitoring of exposure and triage of potentially exposed individuals, who might differ widely in terms of their age, gender, ethnicity, history of exposure and other physico-clinical characteristics. In case of therapeutic exposure, it is also desirable that the method is able to quantitatively asses the level of exposure as well as it's effect on different parts of the body including internal organs. None of the existing methods for monitoring radiation exposure fits the bill. Since, metabolome, is the outcome of the interaction between gene and environment, we set out to explore if changes in metabolic signature can be used as a marker of radiation exposure. A series of experiments in animal models revealed that signatures associated with DNA damage repair can serve as potential noninvasive urinary biomarkers for gamma radiation. It was found that elevation of these metabolites was not affected by history of previous exposure whereas ageing was associated with significant attenuation.



Further analysis revealed that metabolic signature may serve as surrogate marker for tissue-specific effects of exposure to ionizing radiation. Along with these findings this presentation will also elaborate on the prowess of metabolomics in opening new frontiers to advance our understanding of the reorganization of biochemical landscape following radiation exposure. It will also discuss challenges and opportunities in integrating metabolomics into the endeavour to understand the effect of ionizing radiations on human health.

Novel *in vitro* models for the prediction of space radiation and radiotherapy risks

I.S. Schroeder[1], C. Schielke[1], S. Ritter[1], M. Durante[2]
[1]Stem Cell Differentiation and Cytogenetics Group, Biophysics Department, GSI, Darmstadt
[2]Biophysics Department, GSI, Darmstadt and Institut für Festkörperphysik TU Darmstadt

Charged particles are interesting as state of the art tools for cancer therapy, which can be further advanced at FAIR (e.g. focused microbeam (GRID) and ultra-high dose irradiation (FLASH) technologies). Likewise, they offer experimental approaches for space radiation protection. In biomedical research, experimental models commonly are either 2D *in vitro* cell cultures or rodents. 3D tumor spheroids have been used as a proxy of real cancers, but they lack the complexity of the tumor microenvironment. Organotypic tissue slices can be an alternative system for studying normal tissue effects (see abstract by F.Rapp et al., GSI; [1]), but they are generally of animal origin. Thus, risk assessment and identification of molecular mechanisms altered by ionizing radiation are challenging as suitable models that faithfully mimic the regeneration processes e.g. of the human cardiovascular system and the brain are scarce. 3D cardiovascular structures [2] and brain organoids [3] generated using human embryonic stem cells can close the gap between basic and clinical research and have been established at the GSI Stem Cell Differentiation and Cytogenetics Group. These 3D approaches offer a wide range of possibilities: First and foremost, they allow examining the radiation impact at any stage of organ development and regeneration without being dependent on primary cells or tissues. Second, specific sub-regions of the organs (e.g. first/second heart field, atrial/ventricular heart or hippocampus, forebrain, thalamus, and cerebellum of the brain) can be generated and, by fusing those sub-regions, more complex effects of radiation on region-specific interactions/communication can be analyzed. Third, these complex structures can be co-cultured with endothelia cells to support vascularization of brain organoids and cardiac clusters. In our group, the incorporation of microglia as brain innate macrophages in cerebral organoids is the subject of current studies. Individual responses to radiation can be easily determined using induced pluripotent stem cells of patients or astronauts as the starting material for the 3D structures. Finally, the reaction of tumorous and normal cells to radiation can be examined simultaneously in a single organoid and possible interactions can be identified. In summary, the organ-like structures allow a plethora of studies that will facilitate the understanding and prediction of the radiation risk and will substantiate other models such as animal studies.

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(Brain) tissue slice cultures as a system to study radiation effects

B. Djouiai[1], M. Durante[1], C. Fournier [1] and F. Rapp[1]
[1]GSI Helmholtzzentrum für Schwerionenforschung GmbH, Darmstadt, Germany

High energy charged particles produced at accelerators are a useful tool in biology to perform ground based space radiation experiments as well as to develop new methods for cancer therapy. Cell cultures used for *in vitro* experiments often contain only one cell type, whereas animal experiments can be elaborate and expensive. To bridge this gap, and to reduce the number of animal experiments, 3D models like organoids (see also abstract of I. Schroeder, GSI) or tissue slice cultures can be used. Tissue slices contain all typical cells within the respective tissue including extracellular matrix and blood vessels. In addition, from one animal (or patient), many tissue slices can be obtained.

For normal brain tissue, the organotypic hippocampal slice culture technique (OHSC) is known for a long time [1], and we adapted this technique for irradiation experiments at accelerator facilities [2]. The tissue slice system can be particularly suitable to assess the effects of single tracks of energetic heavy ions, as the streak of a heavy swift particle crossing the tissue can be visualised with a DNA DSB marker (such as γH2Ax, 53BP1…) and the response of the remaining tissue is visualised at different distances from the particle traversal. Using OHSC, risk assessment for astronauts during spaceflight with regard to changes in the brain is possible. The effects of Galactic Cosmic Rays (GCR) can be evaluated using charged particles at GSI and/ or FAIR, and different cell types (e.g. neurons, astrocytes and microglia) can be analysed after irradiation. We have previously found DNA damage and changes in proliferation of microglia after particle irradiation. Since microglia play a role in secondary neuronal damage and the onset of chronic neurodegenerative diseases (e.g. Alzheimer's disease), we are now investigating possible mitigators of microglia activation after GCR irradiation.

In addition, tumor tissue -from humans or animals- can be used for slice culture preparation to study radiotherapy- related topics. For example, glioblastoma tissue from humans have been used for *ex vivo* Carbon ion irradiation [3], but other tumor entities are also suitable [4]. This system has the advantage that different slices from one tumor can be treated with different options to a) study effects of different irradiation setups or b) find the best treatment for the respective patient. For the future, novel irradiation techniques could be tested using (tumor) tissue slice cultures. In the context of FAIR, especially irradiation with focused microbeams (GRID) or high dose delivery in a short time (FLASH) techniques could be tested *ex vivo*, and with this data, animal experiments can be planned in more detail.

Funding: ESA IBER-2008 and -2017, DLR (50WB0925 and 50WB1837), FAIR phase-0

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Regulated systems of ISce-I expression for in-depth studies of the biological effects of DSBs and DSB-clusters

S. Mortoga, V. Mladenova, E. Mladenov and G. Iliakis

Institute of Medical Radiation Biology, University of Duisburg-Essen Medical School Hufelandstr.55, 45122 Essen, Germany

Cells exposed to radiation accumulate DNA double strand breaks which are the most critical DNA lesion generating adverse biological consequences and if left unrepaired, could result in chromosomal aberration and cell death. It has been suggested that DSBs could be classified in distinct types, from simple DSBs with ligatable DNA end to DSBs clusters, which could destabilize locally the chromatin structure. While the repair of simple DSBs is well characterized, the responses initiated by the DSBs clusters remain obscure. To date models based on mathematical or computational approaches have been used to assess the effect of DSBs. However, a precise biological model system mimicking DSBs clustering is still missing. In order to study such DSB-cluster associated adverse biological consequences, a model system based on the generation of DSBs by restriction endonuclease (ISce-I) has been established. Rodent CHO cell line harboring ISce-I sites engineered at different configurations with increasing DSB-cluster complexity was characterized for DNA damage responses after induction of DSBs at ISce-I sites. Obtained results show significant correlation between cell killings together with chromosomal aberrations with formation of DSBs clusters and equal activation of DNA Damage Response (DDR) signaling measured by γ-H2AX and 53BP1 foci formation. Surprisingly, live-cell imaging shows that with increasing complexity there is more retention of 53BP1 to the DSBs. Recruitment of 53BP1 at DSBs follows a multitude of upstream events. Evidence suggests that RNF8 and RNF168 – two known E3 ligases – play significant roles in this upstream regulatory signaling cascade via chromatin ubiquitylations and regulate 53BP1 assembly at DSB-flanking chromatin. Therefore, we seek to investigate the plausible roles of these two known regulators of 53BP1 accrual at ISce-I inflicted DSB chromatin. Some preliminary results based on involvement of two novel chromatin-associated ubiquitin ligases (RNF8 and RNF168) in 53BP1 accrual to simple DSBs and DSB clusters as well as in chromosomal translocation formations will be presented.

