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CROSS-CUTTING ACTIVITY

RADIATION RESEARCH

White Paper

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KIT Karlsruher Institut für Technologie

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Imprint

Published by
GSI Helmholtzzentrum für Schwerionenforschung GmbH,
Planckstr. 1, 64291 Darmstadt, Germany

Editor: Marco Durante

Printed by GSI Helmholtzzentrum für Schwerionenforschung GmbH,
Planckstr. 1, 64291 Darmstadt, Germany
Publication date: June 2023

DOI:10.15120/GSI-2023-00685

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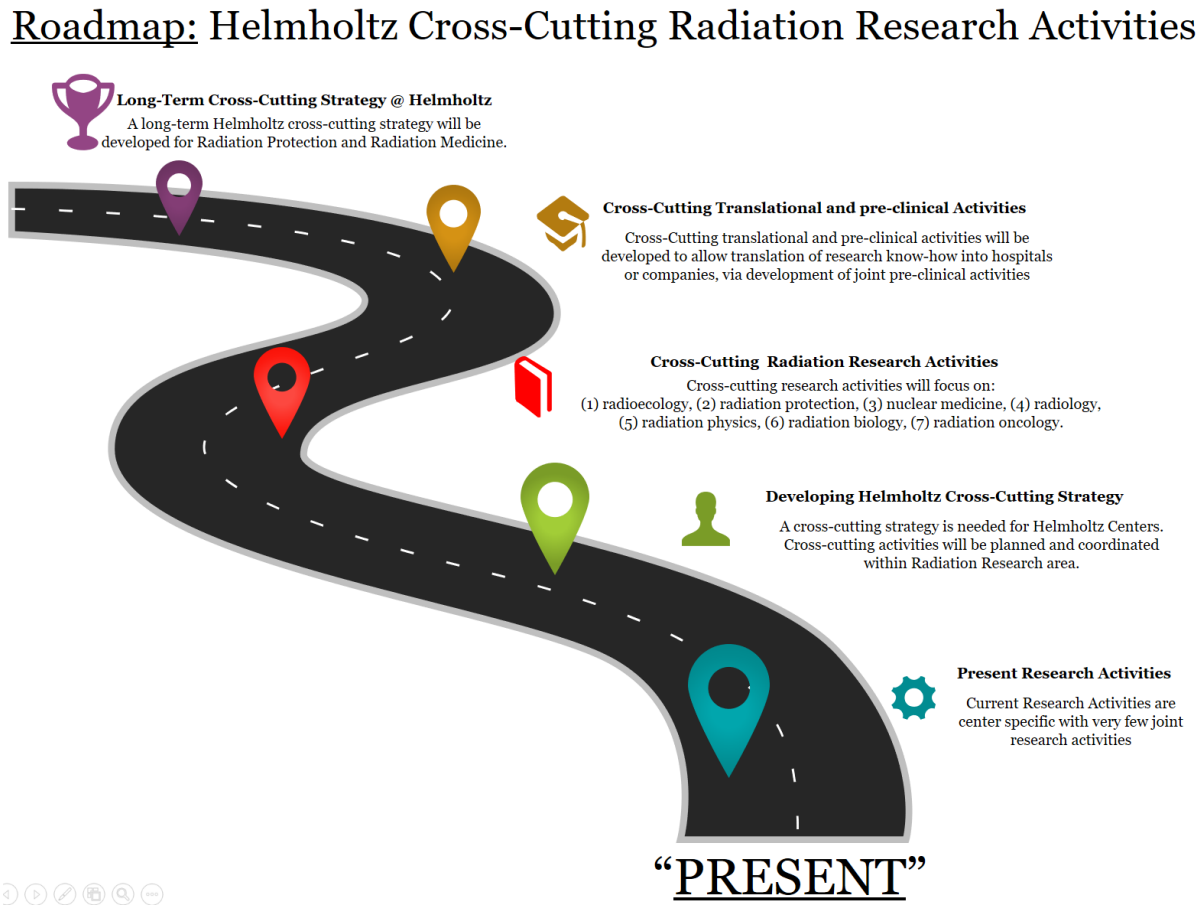
EXECUTIVE SUMMARY

Within the Helmholtz association (HGF), many research activities are center specific with very few joint research activities. The development of cross-cutting activities serves to bring together different research fields, to promote profile-forming key areas and build networks with other scientific partners. We provide a roadmap for developing a long-term cross-cutting strategy at the Helmholtz association for radiation research.



A cross-cutting strategy will be developed for Helmholtz centers performing "Radiation Research" (CCA RR). The main goal of the CCA RR will be to support research among radiation research activities in different Helmholtz research programs (Energy; Earth and Environment; Health; Information; Aeronautics, Space and Transport; Matter). Radiation research is a highly interdisciplinary topic, involving physicians, biologists, chemists, physicists, earth scientists and engineers from ten Helmholtz centers. The cross-cutting "Radiation Research Activities" include research activities in radioecology, radiation protection, nuclear medicine, radiology, radiation physics, radiation biology or radiation oncology. The cross-cutting "translational and pre-clinical

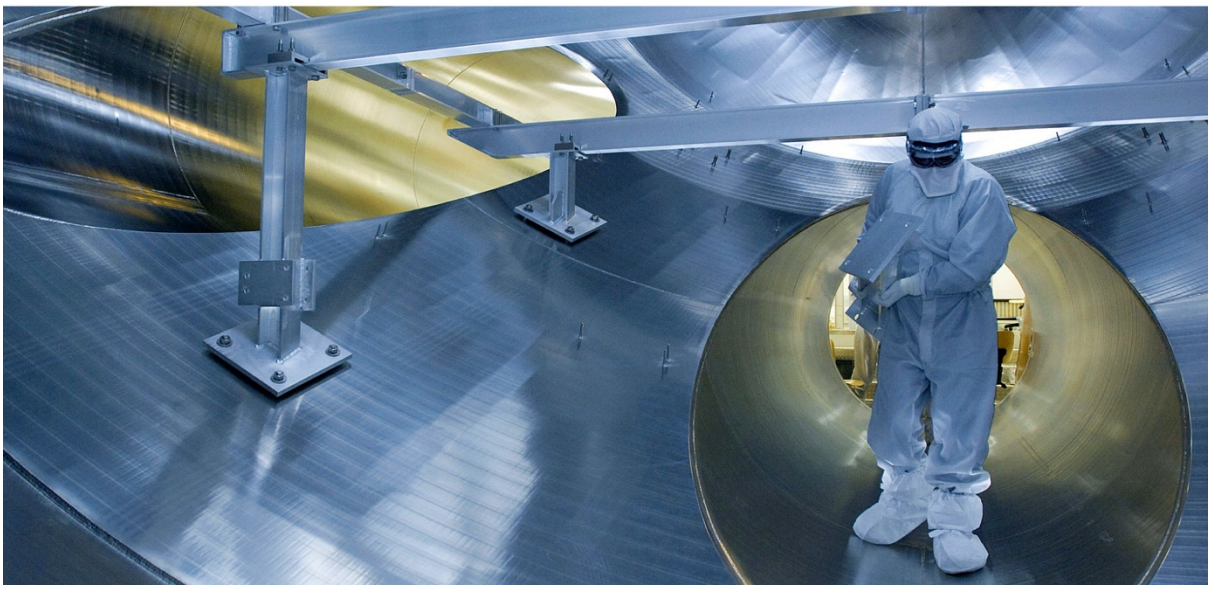
activities" involve the pre-clinical testing and translation of technology developed at the Helmholtz centers into clinical practice or to companies. Pre-clinical studies are fundamental in establishing if new radiation technologies can be used with patients and can benefit significantly from cross-cutting activities. A long-term strategy will be developed for cross-cutting activities at HGF, which will heavily rely on modern infrastructures. The long-term strategy will make the Helmholtz groups – due to their competences in operating and exploiting the scientific benefit of large infrastructures – particularly competitive in the field. The CCA RR was already active in the POF-III funding period. For the POF-IV funding period a further development of the concept was outlined and presented in the proposal for Strategic Evaluation. In this strategy paper the concept will be worked out in detail.

There are several scientific challenges to be tackled in the coming 5-10 years, such as a safe and sustainable nuclear waste management, understanding the risk of exposure to low-doses, enabling human space exploration with acceptable radiation risk, combination of imaging and therapy with radionuclides (theranostics) or external beam radiotherapy, individualized treatments using molecular or imaging biomarkers, or novel applications of particle therapy, including advanced image guidance and novel delivery techniques as well as combined treatments in oncology. Many Helmholtz groups are working on these topics and they may benefit from close collaborations with other centers and other infrastructures. New facilities such as ZRS, HOVER, PT2030, FLASH*lab*@PITZ, and FAIR, will open in the coming years offering new opportunities for the benefit of the scientific community and society in Germany and worldwide.

