THE BIOPHYSICS COLLABORATION FOR RESEARCH AT FAIR

AND OTHER NEW ACCELERATOR FACILITIES

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Applied nuclear physics is ubiquitous in our lives, and is a field in fast and exponential growth. Biomedical application at particle accelerators are particular important, and many current accelerators in Europe built for nuclear physics (e.g. GSI in Germany, KVI in The Netherlands, GANIL in France, INFN-LNS in Italy) have intense and productive biomedical programs covering topics such as radiotherapy with charged particles and radiation protection in space [1].

◂ **P. 27:** The GSI Helmholtz Center in Darmstadt, and the FAIR construction site in September 2018. Photo: T. Middelhauve/ GSI/FAIR

There are now several new accelerators under construction worldwide, that offer new opportunities for the researchers. Most of these very expensive facilities plan biomedical research. But what can the new facilities offer to researchers in biology and medicine worldwide? How should we coordinate the efforts to avoid duplications and instead have synergistic interactions for biomedical research at new accelerators? To address the issue, an International Biophysics Collaboration has been established at the Facility for Antiprotons and Ion Research (FAIR). The first meeting of the Collaboration was held at GSI (Darmstadt, Germany) on May 20-22, 2019 (Figure 1).

FAIR is the new international accelerator facility presently under construction at the site of the GSI *Helmholtzzentrum für Schwerionenforschung* in Darmstadt, Germany (Figure 1). The new facility, where various physics programs can be operated in parallel, will offer outstanding research opportunities and discovery potential for about 3000 scientists from about 50 countries. International Collaborations in hadronic physics, nuclear structure *etc.* are already actively working to prepare the experiments for the opening of FAIR [2].

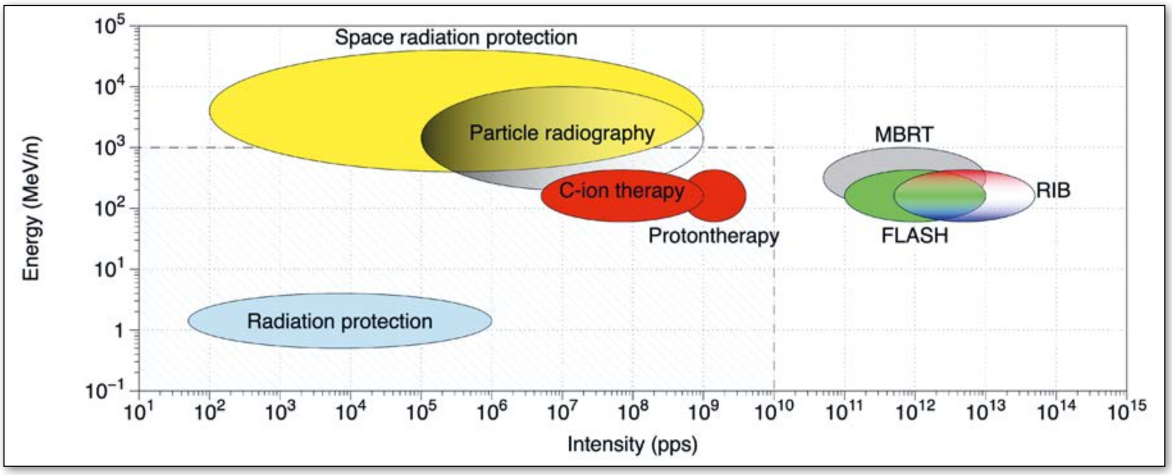
FAIR also hosts an intense and innovative program in applied nuclear physics (APPA) [3], and in particular in biophysics. The expertise stems from the activity of the Biophysics Department at GSI, funded by Prof. Gerhard Kraft, that has pioneered carbon ion therapy in Europe [4] and currently runs the experimental program for space radiation research supported by ESA (IBER program) [5]. In fact, FAIR can offer unique opportunities for biomedical research. The production of very high energy (~10 GeV/n) heavy ions is very important for studies in space radiation protection, both in biology and microelectronics. The high energy can also be used for particle radiography and theranostics, whereas the high intensity of the FAIR beams gives opportunities for using high-energy radioactive ion beams and ultra-high dose rates in particle therapy, and for the production of new radioisotopes (Figure 2) [6].

Similarly to the other FAIR collaborations such as NuSTAR, PANDA, and CBM, the Biophysics Collaboration held a meeting at GSI/FAIR on May 20-22, 2019. With 250 participants from 27 countries in 5 continents, the meeting demonstrated the enormous interest of the scientific community for the biomedical applications at FAIR (figure p.27).