Preliminary gene expression results of cancer cells in hypoxic and normoxic environment under irradiation

J. Jansen[1,2], L. Tirinato[1], M.G. Marafioti[1,3], R. Hanley[1,2], X.Q. Yao[4], F. Pagliari[1], J. Seco[1,2]
[1]German Cancer Research Center DKFZ, Biomedical Physics in Radiation Oncology E041, Heidelberg, Germany; [2]Ruprecht-Karls-Universität, Department of Physics, Heidelberg, Germany; [3]University Magna Graecia of Catanzaro, Department of Experimental Medicine, Catanzaro, Italy; [4]Ryerson University, Department of Physics, Toronto, Canada

Radiotherapy (RT) is one of the main approaches for cancer treatment used alone or in combination with chemotherapy where the main cellular target is nuclear DNA. We investigated how cancer cells (bladder, breast, brain, lung, prostate) react to radiation on a genetic level, where cells were treated with 6 Gy in normoxic (21% O_2) and hypoxic (0.3% O_2) conditions. The gene groups studied with qPCR included DNA repair, cell cycle, cancer stem cell markers, oxygen sensing and metabolic genes.

In general, RT causes genomic damages, either directly by injuring the DNA, or indirectly, by ionizing water molecules, where radiation induces the formation of Reactive Oxygen Species (ROS). X-ray efficacy seems to be compromised by the presence of a Cancer Stem Cell (CSC) sub-population, which is radiation resistant. Moreover, there is mounting evidence that hypoxia changes cellular ROS levels and would protect DNA from oxidative damage and thus conferring radioresistance to CSCs.

Cells irradiated with X-rays in hypoxia show a decrease in the expression of the cancer stem cell marker genes accompanied with a downregulation of metabolic, DNA repair and cell cycle genes, while irradiation under the presence of oxygen causes upregulation of the previously mentioned gene groups. This leads to the conclusion that there is an underlying concept connecting the gene groups. Taking the concept of pathways to a more general approach, one can introduce an oxygen and no-oxygen depending pathway to describe the response of cancer generally to radiation. This work focuses on the effect of X-rays, which will set a baseline on the pathway-response in carbon-treatment.

Human induced pluripotent stem cell derived in vitro models for space radiation biology

O. Smolin[1], M. Mayer[1], F. Frieß[2], A. Heselich[3] and C. Thielemann1

[1] University of Applied Sciences Aschaffenburg, BioMEMS Lab, Aschaffenburg, Germany;
[2] University of Natural Resources and Life Sciences, Institute for Safety and Risk Sciences, Vienna, Austria;
[3] Medical Center of the Goethe University, FORM-Lab, Frankfurt, Germany

Cosmic radiation is considered the main health hazard for human exploration and colonization of the solar system. To predict space radiation related risks on the human health, experimental studies have been performed based on *in vitro* or *in vivo* model systems – typically originating from animals [1]. However, results gained from animal models are not necessarily transferable to human [2]. Therefore, human cell models are highly desirable for radiation research.

Human induced pluripotent stem cells (hiPSC) appear as an ideal model system as they are of human origin and allow personalized risk assessment by using autologous hiPSC lines, f.e. derived from an astronaut's biopsy. hiPSC are similar to human embryonic stem cells (hESC) in many aspects, but the full extent of their relation to hESC is still being assessed and caution must be taken interpreting experimental results.

In this study we exemplarily prove the response of hiPSC-derived cardiomyocytes (hiPSC-CM) to ionizing radiation (IR). hiPSC-CM have been extensively evaluated within a large study and it's potential to mimic clinical drug responses has been proven with functional assays based on with microelectrode arrays (MEA) [3, 4]. Becker at al. employed these assays to study organ-specific responses to X-ray radiation with doses of up to 10 Gy [3]. They found no changes in beat rate for doses below 5 Gy, but a dose-dependent decrease and changes in electrophysiological spatial distribution for higher doses. They also observed cell batch variations for radiation sensitivity and hypothesize that reasons could be variations in cell-cycle status or individual radio-sensitivity of cell types or donors. Latter being of specific interest for our project.

In a first step towards the investigation of individual organ-specific radio-sensitivity, we compared radiation responses of two commercially available hiPSC-CM cell lines (Cor.4U, Ncardia, Köln, Germany and iCell cardiomyocytes, CellularDynamics, USA) at 1 Gy of X-rays. Investigations of radiation-induced effects on electrophysiological properties were performed using the benefits of MEA chips. These chips allow the monitoring of spike shape, field action potential duration, beat rate and signal conduction pathways across the electrode array. Clear differences in the results suggest that donor-specific variations in radio-sensitivity may be superimposed by other effects, such as state of phenotypical maturation.

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Effect of deep space-related conditions on central nervous system performance in multicellular organisms as a function of their genetic background.

G. Berto[1,2], E. Di Schiavi[3], R. Cirio[4,5], R. Sacchi[4,5], S. Giordanengo[5], V. Monaco[4,5], F. Di Cunto[1,2]
[1]Neuroscience Institute Cavalieri Ottolenghi, Torino, Italy; [2]Department of Neuroscience, University of Torino, Italy; [3]IBBR, CNR, Naples, Italy; [4]Department of Physics, Torino, Italy; [5]INFN, Torino, Italy.

In light of future human exploration of deep space, a fundamental need is to understand how terrestrial organisms may be affected by the peculiar conditions that characterize this extreme environment. Moreover, it will be crucial to dissect how the individual genetic structure may facilitate or jeopardize the adaptation to deep space, with specific regards to normal functioning of the central nervous system.

Compared to terrestrial surface, deep space is characterized by combination of microgravity and peculiar radiative environment, dominated by particle shots and galactic cosmic rays. Terrestrial organisms have adapted to maintain their genomic stability in presence of completely different threats, such as gamma rays from natural radioactivity. However, it is essentially unknown how deep space conditions, characterized by high energy charged particles and secondaries produced by their interactions with surrounding materials, may affect genome stability, especially in complex organisms. Modern genomic studies have revealed that all phenotypically 'normal' humans may carry a high number of mutations, which reduce the function of specific genes but do not produce overt phenotypes under standard environmental conditions. It is possible that some of these defects would become significant vulnerability factors upon exposure to deep space environment.

Since the nervous system is particularly sensitive to radiation, a fundamental and particularly challenging question is to predict how deep space conditions may influence the function and plasticity of neural networks controlling the behaviour of multicellular organisms. An even more challenging question would be to establish whether specific genetic variants or variant combinations would make individuals more sensitive to deep space conditions, and which could exert protective effects. In particular, it would be critical to assess which genetic factors may facilitate or prevent neurodegenerative phenomena under deep space conditions.

The main goal of our group would be to analyze the impact of deep space conditions on different aspects of multicellular organisms' biology, including genome stability, behaviour and neurodegeneration, using both terrestial irradiations with radiation fields mimicking the conditions expected in deep space and experiments performed in actual conditions using Cube-Sats platforms.