HGF played a key role in radiation research in Germany in the past and until today: among other achievements, HGF has introduced Monte Carlo track calculations in radiation protection, inverse planning in intensity-modulated radiotherapy and started carbon ion therapy in Europe. The legacy of this tradition is a mandate to also shape the future of the field: a vigorous collaboration among the centers in different research programs and different perspectives onto the subject can lead to new, lasting, and visible results and applications in radiation research.

1

THE CROSS-CUTTING ACTIVITY RADIATION RESEARCH



Ionizing radiation is ubiquitous in our lives with a wide range of exposure rates that span 8-10 orders of magnitude. We are well acquainted with low doses corresponding to eating a banana, flying to America, or having a chest radiography (from μGy[1] to mGy), but we are also familiar with the very high doses corresponding to radiotherapy or sterilization of syringes and medical equipment (several kGy). The study of the effects of low-dose exposures and the exploitation of high-doses in medicine or other applications require comprehensive and interdisciplinary research studies and thus intensive international cooperation. This is an enormous effort started since more than one century ago, and provided numerous fundamental insights and technological innovations. Nevertheless, there are still many open questions and potential to be raised demanding continuous effort in and further development of the field.

The harmful effects of radiation became clear shortly after the discovery of X-rays by Wilhelm Conrad Röntgen in 1895. While high doses clearly induced skin burns and prodromal syndromes, the biological effects of low doses were considered negligible until Hermann Joseph Muller observed in 1927 genetic mutations in *Drosophila* exposed to a wide range of X-ray doses. Following Muller's results and further evidence of a linear relationship between dose and genetic mutations (e.g. those of Nikolay Timofeef-Ressovsky in collaboration with Max Delbrück and Karl Zimmer), the linear-no-threshold (LNT) concept became accepted by radiation geneticists and recommended by international advisory committees for radiation risk assessment from the mid-1950s to the present.

The **LNT model** implies that the radiation risk is proportional to the dose and, unlike chemical mutagens, there is not a threshold below which it can be considered negligible. Because it is generally impossible to reduce radiation exposure to zero in any working environment, the International Commission for Radiological Protection (ICRP) has recommended since 1960s to keep radiation exposure "as low as reasonably achievable" (**ALARA**). In 1977, ICRP added to ALARA "social and economical consideration being taken into account". It was indeed clear that the implications of LNT or ALARA may have imposed very severe constraints to the life of the citizens and costs to the society.

The LNT model (Figure 1.1) is controversial and has been challenged by supporters of the hormesis model claiming low-dose radiation to be actually beneficial and induce a low-level stress useful to protect the organism, or simply that a threshold

1 Ionizing radiation dose is the energy absorbed in a given mass of material. It is measured in gray (Gy). 1 Gy= 1 J/kg

at low doses should be applied, as common in toxicology. On the other hand, more recent observations of non-targeted radiation effects have led some authors to hypothesize a supra-linear curve at low doses. The epidemiological data, especially the life-span study of the survivors of the atomic bombs dropped in Hiroshima and Nagasaki in 1945, has not clarified the issue because late radiation effects, primarily cancer, are small at low doses (<50 mSv, see note[2]) and epidemiological studies are affected by large uncertainty. The topic, which has an enormous socio-economic impact, has gained an exquisite scientific interest on the consequences of DNA damage and repair. The latter is the main problem in **radiation protection**, a field that also includes the effects of radiation in the environment (**radioecology**, a scientific branch coming into focus with the Chernobyl nuclear accident in 1986). Furthermore, the behaviour of radionuclides in the environment is currently only poorly understood and dose predictions for humans and the environment suffer from great uncertainty. Thus, neither the transport nor the transfer of radionuclides in the environment due to their release by natural processes such as weathering or radioactive decay, severe nuclear accidents such as in Chernobyl or Fukushima, mining activities or in the course of deep geological storage of high-level radioactive waste can be reliably modelled at present. This further extends to extra-terrestrial space (**space radiation protection**) considering the unique radiation fields generated by cosmic radiation in deep space.

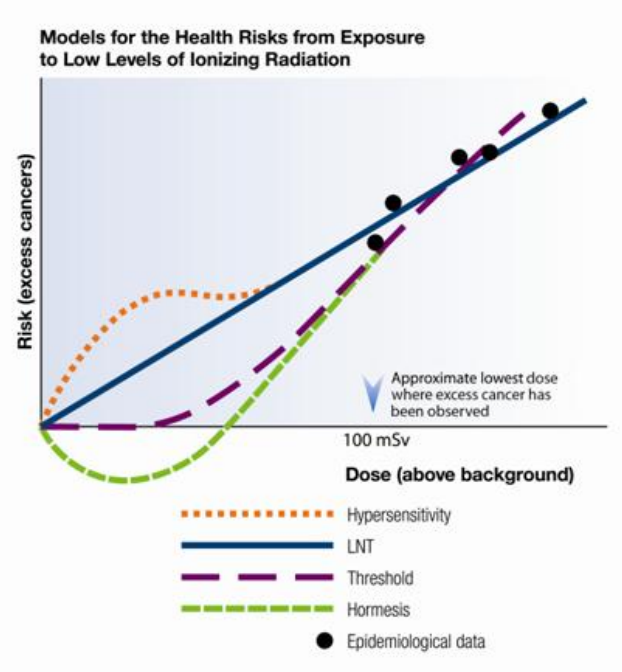


Figure 1.1 Models to describe low-dose radiation effects. Epidemiological data are reliable at doses >50-100 mSv, but at low doses different models have been proposed. Image source: *LNT model, Canadian Nuclear Safety Commission, 2013*, available online on www.nuclearsafety.gc.ca

2 Different radiation qualities induce different biological effects at the same dose (in Gy). For this reason, ICRP adopted the equivalent dose H (in sievert, Sv) defined as $H(Sv)=w_R \cdot D(Gy)$, where w_R is a radiation-dependent weighting factor. For instance, $w_R=1$ for X- and γ-rays, but $w_R=20$ for densely ionizing α-particles.

On the other hand, the medical applications of ionizing radiation were very clear by the time that the radiography of Wilhelm Röntgen's wife hand appeared on the *New York Times* front page on January 16, 1896. This marks the birth of **radiology**, whose evolution is nicely shown in Figure 1.2. With the discovery of natural radioactivity by Henry Becquerel in 1896, it soon became clear that radionuclides could be used for imaging - the birth of **nuclear medicine**. Moreover, the sterilizing effects of ionizing radiation were soon recognized and the first treatments date indeed back to 1896, when Émil Herman Grubbé, a German emigre in USA manufacturing incandescent lamps, treated a woman for breast cancer at the Hahnemann Medical College in Chicago. The evolution of **radiotherapy** in the past century is shown in Figure 1.3, and has led this technology to be an essential part of cancer treatment along with surgery and chemotherapy.

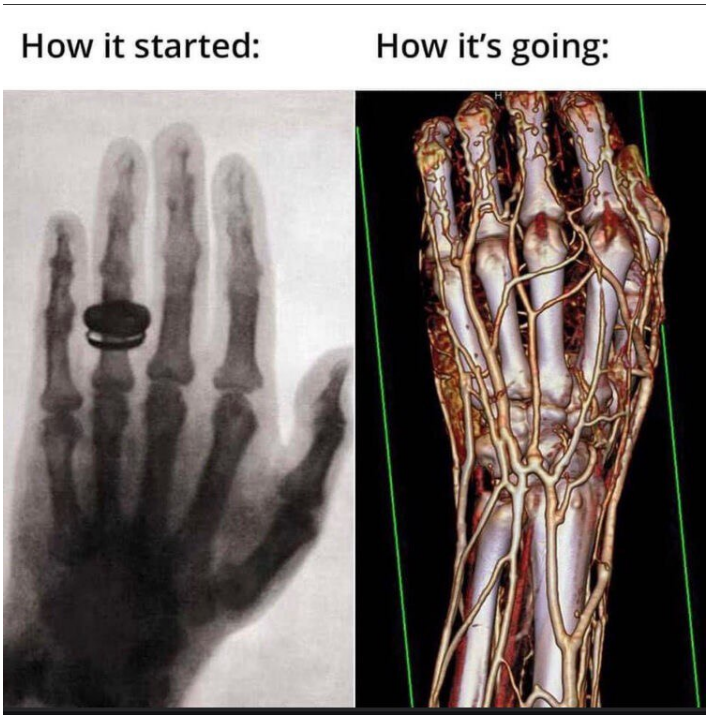


Figure 1.2. Evolution of radiology, from the first Röntgen's radiography in 1896 to modern 3D imaging. The first radiography was originally published on the New York Times on 19.1.1896. The right image, a volumetric rendering of the hand tissue, is taken from the CTisus database (www.ctisus.com).