Several new ideas for experiments at FAIR have been proposed. As shown in Figure 3, high-energy heavy ions are particularly attractive for space radiation protection. In fact (Figure 3), FAIR covers a region of the galactic cosmic ray spectrum which is currently only measured by detectors in space such as the alpha-magnetic spectrometer (AMS) on the International Space Station, but that contributes around 60% of the effective dose to astronauts behind thick shielding [7]. High-energy heavy ions are therefore necessary to measure the biological effectiveness of the ions and to measure shielding effectiveness against cosmic rays (Figure 4). For this reason, it is also important to simulate the full LET spectrum of the galactic cosmic radiation, a facility already available at the NASA Space Radiation Laboratory (NSRL) [8] in Upton, New York, and now planned at FAIR [9].

The high energy makes also possible new solutions in particle therapy. In fact, proton radiography is generally acknowledged as the best method to reduce the uncertainty associated to the conversion of the Hounsfield units (HU) from the CT scans in the water-equivalent pathlengths (WEPL) necessary for proton therapy treatment planning [10]. The image is obtained with X-rays, but the treatment is done with charged particles, hence the HU/WEPL conversion is critical. If the image is directly obtained with protons, this uncertainty is automatically cancelled. Conventional proton radiography projects are bound to low energy (<250 MeV) and are therefore only applicable to selected tumor sites (typically the

▾ **FIG. 1:** Group photo at the Biophysics Collaboration Meeting at GSI, May 20, 2019. Photo by Gabi Otto, GSI.



◂ **FIG. 2:** Biomedical applications at new accelerators. The shaded rectangle includes the (E, I) region covered by particle accelerators. FAIR will provide higher energy and intensity thus allowing experiments in space radiation protection and particle therapy not possible at current heavy ion accelerators. MBRT= minibeam radiotherapy; FLASH = ultra high dose-rate therapy; RIB = radioactive ion beams for therapy and beam visualization. Image from ref. [6]

head-and-neck region). Using this relatively low energy proton beam the technique is plagued by the image blurring caused by the strong elastic scattering of the primary beam, well described by the Moliére theory. These problems are overcome using protons with energies ~GeV and the PRIOR setup built by the plasma physics collaboration at FAIR,where also body tumors can be visualized with high spatial and temporal resolutions [11]. The PaNTERA experiment at FAIR will explore the possibility to use 4.5 GeV protons for radiography and tomography with sub-mm resolution.

The high-intensity offers even more opportunities for particle therapy. In fact, spatially fractionated radiotherapy (SFRT) uses a grid structure to reduce toxicity in normal tissues, thus widening the therapeutic window. So far limited to brain tumors, the high-intensity can allow extensions to body regions, where the movements jeopardize the spatial fractionation. Already successfully tested in animal models with protons [12], at FAIR there is the opportunity to perform these experiments with very heavy ions [13]. In the pilot project at the Lawrence Berkeley Laboratory in the 70-80s, ions as heavy as 40Ar were used in selected patients [14]. The rationale was that only these heavy ions can overcome hypoxia resistance in some aggressive cancers. However, ions heavier than 12C were abandoned in the clinical applications in Asia and Europe, because of the excessive toxicity of very heavy ions in normal tissues. Using SFRT, normal tissue will be spared making attractive the use of heavy ions against very hypoxic tumors. The possibility of using very high energies (> 1GeV/u) permits the exploration of new avenues in charged particles minibeam radiotherapy [15].

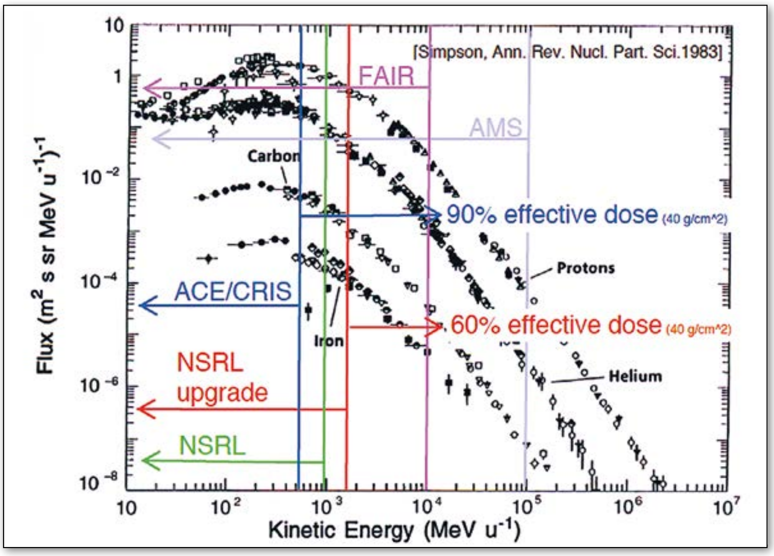
Recent experiments have shown that ultra-high dose rates (>40 Gy/s) spare normal tissue but do not compromise tumor control in animal models (FLASH radiotherapy) [16,17]. These high intensities have been so far been achieved with electrons in modified linacs and with protons at cyclotrons [18], but at FAIR it can be tested with heavy ions.