We aim at implementing a setup capable of hosting the growth of model organism Caenorhabditis elegans in terrestrial simulators and Cube-Sats. The choice of this model organism is justified by the following elements:

- short life cycle (3 days from eggs to adult - 3 weeks from conception to death);
- high resistance to extreme conditions;
- possibility of hibernation;
- small size and ease analysis of neuromuscular phenotypes;
- great adaptability to growth in microfluidic devices;
- great availability of genetically modified strains, allowing to assess the functional relevance of specific genetic alterations and to test sophisticated genetic hypotheses;
- great similarity of proteome with the human proteome.

Using standard and genetically modified strains, together with dynamic microscopy, the following quantities will be measured and correlated with the radiation dose: viability, rate of reproduction, movement, expression of fluorescent markers of stress and damage. Moreover, the degeneration of specific neuronal populations, labeled by expression of fluorescent proteins, will be analyzed [1].

A more sophisticated setup could also include the capability of performing gene sequencing and gene expression analysis, through adaptation of the minION technology.

The final goal will be to validate the most important findings on simplified human models, such as mini-brain cultures, kept under simulated conditions.

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Blocking DNA Activity in Ion Beam Therapy of Cancer Cells

Sergey N. Volkov,

Biophysics of Macromolecules Lab, Bogolyubov Institute for Theoretical Physics, NAS of Ukraine, Kiev 03143, Ukraine

During irradiation of cancer tumor in the method of ion beam therapy the concentration of hydrogen peroxide (H_2O_2) in cell medium grows significantly and remains stable for a relatively long time. However, the role of H_2O_2 molecules in cancer treatment has not been determined yet. In present work the competitive binding of H_2O_2 and H_2O molecules with the sites of DNA specific and nonspecific recognition is under consideration.

Using atom-atom potential functions method and quantum-chemical approach of density functional theory the spatial configurations and possibility to form the stable complexes of H_2O_2 and H_2O molecules with DNA recognition sites are studied. The most probable positions of peroxide and water molecules in the complexes with nucleic bases and backbone phosphate groups are found. The energies of these complexes formation demonstate the advantage of H_2O_2 over H_2O in all analyzed cases [1–3].

The forming of stable complexes of DNA atomic groups with H_2O_2 should lead to DNA activity blocking, and can be one of the important stages of genetic apparatus deactivation in the treatment of cancer. The experimental observations of DNA activity blocking by H_2O_2 molecules and possible effects of these molecules on DNA biological functioning will be discussed.

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Medical Physics

Particle Therapy Now - Have we reached the future?

J. Flanz and H. Paganetti
Department of Radiation Oncology, Massachusetts General Hospital & Harvard Medical School, Boston MA 02114, USA

Introduction:

The growth of available particle therapy facilities in the world has been relatively rapid in the past several years. There is a total now of over 79 institutions with more than 50 planned or under construction. Most "high density" population areas in large hospitals in the US, Japan and Europe now have them and they are being built for the smaller clinics. However, the continuing question is whether the use of particle therapy is cost effective. The definition of this term is wide and varied and requires an analysis of the cost of a treatment (to the patient) and the effectiveness of the treatment (to the patient). These must then be compared to something else. While the issue of lifetime cost for the patient is difficult to get a handle on, the question of effectiveness can have two parts. The first is the clinical effectiveness of the modality. This will be discussed by others. The second is whether the effectiveness has been optimized, or rather what (if any) are the limitations of the existing particle therapy systems which, if improved, can lead to improved effectiveness and lower costs?

Particle Therapy goals:

In the early days of particle therapy, the goals were perhaps more simply defined as a demonstration of the improved physical advantage of Charged Particles and perhaps the higher LET advantage of heavier charged particles. In other words, can they be used to optimize the therapeutic ratio.

Currently the goals have expanded to include several topics including:

- Improved conformality including the end of range, which entails:
  - Improved image guidance
  - Organ motion management
  - Adaptive radiotherapy
  - Among others, and
- Utilizing a biological advantage in a subset of patients based on dosimetric or biological biomarkers
  - understanding proton biology in combination with other therapies
  - serum biomarkers to assign patients to proton therapy
  - imaging biomarkers to adapt treatment regimens
  - model based clinical trials
- Reduced cost to patient, which includes
  - Lower initial cost
  - Increased throughput

The implications of these goals to the system performance will be discussed and how the important properties would be effective towards a biophysics research program aimed at improving the clinical outcome which could include the requirements to obtain clinical deliver of FLASH and microbeams.

Radiotherapy studies with multiple ion beams

O. Sokol[1], M. Durante[1], M. Fuss[1], M. Krämer[1] and E. Scifoni[2]
[1]GSI, Darmstadt, Germany
[2]TIFPA, Trento, Italy

Currently, ion beam therapy is carried out only with protons or carbon ion beams. Although these two modalities are considered as reliable and well-described means of treatment of deep-seated tumors, there are ongoing discussions whether alternative ions or approaches using several ions in a single treatment session can be beneficial for specific tumor cases.

The latter idea of multi-ion therapy was proposed by several research groups. At NIRS, it was suggested using composite particle therapy for optimizing the LET profiles inside the target [1]. Another idea initially proposed in [2] is to use several ion beams for achieving a more uniform RBE profile in the target. Our studies at GSI are dedicated mainly to the improvement of the treatment outcome for hypoxic tumors [3] by irradiating their hypoxic areas with heavier ions while delivering the remaining dose with lighter modalities (TRiP98-MIBO). In future, we are considering more sophisticated optimization scenarios. This might very well include collaboration with clinical imaging groups as well as experiments with animal models.

At the moment there are only a few facilities in the world capable of delivering different ion beams. In addition, reasonably fast switching between different modalities are not always available and so the opportunities for verifying the approaches mentioned above are somewhat limited. The future FAIR-GSI accelerator complex with its wide range of ion species and their energies can provide a suitable environment for challenging multi-ion experiments.

Beyond the p-^{12}C combination other ion types will be examined. While ^{4}He and ^{16}O ions are already considered to be candidates for treating mainly pediatric and hypoxic tumors, respectively, he investigation of physical and radiobiological evidence for using yet more alternative ions, pioneered e.g. at LBL, can be resumed.

In addition, we think of even more exotic ion species, for example positron-emitting isotopes such as ^{11}C or ^{15}O instead of the stable ^{12}C and ^{16}O. Since in the above-mentioned MIBO approach the hypoxic tumor areas are irradiated with high LET radiation in small volumes, the PET signal generated by the radioactive isotopes can improve the precision of beam range verification and thus improve the quality of treatment. In existing accelerators such radioactive isotopes are produced with intensities below 10^5 particles per pulse, which is not sufficient for clinical irradiations. At FAIR, the intensities are expected to be approximately 10^4 times higher, which would enable pre-clinical research under realistic conditions.

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Beam Scanner Development for the Biophysics Researches

V.S. Skachkov, O.S. Sergeeva, A.A. Golubev, A.V. Kantsyrev, V.A. Panyushkin
NRC “Kurchatov institute” – ITEP, Moscow, Russian Federation

Abstract

Beam scanner provides homogeneous irradiation of 200×200 mm target by protons and heavy ions with Z/A = 0.3-0.5 for solving wide range of applied tasks in the materials science and particle effects mechanisms in biological objects research is described. The scanner has been optimized for the hardest case: *Z*/*A*=0.3, energy – 800 MeV/u, emittance – 40 π·mm·mrad to operate in both single and multi-frame modes of sample irradiations. The most compact magnetic dipoles have been found as optimization result, which permits to arrange it together with other required elements at a transport channel. Main characteristics of power supply were obtained and discussed.