Radiation research is therefore a strong and interdisciplinary topic, involving public health, energy, ecology, physics, chemistry, biology, earth sciences, and medicine. It is an active and lively science, whose progress is essential for public health, for the protection of humans and environment from the harmful effects of ionizing radiation and the cure of highly lethal and increasingly prevalent diseases such as cancer.

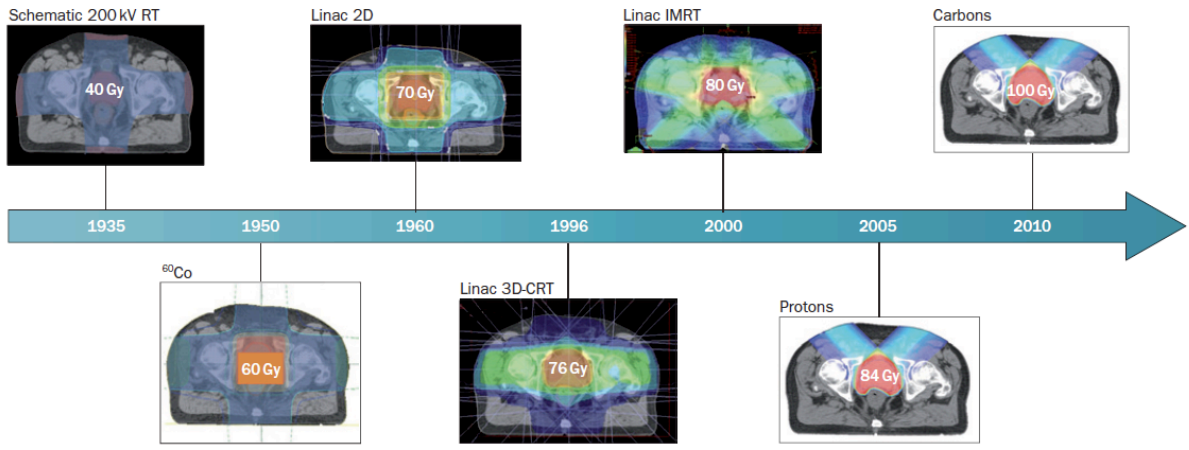


Figure 1.3. Evolution of prostate cancer radiotherapy, from orthovoltage radiotherapy to particle therapy. By increasing the beam energy and the precision of the targeting, it was possible to escalate the dose to the prostate without exceeding the tolerance dose of healthy tissues; allowing the move from palliative irradiation to curative treatment. Abbreviations: Linac, linear electron accelerator; 3D-CRT, 3D-conformal radiotherapy; IMRT, intensity modulated radiotherapy; RT, radiotherapy. Image reproduced from Thariat *et al., Nat. Rev. Clin. Oncol.* (2013).

1.1 RADIATION RESEARCH IN HELMHOLTZ

HGF performs cutting-edge research in essentially all the different nuances of radiation sciences. Ten centers joined the cross-cutting activity radiation research (CCA RR), distributed all over Germany.

HGF has a long-standing tradition in radiation research in many different fields. For instance, HMGU has been leading radiation protection research in Germany since the 1970s; GSI has first introduced carbon ion therapy in Europe in 1997 and is now a world-leading research center in heavy ion biophysics; HZB first started proton therapy in Germany in 1998; DKFZ pioneered inverse treatment planning system optimization algorithms for IMRT, developed one of the first IGRT systems (Siemens Artiste), strongly contributes to carbon ion therapy at the university hospital Heidelberg (HIT) and developed the revolutionary PSMA-PET marker; HZDR was the worldwide first to introduce dual-energy based treatment planning and in-vivo dosimetry based on prompt-gamma imaging to clinical radiotherapy or clinical trials; HI-Jena has a long-standing expertise in the generation of ultra-short intense radiation sources using high-power lasers and their detection for a precise characterization towards applications.

Helmholtz is scientifically excellent in radiation research and covers all the hot topics described above with different expertise: radiation protection (HMGU, FZJ, KIT), space radiation protection (DLR, GSI), nuclear waste management (HZDR, KIT, FZJ), radioecology (HZDR, FZJ), imaging (DKFZ, HZDR, HI-Jena), nuclear medicine (FZJ, HZDR, DKFZ), and radiotherapy (GSI, HZDR, DKFZ, HZB, HMGU, DESY). While the topics are very diverse, the CCA RR aims at identifying common research activities where collaboration can create synergies.

Moreover, as typical in Helmholtz, the CCA should explore future breakthroughs in radiation research with novel, unique **infrastructures** (see Section 3.2).

1.2 RADIATION RESEARCH IN GERMANY

Radiation research in Germany has a basis of institutional funding, i.e. by universities, HGF and other research organizations. In addition, financial support via e.g. the German Research Funding Agency (Deutsche Forschungsgemeinschaft, DFG) or by the German Cancer Aid (Deutsche Krebshilfe, DKH) can be gained for basic, preclinical or clinical research. Another opportunity is governmental funding of radiation research via BMBF (Federal Ministry of Education and Research) or by the European Union (EU), according to defined funding priorities in highly competitive calls.

Radiation research is an interdisciplinary research field and the self-understanding of the respective scientific community is to aim for an improvement of the exploitation of radiation for medical purposes and radiation protection for the sake of human health. The field includes aspects of basic and applied research, i.e.

- Radiation biology
- Epidemiology and radiation risk
- Medical applications and clinical radiobiology
- Radioecology
- Measurement techniques and dosimetry
- Development and provision of new technologies

An important step of support for radiation research was the foundation of the „KVSF“ **(**Kompetenzverbund Strahlenforschung; Competence alliance/network for radiation research) in 2007 by BMBF and BMUV (Federal Ministry of Environment, Nature Conservation and Reactor Safety) to fix guidelines for a dedicated funding strategy by BMBF. This occurred against the background of re-orientation of university chairs in radiation research between 1980 and 2000, where many radiation research institutes were closed and experts suspected a loss of internationally recognized competences, i.e. radiation protection, risk assessment, epidemiology and radioecology, expertise in UV protection and research, basic and clinical radiobiology and radiation physics as well as experimental radio-oncology. The German Radiation Protection Commission (Strahlenschutzkommission – SSK), the German Society for Radiation Oncology (DEGRO), the German Science Council (Deutscher Wissenschaftsrat) and others asked in this situation for:

- Sustainable support of radiation research in Germany, both for improved medical application/ radiation protection

- Education of young radiation researchers and experts should be assured by the Universities

In 2021, SSK published a statement on the current situation of radiation research and application in Germany. The statement included identification of scientific disciplines most relevant for radiation protection, and of German institutions that have been most important in that area in the past (SSK 2021). The statement was written by the SSK on request of the BMUV. In the request, the term "radiation research" was meant in the broadest context of basic and application-oriented science and covered both ionising and non-ionising radiation.

To meet this request, the SSK evaluated about 370 research projects that were funded since 2007 either within the "Kompetenzverbund Strahlenforschung" initiative (KVSF) supported by the Federal Ministry for Education and Research (BMBF), or since 2010 within the "Ressortforschungsplan Strahlenschutz" initiative supported by the BMUV. For ionising radiation the SSK came to the following conclusions:

- *"The SSK emphasized that radiation research requires an interdisciplinary approach involving numerous scientific areas. In the past, radiation research has been considered very important in Germany, and German researchers active in the field still enjoy a high recognition and reputation.*
- *The SSK considered the following research areas particularly important: radiation biology, radio-epidemiology, evaluation of radiation-related risks, medical applications of ionising radiation, radioecology, techniques of measurement, dosimetry, and emergency preparedness including medical emergency response.*
- *About half of the evaluated research projects were performed by only 15 German research institutions. Some of these institutions have more recently reduced or even terminated their activities in radiation research. In the other half of the evaluated projects, many more additional (smaller) institutions were involved. The SSK emphasized that a minimum number of active institutions is required in Germany, to cover the broad expertise needed for the interdisciplinary field of radiation research.*
- *The SSK considered contributions of universities to radiation research important, but missed a clear commitment of them towards excellent radiation research.*
- *In the past the HGF, who addresses the big scientific questions relevant for the society, was a main actor in the field of radiation research. The SSK noted that recently for HGF the significance of radiation research has decreased.*
- *The SSK identified worrying deficiencies in radiation research in Germany, in the following fields: fundamentally-oriented radiobiology, radio-*

epidemiology, evaluation of radiation-related risks, radioecology, techniques of measurement, and dosimetry."