Radioactive ion beams provide a very high signal/noise ratio for online PET imaging and do not suffer from the shift between the peak of the activity and the Bragg peak observed using fragments of stable 12C ions [19]. Short half-life b+-emitting nuclides, such as 10C (t1/2 = 19.29 s), allow truly online beam monitoring with PET detectors. Although already proposed during the pilot project in Berkeley [20], use of radioactive ions in therapy was always hampered by the low intensity. Now these isotopes can be produced at therapeutic intensities at FAIR.

With the start of FAIR-phase-0 in February 2019, these high-intensity experiments are already feasible at the SIS18 synchrotron of GSI. The high energy will be available at SIS100, whose opening is foreseen in 2025.

Unlike other detector-centered collaborations, the International Biophysics Collaborations goes beyond FAIR. In fact, there are many new accelerator facilities under construction all over the world (*e.g.* NICA in Russia, RAON in Korea, FRIB in USA, ELI, SPIRAL2 and SPES

▾ **FIG. 3:** The energy spectrum of H, He, C and Fe ions in the galactic cosmic radiation in deep space. Vertical bars indicate the maximum energies achievable with ground-based accelerators or radiation detectors in low-Earth orbit. ACE/CRIS= Cosmic Ray Isotope Spectrometer (CRIS) on the Advanced Composition Explorer (ACE) spacecraft; NSRL = NASA Space Radiation Laboratory; AMS = Alpha Magnetic Spectrometer. Plot courtesy of John W. Norbury, NASA Langley, VA, USA.



▲ **FIG. 4:** Tests of Martian regolith at the SIS18 accelerator at GSI. Shielding can be exposed to high-energy heavy ions to measure the dose attenuation and the production of neutrons and charged secondaries. Photo by Gabi Otto, GSI.

in Europe, *etc.*) where applied nuclear physics programs are planned and biomedical research will be possible. The International Collaboration will serve all these facilities and will develop research programs and specific devices for use at various accelerators. Accelerators currently operating for biomedical research are also part of the collaboration and contribute with their local research program and with hardware to be built with the other facilities. Experimental collaborations in biophysics are already active in FAIR-phase-0 (*e.g.* PaNTERA [11], FOOT [21] and IBER [5]) and the Biophysics Collaboration has the task to supervise and support these experimental activities also in funding applications.

Vincenzo Patera (University of Rome "la Sapienza", Italy) and Yolanda Prezado (CNRS, Orsay, France) have been elected spokesperson and deputy spokesperson of the collaboration respectively. The collaboration webpage is: www.gsi.de/bio-coll ■

About the Authors

Marco Durante is Director of the Biophysics Department at GSI Helmholtz Center for Heavy Ion Research (Darmstadt, Germany) and Full Professor of Physics at the Technical University of Darmstadt. He is generally recognized as world leader in the field of particle radiobiology and medical physics and is co-author of over 300 papers in peer-reviewed scientific journals (h-index=45) and one patent on proton therapy. He has been awarded several prizes for his contributions to charged particle biophysics.

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Yolanda Prezado is a permanent scientist at CNRS (France). She holds a Diploma in Advanced Studies in Particle Accelerators (2000) and a Ph.D. in Experimental Nuclear Physics (2003). She is a board-certified medical physicist (2007), with clinical experience. She has been developing her research in radiation therapy with research interests including Grid and minibeam radiation therapy, dose calculations (Monte Carlo simulations), small field dosimetry and radiobiology. She is currently the chair of the Science Committee of the European Federation of Medical Physics (2019-2020, elected).

> **"High intensity is useful for several therapy-related applications such as FLASH, minibeams, and radioactive ion beams"**

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