Medical-physics challenges from radiation therapy with Facility for Antiproton and Ion Research (FAIR)

N. Matsufuji[1]
[1]NIRS-QST, Chiba, Japan

The beam of ultra-high intensity, energy, and Z (atomic number) particles produced by the FAIR accelerator is in a class of its own and will open a new era in radiation therapy. Here I discuss upcoming medical-physics issues involved in using FAIR for radiotherapy with stable beams.

High intensity The high beam intensity is the most important characteristic of FAIR. While an ordinary ion-beam-therapy machine takes about 1 minute to deliver 1 Gy to a target, FAIR can do so in less than 1 second. This will enable instantaneous therapeutic shots while a patient holds his/her breath, just like a chest-X-ray examination. Such instantaneous shots can be beneficial for treating moving targets or pediatric patients by reducing the internal margins or eliminating the need for anesthetics or sedatives, as are applied in current radiotherapy. The primary challenge for medical physics concerns beam delivery. A modern active-scanning magnet can sweep a beam at a speed of 100 m/s [1]; however, the energy-changing system and associated monitoring devices remain challenges. Passive beam delivery is an alternative solution. Among such approaches, the double-scatter system [2], coupled with a ridge filter and a compensator, involves only static devices, so the performance is in principle not limited by the beam intensity.

High energy Even uranium ions can penetrate through a patient's body when accelerated by FAIR. Shooting-through irradiation was tried with light ion beams in the early days, when geometrical information about the target and the organs-at-risk inside a patient's body were unavailable. Today, as with X-ray CT (computed tomography), we should definitely make use of the Bragg peak. High-energy ion beams can then be used for diagnostic purposes. In the coming adaptive radiotherapy, it will be possible to modify the treatment plan on the fly to adapt to physiological changes before irradiation. The residual range of the penetrating ions contains important information about the integral stopping power along its trajectory. The choice of an optimum ion species for diagnostic purposes is a matter of study; heavier ions are advantageous for multiple scattering, but they cause more frequent nuclear fragmentation. The measurement goal for primary or secondary radiation is also of interest, together with the choice of measurement method. In addition to a conventional Time-Of-Flight (TOF) measurement or a full-stop bulk detector, new approaches such as Cherenkov-ring detectors may be alternative choices.

High Z The use of ultra-heavy ions for therapy is a matter of concern. From the viewpoint of dose localization, ions heavier than neon are currently regarded as inappropriate due to their less-prominent Bragg peaks and more frequent nuclear fragmentation. The so-called "overkill phenomenon" also diminishes the biological effectiveness at the Bragg peak. Here mini-beam (grid) irradiation [3] may provide an alternative figure of merit. By delivering the ion beam as sparsely placed mini beams each less than 1 mm wide, it is expected that normal tissue at the point of entrance of the beam can be spared if the tissue has a significant volume effect. The highly heterogeneous dose distribution may also allow for the use of ultra-heavy ion beams.

Impact on related fields Radiotherapy with FAIR will promote various studies in related fields. For example, both in Germany [4] and Japan [5] the biological effectiveness of a therapeutic ion beam is determined during treatment planning, based on the microscopic energy deposition by the incident ions. At FAIR, the radial dose distribution, termed the "track structure" of the ions, spreads broadly over the cells and tissues. It will be interesting to investigate whether current biological models are still valid for determining the biological effectiveness at FAIR. Clarification of the intensity (dose-rate) dependence is also needed, both for the acute cellular response and for late tissue response, such as carcinogenesis.

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Online beam and range monitoring in a static toroidal gantry delivery configuration

L. Bottura[1], P. Cerello[2], E. Felcini[1], V. Ferrero[2], V. Monaco[2,3], F. Pennazio[2], G. de Rijk[1]
[1]CERN, Geneva, Switzerland; [2]INFN, Torino, Italy, [3]Department of Physics, University of Torino, Italy

GaToroid [1] is a novel fixed toroidal gantry, based on superconducting magnets, able to deliver the dose at discrete number of angles without rotation of the magnets. The basic principle is to use axial-symmetric magnetic field between each pair of coils constituting the torus to bend and focus accelerated particles to the isocenter. The *Vector Magnet*, an upstream bending magnet, rotating or combined vertical/horizontal, is used to steer the particles into the gantry with a proper angle, depending on the beam rigidity and the required angles of treatment.

2D particle tracking has been integrated in the magnet design to optimize the coil geometry and field profile, aiming to precise beam focusing at isocenter in the whole range of treatment energies with steady- state toroidal field. Furthermore, 3D particle tracking in vacuum has been developed to simulate the beam and reconstruct the transfer matrix of this unique shaped gantry. Angle deviations can be properly applied to the *Vector Magnet* to perform beam scanning around the isocenter, without the need of classical downstream scanning systems.

Large acceptance, steady-state configuration and superconducting magnets allow a reduction of size, weight and cost of the gantries and its related infrastructures, creating an attractive alternative to the state- of-the-art.

GaToroid integrates the design of a beam monitoring system based on high timing resolution pixelated silicon detectors [2] that will match the beam delivery windows and of a high–precision PET-based online range monitoring [3] that exploits the azimuthal gaps between the beam entrance windows.

The fully integrated delivery and monitoring system would allow:

- highly flexible and fast beam delivery, with a static gantry much lighter and smaller than the existing ones, subjected to no restrictions on beam timing, beam energy or positioning precision associated to its movement;
- beam monitoring with single particle counting capability for fast measurement of beam fluence and position;
- online range monitoring by means of a 3D measurement of the beam-induced activity distribution and of the prompt gamma emission profile, with the goal of an overall range precision of about 1mm obtained during the treatment.

Preliminary results of the system design simulations and of the expected performance will be presented.

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A High-Granularity Digital Tracking Calorimeter Optimized for Proton CT

P. Piersimoni[1], and O.S. Grøttvik[1] for the Bergen pCT collaboration
[1]Department of Physics and Technology, University of Bergen, 5007 Bergen, Norway

Proton Computed Tomography (pCT) has been extensively studied in the last decade since it may lead to reduction of uncertainties in proton therapy treatment planning since it allows the direct reconstruction of a 3D map of the relative stopping power (RSP, that is the stopping power of a specific material divided by that of water) values in the target. Currently, the conversion from Hounsfield unit (HU)(used in conventional x-ray CT) to RSP is one of the primary sources of uncertainties in treatment planning. A pCT scan consists of shooting high energetic beams against an object of interest and reconstructing the path of each single proton history, for different angles in a tomographic fashion. For this purpose, a tracking system (for the particle position and displacement measurement) and an energy/range detector are needed [1].

The Bergen pCT collaboration has recently designed and constructed a prototype of an extremely high-granularity digital tracking calorimeter [2], and it is currently working on the development of a second prototype. This new prototype, optimized for pCT, has been designed and simulated [3] as a multilayer structure made of several detector/absorber sandwich layers, with aluminum used as the absorber. The detector is realized with CMOS technology commercially available. Therefore, many layers of large area sensors necessary for a pCT scanner are feasible. In the new design, the sensor layers consist of ALPIDE chips, Monolithic Active Pixel Sensors (MAPS), initially developed for the upgrade of the inner tracking system of the ALICE experiment at the LHC (CERN). The new optimized prototype can handle proton rates as well as to provide range resolution noticeably higher with respect to the first prototype. To cover a lateral size sufficient to image a human head, the aperture of the new detector is 27 cm x 18 cm.