In more general terms, the SSK made the following additional statements (excerpt):

- *"Given the high societal relevance of radiation research, the SSK considered a holistic and interdisciplinary collaboration with social sciences and humanities important."*
- *"Maintaining and upgrading infrastructure was considered a prerequisite for keeping competence in radiation research. Consequently, the SSK called for a sustainable strategy to keep proven installations alive and enhance modern infrastructure."*
- *"… the SSK considered the additional supplementary cooperation of various actors including universities, the research centers of the HGF, and public research and development efforts of federal and state institutions as decisive."*
- *"The SSK supported the idea to integrate radiation research into national research initiatives…"*

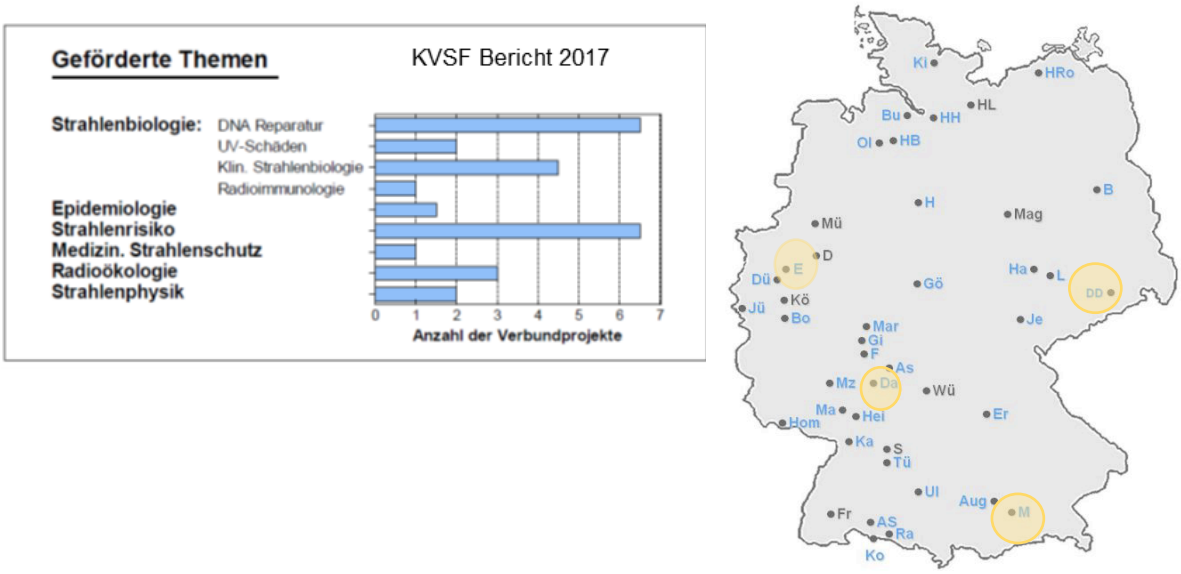


Figure 1.4 Main research topics funded by BMBF since the foundation of "KVSF" (a). Local "clusters" (yellow circles) of competence in radiation research (b). From KVSF-Bericht 2017.

The SSK concluded that *"German research and technology will substantially benefit if the competence in the identified scientific areas will be recovered, maintained, and enhanced. It is only then that German scientists involved in radiation research and radiation protection can contribute to the international scientific debate."*

In the following years, mainly the topics of radiation research shown in Figure 1.4 were funded, mostly joint research projects, meeting the requirements of competence preservation of understanding of radiation induced effects in humans, promotion of young talents, and interdisciplinary networking. This funding format led to the establishment of synergistic local clusters of research institutions, universities and clinical units.

Outlook

For radiation protection, profound knowledge about the mechanisms underlying biological radiation responses is essential for adapted and new concepts (occupational and medical exposure, exposure to natural sources of radiation). For the development of innovative protocols in radiotherapy (e.g. physical/technological optimization including online-adaptive treatments and MR-integrated photon or proton beam therapy, combined treatments, comprehensive integration of biological knowledge into clinical treatments, FLASH etc.), high-level preclinical research is essential from a physics as well as from a biology and clinical perspective.

1.3 RADIATION RESEARCH IN EUROPE

Radiation protection research in Europe is organized by several radiation research platforms that form the MEENAS (MELODI[3], EURADOS[4], EURAMED[5], NERIS[6], ALLIANCE[7], SHARE[8]) consortium. The missions of this consortium are to promote the integration and the efficiency of European R&D in radiation protection to better protect humans and the environment against the risk of ionizing radiation, to develop and implement the joint roadmap, to maintain and develop European research capacities, to encourage scientific education and training and foster key research infrastructures in the field of radiation protection, and to foster international collaboration and collaboration with sister organizations and networks in a non-exclusive manner by open interaction with the wider research community and stakeholders[9].

Several relevant European projects with participating Helmholtz groups are ongoing and address specific topics. The MEDIRAD project focuses on cardiovascular effects and diseases from radiotherapy in breast cancer patients and cancer following CT-scan among children. The HARMONIC project investigates short to medium-term health outcomes (endocrine dysfunction, cardiovascular toxicities, second primary cancers and neurovascular damage) in paediatric patients undergoing interventional

[3] https://melodi-online.eu/
[4] https://eurados.sckcen.be/
[5] https://www.euramed.eu/
[6] https://www.eu-neris.net/
[7] http://www.er-alliance.eu/
[8] https://www.ssh-share.eu/
[9] https://eu-meenas.net/doku.php

cardiology or proton therapy. The RADONORM project considers the risks associated with radon and other sources of NORM exposure, the risks arising from combined exposures and elements of radon dosimetry. The SINFONIA project considers cancer risks associated with medical exposures, including those at low doses.

The **CONCERT-European Joint Programme for the Integration of Radiation Protection Research**[10] under Horizon 2020 was operating as an umbrella structure for the research initiatives by the radiation protection research platforms MELODI, ALLIANCE, NERIS, EURADOS and EURAMED. CONCERT was a co-funded action that aimed at attracting and pooling national research efforts with European ones in order to make better use of public R&D resources and to tackle common European challenges in radiation protection more effectively by joint research efforts in key areas. The aim of the CONCERT Joint Program was to bring together relevant funding agencies to integrate European research and to administer calls for research proposals in radiation protection on behalf of the EU. CONCERT started its work in June 2015 and was completed in 2020. CONCERT was based on program owners (PO) and managers (PM) and linked third-parties. For HGF, the PM was HMGU. In July 2021 EU issued a new call including **European Partnership for research in radiation protection and detection of ionizing radiation** (HORIZON-EURATOM-2021-NRT-01-09). In February 2022 in the frame of Horizon Europe the successor project **PIANOFORTE** (Partnership for European research in radiation protection and detection of ionizing radiation towards a safer use and improved protection of the environment and human health) was approved.

It will contribute to all of the following outcomes:

- Establishing improved risk estimates for the justification of practices and optimization of radiological protection of members of the public, patients, workers and environment in all exposure situations (medical, natural, occupational, accidental, including co-exposure and overlapping risks), in order to support the implementation of the Basic Safety Standards Directive.
- Advancing state-of-the-art understanding of the link between exposure characteristics (radiation quality, dose and dose-rate) and cancer and non-cancer effects, including optimized detection and dosimetry.

For HGF, the PM in the new EURATOM program will be HZDR.
The topic of radiation medicine is not organized in platforms, but has received several EU grants. Examples are:

- EuCanImage[11], Horizon 2020 research project building a European cancer imaging platform to enhance the potential of Artificial Intelligence in oncology;

10 https://www.concert-h2020.eu/
11 https://eucanimage.eu/

- Euro-BioImaging[12], the European landmark research infrastructure for biological and biomedical imaging as recognised by the European Strategy Forum on Research Infrastructures (ESFRI);
- INSPIRE[13], the Horizon2020 Infrastructure project on proton therapy in Europe;
- HITRI+[14], the Horizon2020 Infrastructure project on hevy ion therapy in Europe;
- RAPTOR[15], a Marie Curie Innovative Training Network (ITN) on real-time adaptive particle therapy;
- PRISMAP[16], the Infrastructure EU project on radioisotope production in medicine.
- PROTECT, a randomised proton versus photon radiotherapy trial in esophageal cancer
- EMPIR[17], the European Metrology program for innovation and research.

These projects have important Helmholtz participation. Moreover, Helmholtz members received prestigious ERC grants, for instance the Advanced Grant BARB[18] to explore the use of radioactive ion beams (such as ^{11}C or ^{15}O) for simultaneous treatment and beam visualization in oncology.

As discussed previously, Helmholtz has a leading role in particle therapy in Europe. It is a key member of the European Particle Therapy Network (EPTN)[19], and actively participates in the Particle Therapy Co-Operative Group (PTCOG)[20], which includes all particle therapy centers in the world, where a Helmholtz representative is currently vice-chair.