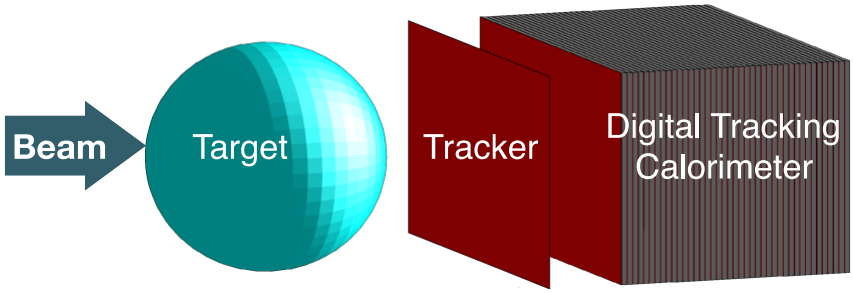

Figure 1: The schematic design of the new pCT scanner prototype.

The longitudinal segmentation consists of 41 sensor layers (figure 1, on the right-hand side) interleaved with 3.5 cm thick aluminum absorbers. Every active layer has 108 ALPIDE chips, read out by a Xilinx Ultrascale+ FPGA via a serial 1.2 Gbps link per chip. The asynchronous data recovery is obtained with dynamic phase adjustment logic in fabric using regular I/O pins. The two front-layers (figure 1) of the detector are spaced by 2 cm without an absorber in between and are extremely thin (total thickness per layer less than 300-400 μm) in order to minimize multiple scattering. The ALPIDE used for the prototype has a front-face thickness of 50 μm. The Al-pads of the ALPIDE sensors are ultrasonically bonded onto thin traces of pure aluminum on a polyimide flex. These chip-cables are then bonded to a larger flex PCB carrying nine sensors (the technology is provided by LTU, Kharkiv, Ukraine). The first flex-mounted ALPIDEs are currently being benchmarked in the laboratory, together with the new readout chain.

The ALPIDE sensors have been extensively tested in electron and hadron beams by the ALICE collaboration, including tests with irradiated sensors. Beam tests tailored to the pCT operation have been performed, i.e., proton and He-beams with energies from a few MeV to 250 MeV/u, including 1 μm micro-beams provided by ANSTO, Australia, and high-energetic (50 – 220 MeV/u) proton and helium beams at the Heidelberg Ion-Beam Therapy Center (HIT) in Germany.

The aim of these tests is threefold:

- to study the cluster size vs. linear energy transfer (LET) in the epitaxial layer;
- to evaluate the maximum rate (particles per 10 μs/ frame) the chip can handle;
- to establish the limit of radiation hardness of the sensor under pCT running conditions.

The data from these tests are being analyzed and will be reported.

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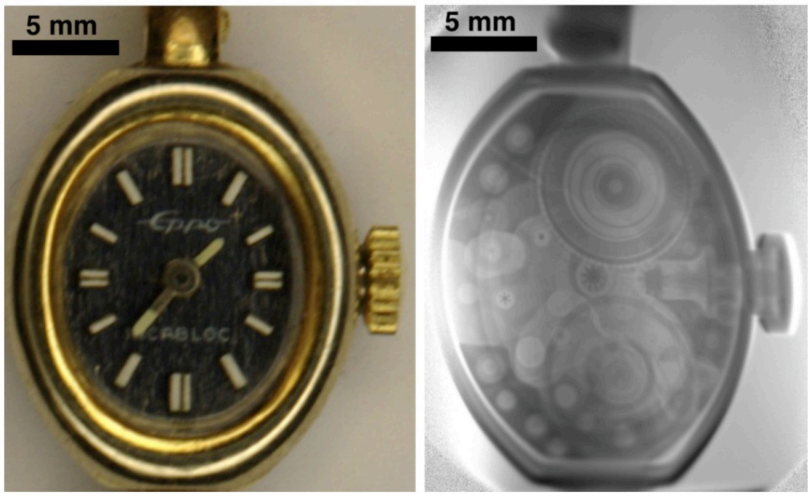
PRIOR – Proton Microscope for FAIR

D. Varentsov[1]
[1]GSI, Darmstadt, Germany

High energy proton microscopy (HEPM) or radiography is a novel technique for probing the interior of dense objects in static or dynamic experiments by mono-energetic beams of GeV-energy protons [1]. A special system of magnetic lenses is employed for imaging and aberrations correction. Using this technique, one can measure the areal density distribution of a thick sample with sub-percent accuracy, micrometer-scale spatial and nanosecond-scale temporal resolutions. HEPM diagnostic technique is of considerable interest for dense plasma physics and materials research.

Protons having energies in the GeV range have also been proposed as an alternative to Bragg-peak hadron therapy [2]. This strategy reduces lateral scattering and overcomes uncertainties of particle range and relative biological effectiveness. Recently, a new project called PaNTERA (Proton Therapy and Radiography) which exploits the HEPM technique for image-guided stereotactic particle radiosurgery has been launched by GSI, LANL and TUD. The first experiments with 800 MeV pRad setup at LANL on imaging of biological and tissue-equivalent targets as well as the CT with high-energy protons have demonstrated the potential of this novel imaging method for biophysics and medicine [3].



The PRIOR (Proton Microscope for FAIR) facility will use 1 - 5 GeV intense proton beams from SIS-18 or SIS-100 synchrotrons and will allow for a significant step forward in spatial (10-15 μm) and temporal (5-10 ns) resolution. In 2014, a PRIOR prototype (PRIOR-I) has been constructed and successfully commissioned at the HHT area of GSI in static and dynamic experiments with intense 3.6 GeV proton beam from SIS-18 [4]. The PRIOR-I employs high-gradient (120 T/m) NdFeB permanent magnet quadrupole lenses. The commissioning of PRIOR-I has demonstrated 30 μm spatial and 10 ns temporal resolution with remarkable density sensitivity (see Fig. 1).

Figure 1: PRIOR 3.6 GeV proton radiograph of a tiny mechanical watch. Despite a thick stainless steel case back, the fine details of the interior of the watch are well resolved: the crown and the mainspring, pivots and wheels, jewels, etc.

The final design of the PRIOR proton microscope (PRIOR-II) employs small but strong and radiation-resistant electromagnets. The setup will be first used at GSI for static and dynamic experiments, and later will be transferred to the new experimental area at FAIR. PRIOR-II will provide a magnification of about 3.5 at GSI and up to 8 at FAIR with 10 μm spatial resolution at the object. The first experiments with the PRIOR-II facility at GSI are planned for 2020.

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The PaNTERA Project - Proton Radiography towards medical applications

M. Schanz[1], M. Durante[1], M. Krämer[1], D. Varentsov[1]
[1] GSI Helmholtzzentrum für Schwerionenforschung GmbH, 64291 Darmstadt

Heavy ion tumor therapy is a current state of the art technique enabling the effective and precise irradiation and inactivation of tumor tissue even close to organs at risk. Despite significant advances regarding the effectiveness and precision of this technique during the past years, the patient data, which is mandatory for the calculation of the complex treatment plans (TPs), is still captured using conventional X-ray Computed Tomography (xCT) machines. Those xCT devices are nowadays capable of delivering a spatial resolution performance in the mm-range, however, the tissue density and ion stopping power maps mandatory for the TP remain inaccessible due to the fact that the imaging is done with X-rays (photons). The standard method is a conventional lookup table (HLUT - Hounsfield Lookup Table) obtained by linear interpolation of few measurements which is used for converting the xCT HUs to water equivalent path length (WEPL) required for TP. This quantity contains the tissue density and the ion stopping power and due to the conversion also errors up to several percent. Further improvements regarding a more precise treatment will therefore require the use of different imaging techniques.

High energy proton radiography — besides dual energy CT (DECT) and single proton tracking — is one of the promising alternatives to the conventional xCT HLUT procedure. Whereas DECT machines are already available in clinics but rarely used for TP, proton radiography could directly employ the particles delivered by the accelerator for imaging, thus completely eliminating the need for separate imaging devices or unit conversions. Compared to the competing technologies it offers several advantages, e.g. a spatial resolution in the µm range and an extremely fast image capturing process.

The PaNTERA project (Proton Therapy and Radiography) is a joint project of the Los Alamos National Lab (LANL), USA, and GSI, exploiting the capabilities of high energy proton radiography for medical applications. In a first stage of the project the general feasibility of medical imaging using this technique was demonstrated by imaging the Matroshka phantom [1] at the LANL accelerator facility.

Further investigations were then performed regarding the density reconstruction capabilities using a clinical head phantom. The phantom was imaged with conventional X-rays at the HIT in Heidelberg. Also, a high energy proton CT was captured at the LANL. As an additional intermediate option, a recalibration approach was performed using X-ray base data from Heidelberg and single high energy proton projections instead of the conventional HLUT [2]. All three methods were compared regarding their density reconstruction accuracy and suitability for TP revealing a significant deviation of the clinical HLUT from theoretical values and demonstrating the applicability of proton radiography for medical purposes.

Further investigations on medical imaging employing this technique will be performed at the upcoming PRIOR-II proton radiography facility, which is scheduled for commissioning during FAIR Phase-0 in early 2020.

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A novel approach for the monitoring of ion beams: where we are

S.Giordanengo[1], O. Hammad Ali[1,2], N. Cartiglia[1], F. Fausti[1], F. Mas Milian[2,3], V. Monaco[1,2], R. Sacchi[1,2], Z. Shakarami[1,2], A. Staiano[1], A. Vignati[1], R. Cirio[1,2]

[1]INFN Division of Torino, Via Giuria 1, Torino, Italy; [2]Università degli Studi di Torino, Physics Department, Via Giuria 1, Torino, Italy; [3]Universidade Estadual de Santa Cruz, Ilheus, Brazil

Present online ion beam monitoring systems for particle therapy are based on gas ionization chambers as they offer reliable operation, with limited maintenance. Together with their positive aspects, ionization chambers also feature severe limitations in sensitivity and speed, and therefore cannot support very fast and low dose delivery strategies with the required accuracy.

INFN and University of Torino are working on a novel approach to the beam monitoring, moving from integrating the current in the gas volume of the chamber to counting in real-time every single particle delivered to the patient. To that aim, the development of two small (3x3 cm^2) prototypes of beam monitors based on Ultra Fast Silicon Detector (UFSD) [1] technology is ongoing to provide two detectors able to measure online the number of particles and the energy of the beam's particles respectively [2]. Recent and promising results achieved within the "MoVeIT- Modeling and Verification for Ion beam Treatment planning" INFN project will be presented. In detail, we will show:

- The possibility to count individual protons up to 10^9 p/cm^2s, using detectors segmented in strips of 2 mm^2 area each and with active thickness of 50 µm. Prototype strip sensors have been produced in two geometries (30 mm and 15 mm length). Different doping modalities were tested for radiation hardness optimization. Beam test characterization and signal pileup inefficiencies will also be shown.
- A dedicated VLSI readout chip (named ABACUS) has been designed and produced to deal with a single proton signal of nanosecond duration and with 10^8 Hz signal rate on each channel. The ABACUS characterization and on beam preliminary performances in reading out UFSD strips will be presented.

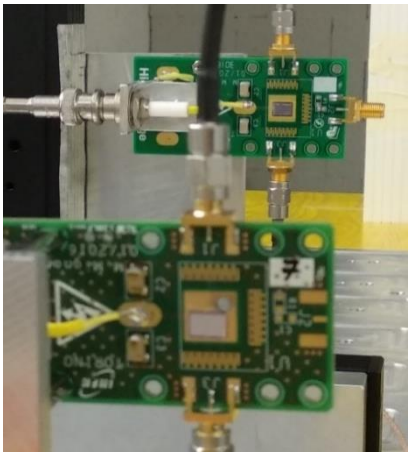

Figure 2. Two UFSD strips arranged in a telescope for beam energy measurement.

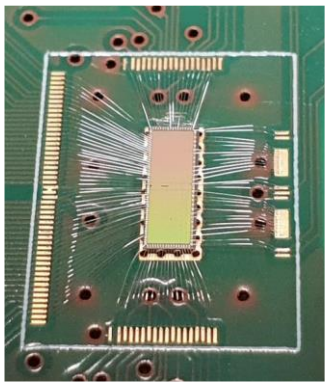

Figure 1. Strip detector wired-bonded to the ABACUS readout chip.

- The second device under construction measures protons' time-of-flight (TOF) between two UFSDs in a telescope configuration (Figure 2), using the constant fraction algorithm to compensate for time-walk effects. From measured TOF values, the corresponding beam energies are obtained through an analytical approximation validated with Geant4. Following preliminary tests with UFSD pads, dedicated strip sensors were produced and thinned to 100 um, covering an area of 4x4 mm^2. Combinatorial methods to identify coincidences among strips are being studied.

The work presented has been performed in collaboration with the UFSD research group of INFN-Torino who is leading the five-years *UFSD* European ERC Advanced project and will lead the Italian *4DInSiDe: Innovative Silicon Detectors for particle tracking in 4Dimensions* project in the next three years. Both these projects are based on Low Gain Avalanche Detector (LGAD) technology: the ERC is studying the characteristics of several possible sensor flavours while *4DInSiDe* will use LGAD optimized to develop new particle detectors able to concurrently deliver excellent time and position resolution with high efficiency, at a high rate and in harsh radiation environments. We are partner of the *4DInSide* collaboration with the task of designing new detectors for the monitoring of therapeutic ion beams.

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Hadron beam time tracker for time-of-flight measurements of prompt-gamma

P. Magalhaes Martins[1,2], R. Dal Bello[1,3], G. Hermann[4], T. Kihm[4], M. Seimetz[5], J. Seco[1,3]

[1]German Cancer Research Center - DKFZ, Division of Biomedical Physics in Radiation Oncology, Heidelberg, Germany

[2]Instituto de Biofísica e Engenharia Biomédica - IBEB, Faculty of Sciences of the University of Lisbon, Lisbon, Portugal

[3]University of Heidelberg, Department of Physics and Astronomy, Heidelberg, Germany

[4]Max Planck Institute for Nuclear Physics, Heidelberg, Germany

[5]Instituto de Instrumentación para Imagen Molecular (I3M), CSIC-Universitat Politècnica de València, Valencia, Spain

Prompt gamma imaging (PGI) is nowadays a well-established technique for range control in particle therapy. However, the arrival time information of the particles needed for PGI is still affected either by accelerator related proton bunch drifts against the radio frequency in cyclotron facilities or by the irregular time microstructure of ion beams extracted in synchrotron facilities. Several solutions have been proposed to circumvent this issue, e.g. bunch monitors [1] or hodoscopes [2]. None of them have been capable so far to cope with the clinical high particle intensities within the full field of irradiation. We present a first clinical prototype of a hadron beam time tracker capable of detecting single particles within ion bunches (Fig. 1) with very good time resolution (Fig. 2). This prototype was able to provide time-of-flight information for the four beam species currently accelerated at clinical intensities at the Heidelberg Ion-Beam Therapy Center (HIT).