12 https://www.eurobioimaging.eu/
13 https://protonsinspire.eu/
14 https://www.hitriplus.eu/
15 https://raptor-consortium.com/
16 https://www.prismap.eu/
17 https://www.euramet.org/research-innovation/research-empir/
18 https://www.gsi.de/BARB
19 https://www.estro.org/Science/EPTN
20 https://www.ptcog.ch/

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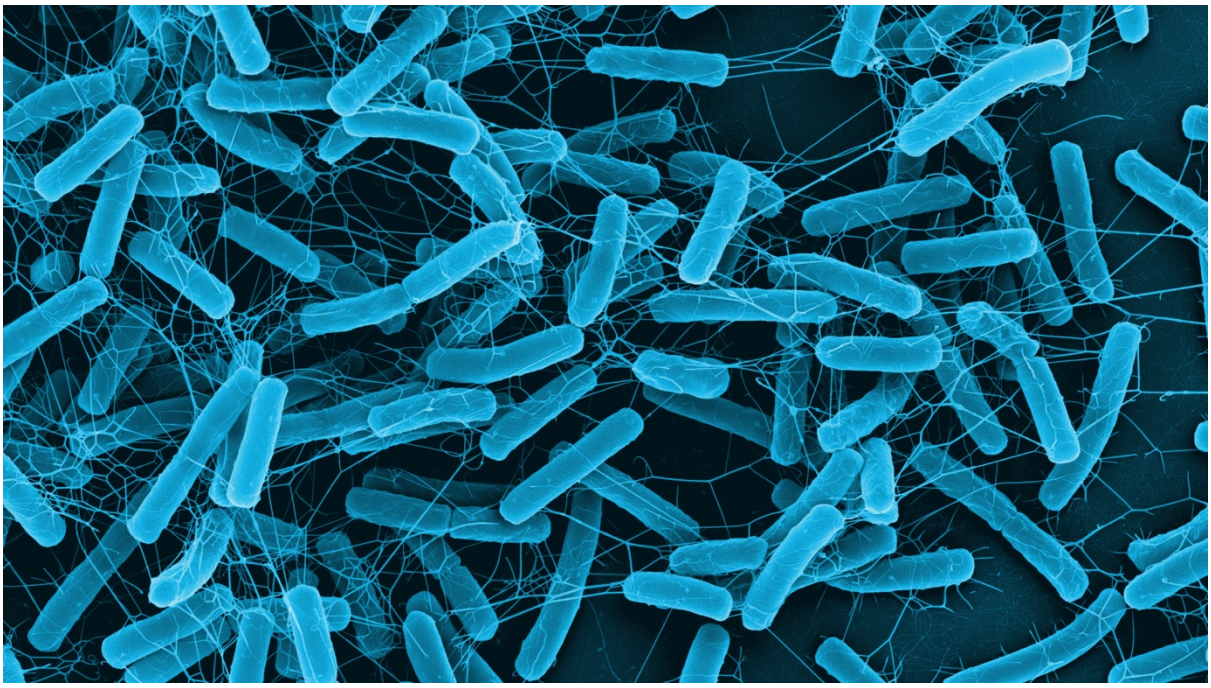
CHALLENGES OF THE COMING 5 – 10 YEARS



2.1 RADIATION PROTECTION

Radiation protection in Helmholtz covers the areas of radioecology, nuclear waste management, nuclear emergency, space radiation protection, and risk of low-dose exposure.

2.1.1 Radioecology

Radionuclides are ubiquitous in the environment. They are of natural or anthropogenic origin. **Natural occurring radionuclides**, e.g., ^{40}K, ^{232}Th, ^{235}U, ^{238}U as well as their decay products are present on the Earth since its beginning. In general, the concentration of naturally occurring radioactive materials (NORM) is low, but local enrichment and human activities such as ore mining and processing, phosphate fertilizer production, fossil fuel extraction and processing, coal combustion, use of geothermal energy etc., lead to accumulations of radionuclides and thus generate higher levels of exposure.

In addition, **artificial or anthropogenic radionuclides** can be found in the environment, originating not only from reactor accidents and nuclear weapons testing, but also from continuous medical, military, and technical use. With regard to the safe dismantling of nuclear power plants, the intermediate storage and disposal of highly active nuclear waste, anthropogenic radionuclides and their potential release into the environment come more into focus. Due to the release of naturally occurring or anthropogenic radionuclides in the environment, they can migrate through groundwater and soil up to the food chain and can be distributed in air, resulting in health hazards for human and wildlife (Figure 2.1). Thus, the prediction of migration and transfer of radionuclides in the environment is of high societal relevance.

The effects of radionuclides on the environment have so far mostly been described using statistical methods and the models currently in use have large uncertainties. Therefore, more in-depth **radioecological research** with a process understanding spanning spatial and time scales is required to describe and model the fate and effects of radionuclides in the environment, including the food chain. In particular, there are still large knowledge gaps associated with the behavior of actinides, and fission products such as plutonium, americium, neptunium, and uranium, in the environment and especially in the biosphere. This can be remedied by an active, long-term and internationally linked top-level research program including an

education and training strategy for students and young scientists in radioecology to ensure the continuity and sustainability of radioecological research. By means of a molecular process understanding, radioecological models can finally be improved and the associated uncertainties in dose and risk assessment be reduced. In addition, such comprehensive knowledge also allows the creation of a catalogue of measures for the safe protection of humans and the environment from the risks of ionizing radiation.

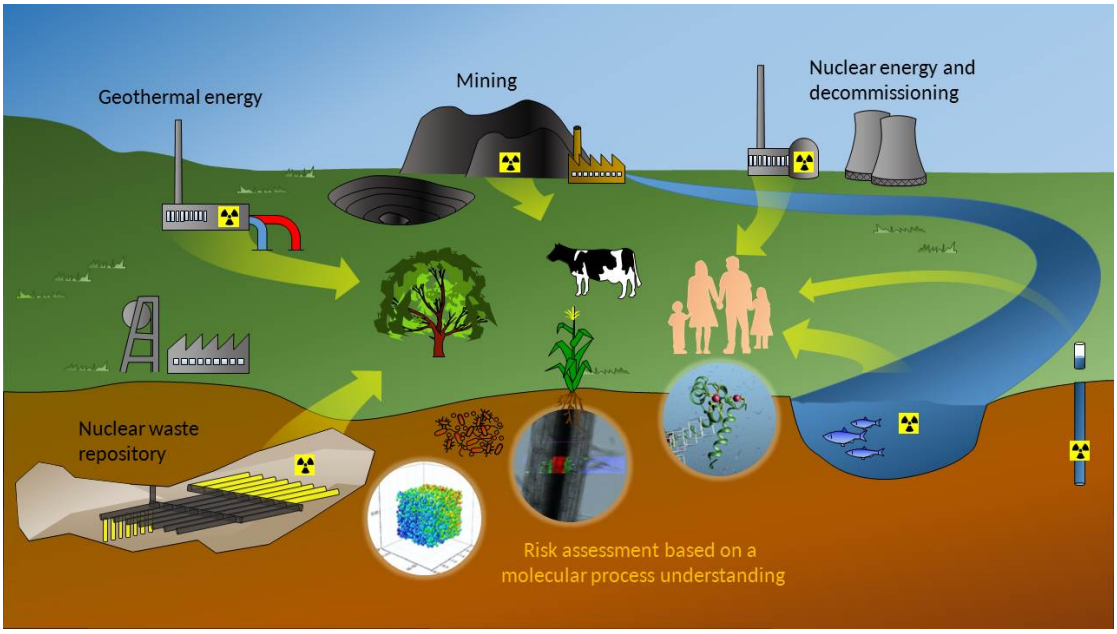


Figure 2.1 Possible pathways of radionuclide release into the environment, its relevance to humans and environment as well as ongoing research activities.

Current activities in the field of radioecology (HZDR, FZJ) focus on the development of biogeochemical research investigating the complex interplay of radionuclides with the geo- and biosphere. In this context, studies on the radionuclide entry into the food chain are currently of highest priority and are performed with soil-inhabiting microorganisms, fungi and plants. The underlying interaction mechanisms are studied from the level of biomolecules to single cells and whole organisms, taking into account geochemical parameters. For this, molecular biological, biophysical, analytical, spectroscopic, and microscopic methods are combined to obtain a detailed **molecular process understanding** that would pave the way to more realistic mechanistic models for radionuclide uptake to and transport within living organisms.

A challenge of radioecology represents the quantification of the hardly measurable effects of **low dose exposure** on living systems, for which, in general, no predictive mechanistic knowledge is available. By combining calorimetric methods with biochemical analyses in a unique research approach, the isotope-based differentiation between **radio- and chemotoxicity** is under investigation.

Molecular structures that serve for the regulation of biological processes by essential metal ions are often target molecules for non-essential potential toxic metals such as radionuclides. Therefore, we are currently investigating the effects of radionuclides on metabolically relevant target molecules, e.g., proteins and DNA, and their function as well as their fate in the cell and in the organism.
Another research approach aims at the evaluation of sites for bioeconomic production. On these contaminated sites, it is to be investigated whether basic materials/raw materials can be produced that can be used in bioeconomic processes.