Fig. 1

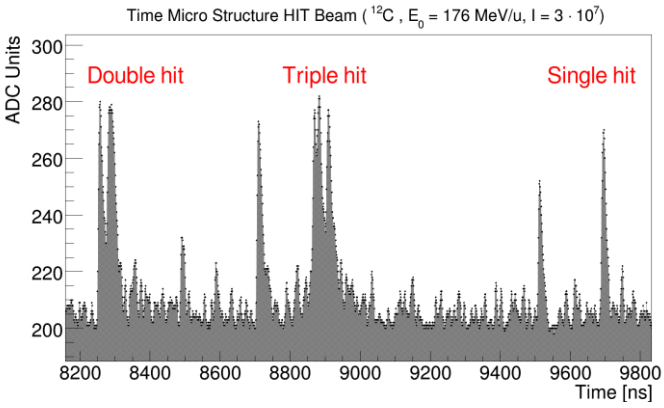
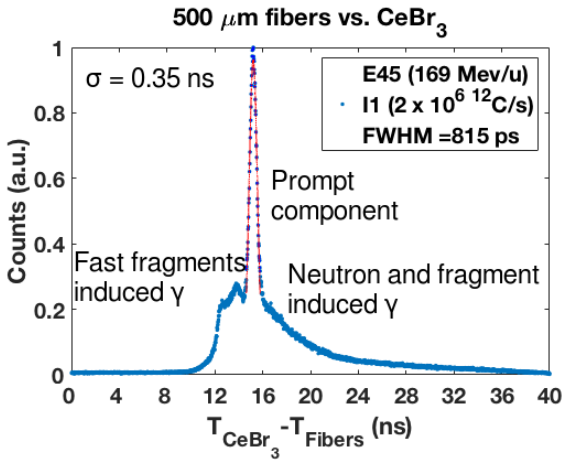


Fig. 2



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MoVe IT, Modeling and verification for ion beam treatment planning: new insights from FAIR beams?

E. Scifoni[1] and the MoVe IT collaboration
[1]TIFPA-INFN, Trento, Italy;

The MoVe IT, modelling and verification for ion beam treatment planning, project is a collaborative effort between 5 INFN groups (TIFPA, LNS, Naples, Milan, Turin) and GSI, plus contribution of different other centers, funded in the context of the INFN-CSN-5 Call framework for 2017-2019.

The main scope of MoVe IT is extending our understanding in physical and radiobiological characteristics of protons and ion beams and translate this information through dedicated models in biologically oriented treatment planning, also including their impact in NTCP /TCP quantification for different tissues. At the same time new, dedicated dosimetric verification approaches are developed, both on the level of new energy and particle counters and on biologically based dosimetry, using different targets allowing for example a highly resolved measurement of RBE and tissue response in hypoxia.

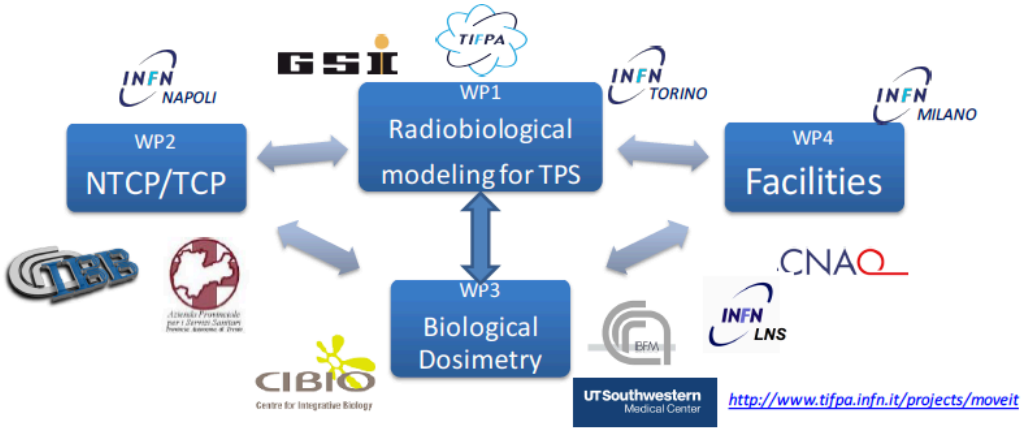

Figure 1: Scheme of the MoVe IT collaboration and workpackages' connections.

Among the main questions explored there are impact of different ions in hypoxia [1,2], RBE of proton beams [3] including target nuclear fragmentation [4], NTCP modelling specific for protons versus photon plans [5] set up of dedicated particle radiobiology facilities [6].

A summary of the present results, gained from the groups working in this framework will be reported and possible outlooks in the context of FAIR offered beams will be listed. These includes radiobiological questions explorable with such particles, and potential therapeutic applications of the latter.

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Radionuclides

Radioisotope Production at New Accelerators

U. Köster[1]
[1]Institut Laue-Langevin, 71 avenue des Martyrs, 38042 Grenoble, France

Nuclear medicine is well known for its diagnostic applications of radionuclides such as *SPECT* (single photon emission computed tomography) and *PET* (positron emission tomography) respectively and over 30 million of such imaging procedures are performed every year world-wide. The required radionuclides are produced either in research reactors (in particular ^{99}Mo for ^{99}Mo/^{99m}Tc generators) or with cyclotrons (in particular ^{18}F, ^{123}I, ^{201}Tl, etc.).

While therapeutic applications of radiopharmaceuticals were restricted for long time to relatively rare diseases (such as thyroid cancer), new targeted radionuclide therapies for different types of cancer and other diseases are now coming into clinical practice. There is a promising future for *theranostics*, a type of personalized medicine where a targeted radionuclide therapy is individually optimized, based on imaging with a companion diagnostic radiopharmaceutical. Ideally such applications are performed with so-called *matched pairs* of diagnostic and therapeutic isotopes of the same chemical element. Some of these novel radioisotopes require also new production methods.

Over 1000 cyclotrons world-wide are routinely producing radioisotopes for nuclear medicine [1]. Most of these industrial cyclotrons provide exclusively proton beams with energies up to ≈20 MeV. Few industrial cyclotrons exist that provide intense beams of 30 MeV protons, but the number of high power accelerators providing still higher proton beam energies or beams of different projectiles is very limited. In practice this restricts the development and supply of promising radioisotopes for novel nuclear medicine applications.

New accelerators with unique capabilities in terms of particle energy or diversity of beams can help to overcome this hurdle. Often such accelerators are not dedicated for radioisotope production alone, but have multiple applications that are served in a beam-share or time-share mode. I will review accelerators that are already successfully operating in this way and new accelerators that could open new possibilities for novel radioisotopes for nuclear medicine.

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Research on the production of therapeutic ^{105}Rh with deuteron beam

Mateusz Sitarz[1,2,3], Arnaud Guertin[4], Férid Haddad[1,4], Tomasz Matulewicz[2], Etienne Nigron[4], Aleksander Bilewicz[5]

[1]GIP ARRONAX, Saint-Herblain, France; [2]Faculty of Physics, University of Warsaw, Warsaw, Poland; [3]Heavy Ion Laboratory, University of Warsaw, Warsaw, Poland; [4]Laboratoire Subatech, CNRS/IN2P3, IMT Atlantique, Université de Nantes, Nantes, France; [5]Institute of Nuclear Chemistry and Technology, Warsaw, Poland

The radioisotope of ^{105}Rh is a medium-soft β^--particle emitter [$E_{\beta1,max}$ = 560 keV (70%), $E_{\beta2,max}$ = 250 keV (30%)] with a 35.4 h half-life, which is suitable for radiolabelling monoclonal antibody fragments and accurately delivering the radiation dose to small tumours (1-2 mm). Moreover, it demonstrates low energy γ-emission [319 keV (19%)] which is appropriate for imaging the distribution of the radionuclide in the human body. The advantage of ^{105}Rh is formation of kinetically inert complexes [1,2], which are very stable in vivo. For example, recent preclinical studies on ^{105}Rh-EDTMP reported rapid blood clearance and selective uptake in the bone, offering promising treatment of pain related to bone metastases [3].

Today, the ^{105}Rh radioisotope can be produced with high specific activity via (n,γ) reaction on highly enriched ^{104}Ru target followed by the subsequent β- decay of the ^{105}Ru ($T_{1/2}$ = 4.4 h) [4]. Using cyclotrons, the proton and deuteron induced reactions on palladium were proposed but the production cross-sections are relatively low [5,6]. In ARRONAX, we proposed the ^{104}Rh(d,x) reaction and measured its cross-section up to 18 MeV (Figure 1) with the use of a natural rhodium target. Here, the ^{105}Rh is formed in the direct reaction as well as from the decay of ^{105}Ru and ^{105m}Rh ($T_{1/2}$ = 43 s). We have also re-evaluated the excitation function measured in 1969 [7] and provided the production cross-section data for the co-produced radioactive impurities. However, the large-scale production requires enriched ^{104}Ru target, which would practically eliminate the impurities and reach the yield of 30 MBq/μAh at 15 MeV. This translates to 55 GBq of ^{105}Ru after a one day irradiation with a commercially available 100 μA deuteron beam and 260 mg/cm^2 enriched ^{104}Ru target. Since the activity produced in similar neutron bombardment of 100 mg target was around 30 GBq [4], the deuteron route is an interesting alternative for the ^{105}Rh production without the access to a reactor.

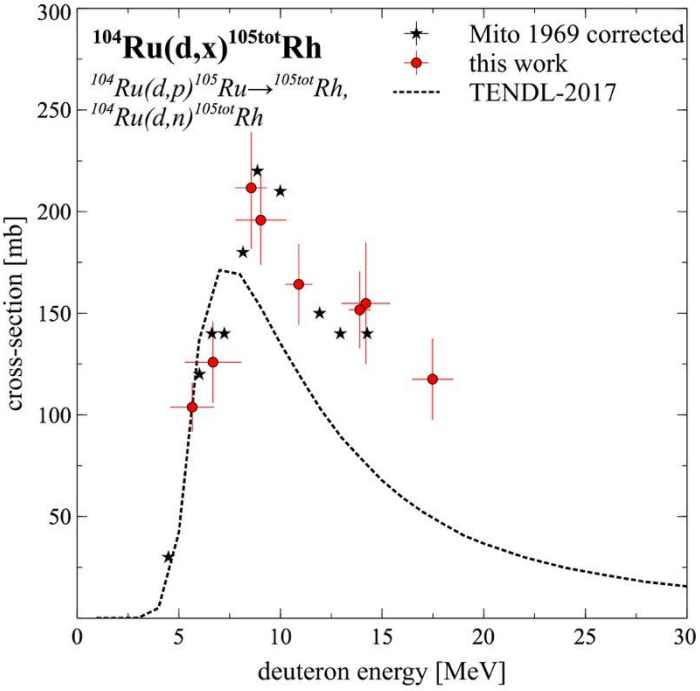

Figure 1: Measured cross-section for ^{104}Ru(d,x)^{105}Rh.

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The ISOLPHARM project: production at SPES of high specific radionuclides as radiopharmaceutical precursors

A. Andrighetto[a], F. Borgna[b], M. Ballan[a], S. Corradetti[a], E. Vettorato[b], A. Monetti[a], M. Rossignoli[a], M. Manzolaro[a], D. Scarpa[a], G. Prete[a] and N. Realdon[b]

[a] INFN, Laboratori Nazionali di Legnaro, Viale dell'Università, 2, 35020 Legnaro (PD), Italy
[b] Department of Pharmaceutical Sciences, University of Padua, Via Marzolo, 5 35100 – Padova, Italy.

At INFN-LNL (Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro) a new facility for the production of radioactive ion beams is implemented, SPES (Selective Production of Exotic Species). This new facility, besides being operated for nuclear physics studies, may play a pivotal role in the production of medically relevant radionuclides by means of the ISOL (Isotope Separation On-Line) technique.

The production of the radioactive isotopes will be obtained by nuclear reactions induced by 40 MeV protons, accelerated by a cyclotron that will collide on a production target. The formed beam will be subsequently directed and focalized using different electromagnetic systems, and purified in order to have a pure isotope beam without contaminants.

The core of the method is the possibility to obtain pure isobaric beams following mass separation; in this way no isotopic contaminations will be present in the beam and afterwards in the trapping substrate. Only potential isobaric contaminations can affect radiochemical and radionuclide purity, but proper methods can be developed to separate chemically different elements

The goal of the ISOLPHARM project is to provide a feasibility study for an innovative technology for the production of extremely very high specific activity beta emitting radionuclides as radiopharmaceutical precursors. This technique will allow to obtain radiopharmaceuticals, impossible in most cases to obtain in the standard production facilities, with lower costs with respect to traditional techniques and reduced environmental impact.

The steps to be addressed for the preparation of the radiopharmaceutical are: 1) Trapping of the radionuclide of interest present in the beam by means of the construction and placement of a suitable substrate; 2) Preparation of a medicinal product compatible with the method of administration; 3) Agreement with the requirements of quality guaranteed by compliance with the principles of Good Manufacturing Practice (GMP) in the field of radiopharmaceuticals.

RAON, a new accelerator for biophysics research

W.Y. Park[1], H.T. Chung[2], J.K. Kim[3], K.H. Kim[4], S.B. Lee[5], J.K. Woo[6], D. Liu[6]
[1] Chugbuk National University; [2] Seoul National University; [3] Daegu Catholic University; [4] Chungnam National University Hospital; [5] National Cancer Center Korea; [6] Jeju National University, South Korea

RAON is a rare isotope beam facility of Rare Isotope Science Project (RISP), which was started from 2011. RAON is going to be complete by December 2021. The major accelerator components is almost complete, and subsequent testing is ongoing. RAON is to deliver various stable ions from protons to uranium atoms and rare isotope beam (RIB) with energies from a few keV to hundreds of MeV/nucleon [1]. RAON is going to be exploited for the study of various science fields such as, nuclear physics, nuclear astrophysics, bio- and medical-science, neutron science, and material science, etc [1]. RAON is to combine two distinct rare isotope production methods: Isotope Separation On-Line (ISOL) and In-flight fragmentation (IF). RAON will be equipped with a proton cyclotron as the driver for the ISOL system, a post-accelerator (SCL3) for the ISOL system and a heavy ion linear accelerator (SCL2) as the driver for the IF system. A rare isotope beam produced by ISOL is accelerated through a post-accelerator (SCL3) and then can be fed into a main driver linac (SCL2) to be accelerated up to ~200 MeV/u of beam energy and finally delivered into IF system. The ISOL system utilizes a 70 MeV H^- cyclotron as a proton driver to produce relatively pure and low energy rare isotopes. By combining ISOL and IF method wider range of exotic and rare isotope beams is expected to be produced. Each end of ISOL and IF system connects to various experiment systems [2]. Priority biophysics experiments can be relative biological effectiveness (RBE) study of various heavy ions, cancer treatment study using very high dose rate heavy ions, study on biologically optimized treatment using multiple ions, treatment study of degenerative and metastatic brain diseases by combining of nanoparticles with heavy ions, cancer treatment study by combining heavy ions and immune modulation, cancer treatment study using radioisotope beams, and mutation induction and bio-effect analysis on plant and microorganism.

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