In addition to the actual research, the HZDR is an active member of the **European Radioecology Alliance (ALLIANCE)**, which coordinates and promotes research in radioecology in Europe (see Section 1.3). Within this membership, contributions to the revision of the Strategic Research Agenda (SRA) for radioecology and the development of a joint roadmap for radiation protection in Europe were made. Moreover, HZDR leads the topical working group on naturally occurring radioactive materials (NORM), which carries out research related to the science-based risk assessment, remediation and regulation of NORM-impacted sites and industries. These activities offer possibilities for multidisciplinary exchange and collaboration in the field of radioecology on the European level.

Future activities in radioecology focus on the implementation of biological processes in existing reactive transport models (Figure 2.2). For that complex metabolic processes of complete biologic communities have to be elucidated, key processes have to be identified and parameterized. The aim is to predict the radionuclide transport in the environment under consideration of biological processes and their effects, e.g., the modification of mineral interfaces and changes in the radionuclide bioavailability.

The determination of radionuclides and their speciation in environmental compartments represents a great challenge due to their partly occurring trace concentrations in complex matrices. Moreover, the description of the central function of interfaces for the exchange and reactivity of radionuclides in biologic systems requires sophisticated methods. Lysimeters are to be used as one of the important infrastructures to conduct field experiments under realistic field conditions. In lysimeters, radioactive test substances can be used in undisturbed ecosystem sections taking into account the natural water and matter balance. In addition, water, soil and gas samples can be taken at high resolution in order to examine them with regard to the different variables. The establishment of intense collaborations in the field of accelerator mass spectrometry (research field matter) and within the Center of Interface Studies (research field energy) will create **synergistic effects** that contribute to the elucidation of the environmentally relevant processes on a molecular and cellular level.

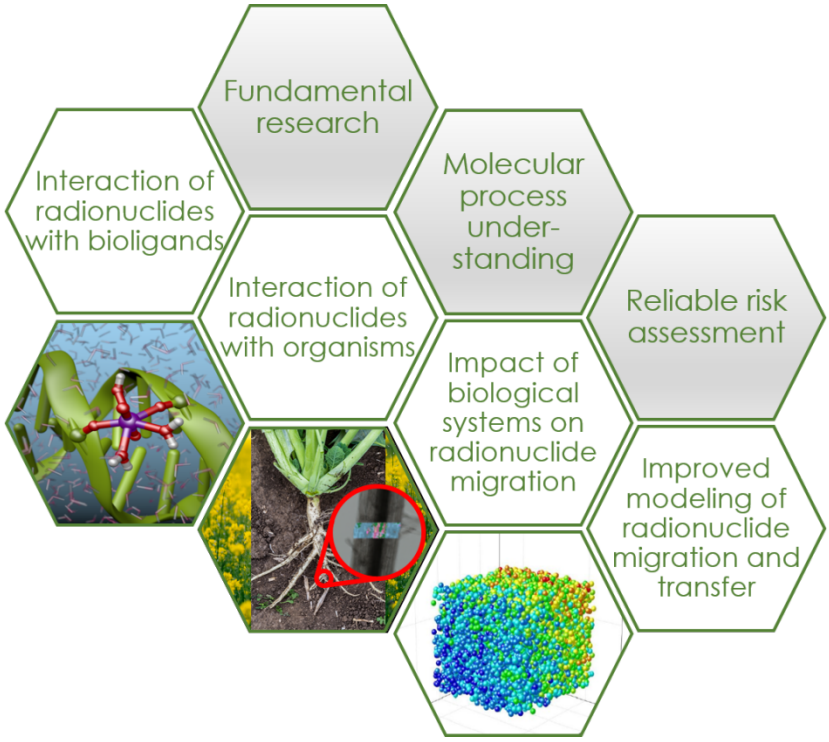


Figure 2.2 Research strategy for an improved risk assessment (middle image created with images from iStock.com/Olga Seifutdinova and iStock.com/leskas)

As an interdisciplinary and complex research field, radioecology requires a corresponding infrastructure. For this reason, the construction of a radiotechnical center as part of the **HOVER research platform** (HZDR, KIT, FZJ) is currently in the development phase. The radiotechnical center will be built at the Dresden-Rossendorf research site beginning in 2022. It will enable the investigation of the cross-scale behavior of radionuclides in environmental compartments. In a next step, the Helmholtz Roadmap for Research Infrastructure 2021 envisages the establishment of a **Center for Radioecology and Radiation Research (ZRS)**, also in Dresden-Rossendorf starting from 2027. On the one hand, this includes, the establishment of a globally unique research platform for the correlative, spatially and temporally resolved detection of interaction processes of complex environmental samples with molecular detail (chemical cryomicroscopy, spectrometry, spectroscopy, electron microscopy) and on the other hand the use of complementary methods for the structural elucidation of radionuclide complexes with low-molecular bioligands and biological macromolecules (protein NMR, cryo-TEM).

The necessity of the continued assessment of the risks based on naturally occurring and anthropogenic radionuclides and the development of concepts for radiation protection requires a high level of scientific competence now and in the future. Interdisciplinary research is needed to obtain, maintain and develop this competence. One prerequisite for this is the **education of young scientists** in the field of radioecology. Taking into account the high degree of interdisciplinarity in this

research area, an intensive scientific exchange between the Helmholtz institutes as well as with other research institutes and universities at national and international level is essential. For this reason, a scientific platform with regular meetings and workshops is required to present and discuss current research work and to develop and implement ideas for joint projects, provided that appropriate funding is available. In addition, an intensive exchange of young scientists between the different research locations by means of short-term stays is aimed at.

2.1.2 Nuclear waste management

Radiation protection research in Helmholtz in the context of nuclear waste management concerns mainly issues of the accurate determination of the exposures in different radiation scenarios and the development of solutions to keep doses as low as reasonably achievable (ALARA principle). Additionally, the development of strategies to **minimize potential risks from decommissioning and disposal of nuclear waste** is essential and also a topic within the HOVER research platform (KIT, HZDR, FZJ). The establishment of respective models and codes to estimate radionuclide inventories introduced by neutron activation is an important step. Within a FORKA[21] initiative, this is already accompanied by respective chemical analytics to validate the prognostic capabilities of such models.

This includes planning and **optimization of radiation protection in handling scenarios for decommissioning and disposal**. Monte-Carlo transport calculations, e.g. with MCNP, allow for the careful analysis and simulation of potential individual radiological exposure scenarios for workers during specific operations for decommissioning and disposal. Comparative simulations of occupational radiation exposure scenarios in various radioactive waste disposal concepts as well as in interim storage facilities enable the ALARA principle.

To complete the simulations with measurements also advanced neutron dosimetry techniques and advanced neutron personal dosimetry are desirable. The integrity of spent nuclear fuel (SNF) rods during **extended interim dry storage** and the long-term behavior of SNF in a **final disposal** is of concern. In particular, for spent MOX fuel and for high burn-up UOx fuel the integrity of the fuels' cladding is continuously impaired due to pellet-cladding-interactions and radiation–induced damages (Figure 2.3). The influence of the radiation field on possible chemical mechanisms of cladding corrosion at the pellet/cladding interface and the associated degradation of cladding mechanical properties need to be investigated. Though, geological or geo-technical barrier system may prevent to some extent groundwater contacting the fuel, intrusion of solutions into disposal rooms has to be taken into account within the long-term safety case of a SNF repository. Groundwater in contact

[21] BMBF Förderkonzept 'Forschung für den Rückbau kerntechnischer Anlagen'

with SNF could radiolytically produce oxidants which oxidize the relatively stable UO_2(s) matrix of SNF into much more soluble U(VI), as long as concentrations of inhibitors such as H_2 are sufficiently low.

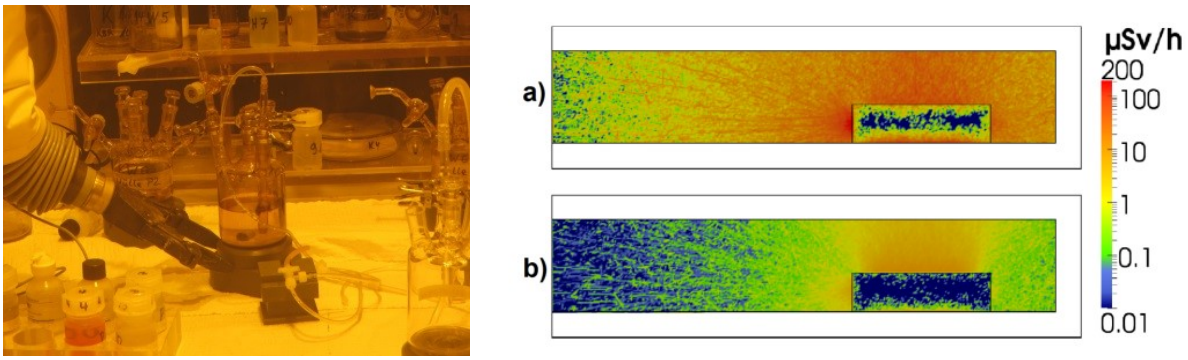


Figure 2.3 Left: Experiments on the corrosion of SNF in the shielded box line of KIT-INE. Right: Numerical simulations of the local dose distribution in a repository around a cask containing SNF a) with backscattering of the surrounding host rock b) free in air. For simulation reasons (surface source), the content of the cask is shown as void.

As a consequence, matrix bound radionuclides are released. In order to assess quantitatively the concentration of radiolytic oxidants an accurate radiation field/dose identification in the close vicinity of the fuel rods is important. Therefore **advanced dosimetry systems** are necessary to evaluate α-β-γ-contributions in the mixed radiation field. Obtaining experimental data on radiation fields near SNF pellets is a great challenge, because this requires measurements in a radiation environment with high doses. Especially, measurements on SNF pellets implies working in hot cells or shielded boxes by means of remote handling, which places special demands on the experiments or detector systems to be carried out. A major issue here is to fulfill this demand in a spatially resolved manner to account for the heterogeneous distribution of the α-, β- and γ-emitters within the nuclear fuel pellet and on its surface.

Another aspect to follow the **ALARA principle** is to reduce the possible amount of doses for workers during decommissioning procedures. Several further projects are financed by the BMBF initiative FORKA. A promising step in this direction is the development of a ‘contamination array’. This array comprises the development of specific robots for automated measurement of contaminated wall surfaces and the detection of impurities including online storage of the data for documentation. With the use of BIM (Building Information Modelling) Systems, the radiation level of surfaces can be digitalized and modelled. In a following step, the automated decontamination of the respective wall surfaces will be carried out.

Embedded into the Nuclear Waste Management research field, several activities are in progress that aim on a more realistic characterization of radionuclide migration patterns through the geo- and ecosphere using a combination of wet chemistry with advanced spectroscopic, microscopic and diffraction methods. This

certainly impacts modelling, namely new approaches for mechanistic distribution coefficients (smart Kd concept) have been established and already coupled to reactive transport codes, including respective thermodynamic databases (RES³T, THEREDA). A transfer of this paradigm to radioecology is the next step envisaged.

Last but not least, **education and training as well as maintenance of competence** is another important and essential aspect for nuclear waste management and radiation protection research in Helmholtz.

2.1.3 Nuclear emergency

Research for nuclear emergency cases is facing many challenges that are present in radiological impact assessments and countermeasure strategies during all phases of radiological and nuclear events. This is done by setting-up a trans-disciplinary and inclusive framework for preparedness for emergency response and recovery. As a consequence of the accident in Chernobyl a decision support system (DSS) was initiated and developed by KIT (previously Research Center Karlsruhe) and its features have been improved over decades in past and current projects, as well as cooperations with regulatory and radiation protection agencies around the world.

So far about 40 countries world-wide have nowadays JRodos (Java based Real-time On-line DecisiOn Support) installations among them many European Member States. It is actively used in developing countermeasure strategies for the emergency and countermeasure phases of potential future accidents. It supports training and exercising to provide decision makers with relevant information to minimise the consequences of the emergency.

Starting with source terms for radionuclide releases into the environment, key simulation models of JRodos simulate transport and dispersion in the atmosphere water and food chain, followed by simulation of countermeasures. The information JRodos provides include predicted radionuclide activities in environmental media, such as air, soil (Figure 2.4), water and agricultural products. The corresponding doses to populations and recommendation regarding the arrival of contamination plumes in certain areas (Figure 2.5) as well as deterministic and probabilistic countermeasure areas (Figure 2.6) are also part of the model results. Urban and agricultural countermeasures to reduce these doses are then calculated in additional modules.

To improve the JRodos software and meet the challenges in radiological impact assessment during all phases of nuclear and radiological events, the atmospheric transport and dispersion modelling, dose modelling, terrestrial and hydrological modelling will be further developed over the next years.

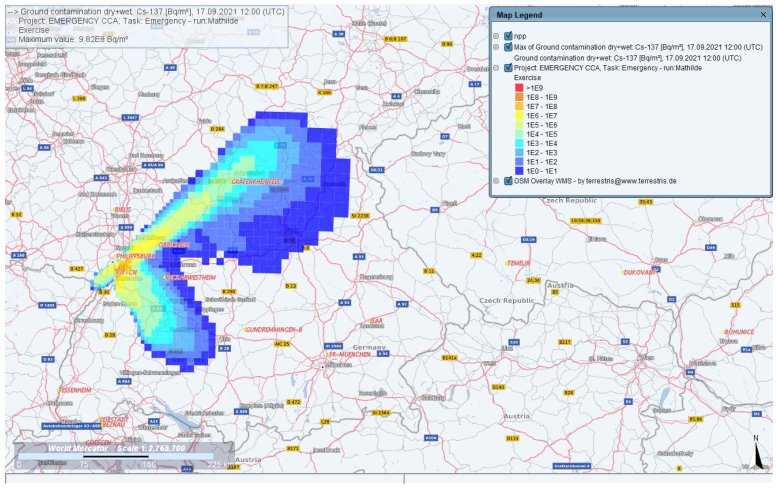


Figure 2.4 Ground contamination with Cs-137 by dry and wet deposition after a hypothetical nuclear power plant accident with a release of radionuclides into the atmosphere

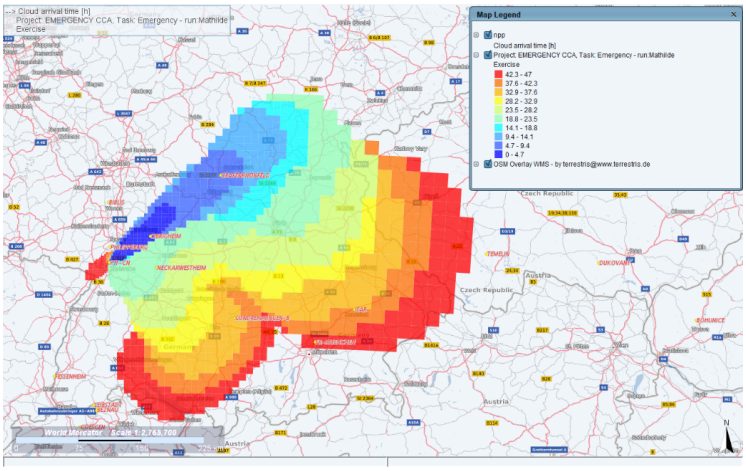


Figure 2.5 Cloud arrival time after a hypothetical nuclear power plant accident with a release of radionuclides into the atmosphere

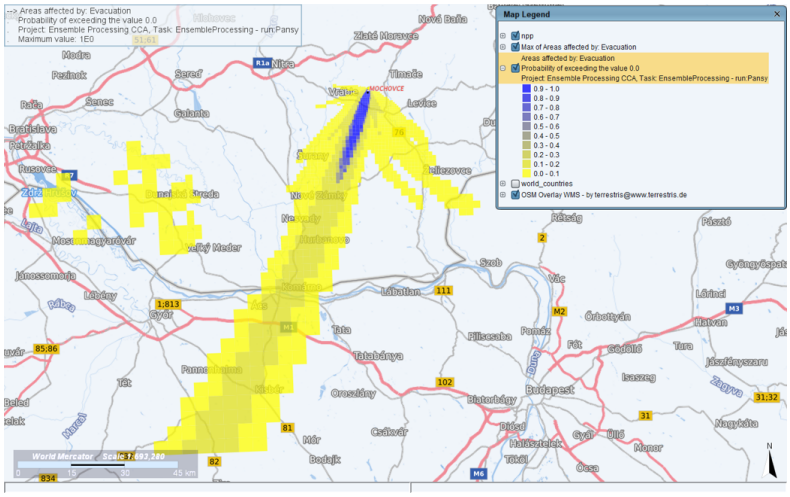


Figure 2.6 JRodos ENSEMBLE generator and processing tool, showing probabilities for the need of evacuation in certain areas after an hypothetical nuclear power plant accident with a release of radionuclides into the atmosphere.

The atmospheric dispersion model FLEXPART (Figure 2.7) is currently incorporated into JRodos to improve the far range dispersion modelling and add functionalities such as backward calculations for the identification of radionuclide release locations. To improve the data assimilation, current developments in the data sciences including big data, data fusion and artificial intelligence will be used to improve source term estimation and impact assessment. This approach is currently used in improving a source term reconstruction module in JRodos.

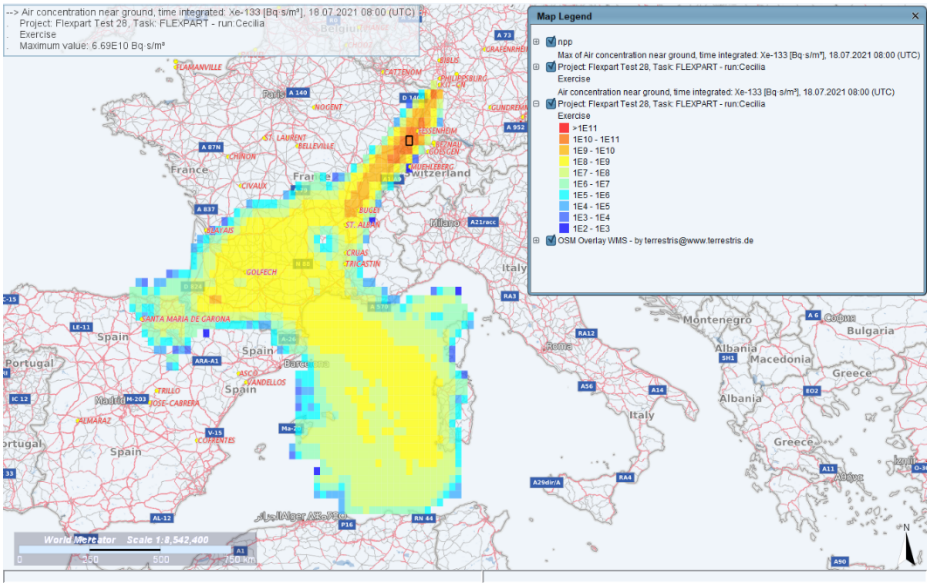


Figure 2.7 FLEXPART calculated time integrated air contamination with Xe-133 after a hypothetical nuclear power plant accident with a release of radionuclides into the atmosphere.

Future activities are planned as part of the Strategic Research Agenda of the European platform NERIS as well as in cooperation with the BfS and several international partners. These further developments build on the results of the European research projects PREPARE and OPERA and the recently completed CONFIDENCE activities that were part of the European project CONCERT (see Section 1.3).

2.1.4 Space radiation protection

In the coming years, continued presence of humans in low Earth orbit (LEO), the return to the Moon and the increase in space tourism will require innovative approaches for space radiation protection. Human spaceflight involves chronic low-dose whole-body exposure of astronauts to **galactic cosmic rays** (GCR) as the high-energy particles cannot be effectively shielded. Without the protection of the Earth's atmosphere and the Earth's electromagnetic shield, the exposure to GCR in deep space can be, dependent on shielding, up 770 times higher than on ground, and is

250 times higher on the International Space Station (ISS) compared to terrestrial levels. Beyond LEO, radiation exposure and risk may be prohibitive for deep space flight missions without effective countermeasures or new capabilities (Figure 2.8).

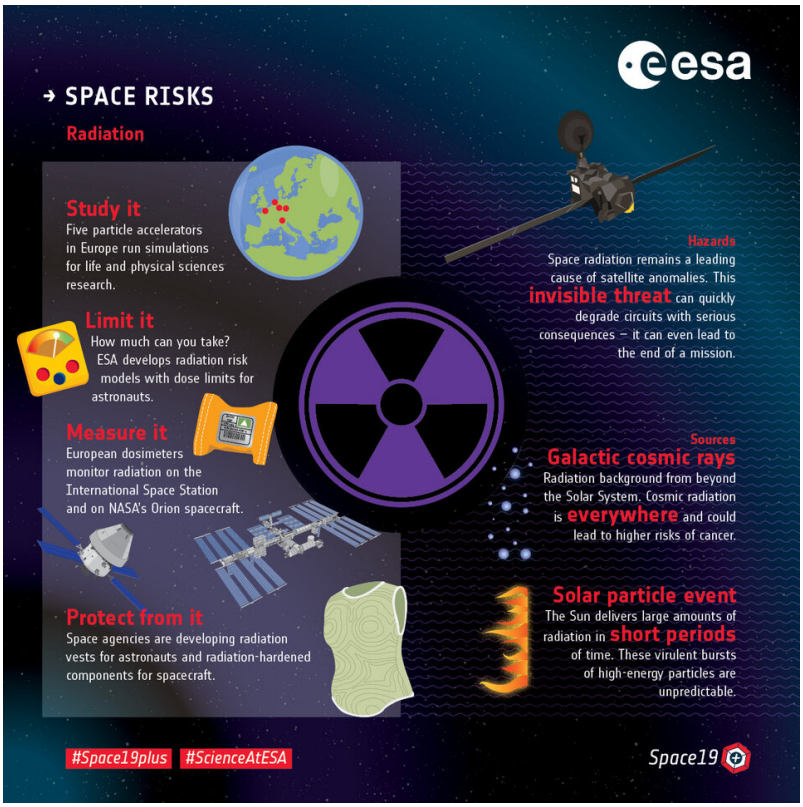


Figure 2.8 A graphical representation produced by ESA of the risks and mitigation strategies for exposure to cosmic radiation.

Currently, space radiation protection for astronauts on the ISS encompasses amongst others personal and area dose monitoring, information about risks and risk mitigation strategies, efforts to improve shielding and space weather warnings e.g. for scheduling extravehicular activities.

Beyond LEO, protection by the Earth's magnetosphere ceases. During deep space missions, solar particle events (SPE) bear the risk of exposure to protons at higher dose rates which can accumulate to health- and even life-threatening doses in case of insufficient shielding. Therefore, warning systems for SPE and shelters are crucial.

Missions to the Moon open opportunities to understand the dose distribution in the human body and the effect of personal shielding equipment such as a vest – this will be tested in the MATROSHKA AstroRad Radiation Experiment (**MARE**) developed by the DLR[22] on NASA's Artemis-1 mission around the Moon. Active dosimeters

22 https://www.dlr.de/me/en/desktopdefault.aspx/tabid-14114/

capable of detecting most of the complex radiation field in space and providing relevant dose quantities will have to be improved and miniaturized for astronautic and robotic exploration missions.

Radiation resistance mechanisms are of great interest in radiation biology. Some extremophile organisms show extraordinary radiation resistance such as *Ignicoccus hospitalis*, an anaerobic hyperthermophilic chemolithoautotrophic Sulphur-reducing Archaeon from deep-sea hydrothermal vents. DLR currently investigates the resistance mechanisms of *I. hospitalis* in cooperation with the Helmholz-Zentrum Potsdam (Deutsches GeoForschungsZentrum GFZ).

Efforts to protect astronauts from the harmful GCR require a much better understanding of the effects of GCR on humans. Although heavy ions make up only ~ 1 % of GCR, they contribute strongly to their biological effects as they induce complex, difficult to repair DNA damage. This damage can lead to a strong sustained DNA damage response, sustained gene expression changes and chromosomal aberrations, resulting in detrimental outcomes such as cell death, premature ageing and disturbed function. Because the quality of radiation is different in space and on Earth, risk estimates are affected by large uncertainties (Figure 2.9) that, in the absence of large epidemiological data, can only be reduced with research studies. The ideal platform for this activity are **high-energy particle accelerators**. Already at the beginning of this century, NASA has funded the construction of a dedicated beamline (NSRL)[23] at the Brookhaven National Laboratory (Upton, NY) for ground-based studies of heavy ion radiobiology. In Europe, the only accelerator able to simulate the high energy and charge of the cosmic rays on Earth is the GSI synchrotron SIS18, and indeed ESA has launched since 2008 a European ground-based space radiation protection called IBER (Investigations of Biological Effects of Radiation)[24]. Within that program, in the course of the past years over 30 experiments received beamtime at GSI to study radiobiology and countermeasures for space radiation exposure, including a few DLR experiments.

Within the framework contract GSI-ESA, several other activities have been funded, including a comprehensive measurements campaign to select novel materials for shielding in space (ROSSINI; Figure 2.10), testing of microelectronics to be used in satellite and spacecraft (also within the EU Infrastructure project RADNEXT[25]), and a Summer School[26] for graduate students on space radiation protection held in Darmstadt at ESOC and GSI. The ongoing construction of the FAIR facility in Darmstadt (see Section 3.2) opens excellent opportunity for space radiation protection in Helmholtz. The new SIS100 synchrotron will accelerate heavy ions up to 10 GeV/n, making FAIR the best ground-based simulator of GCR worldwide. A GCR-simulator,

23 https://www.bnl.gov/nsrl/
24 https://www.gsi.de/IBER
25 https://radnext.web.cern.ch/
26 https://www.gsi.de/esa-fair-summer-school.htm

able to simulate the full spectrum, is currently under construction at GSI (funded by ESA) and will be the first installation at FAIR.

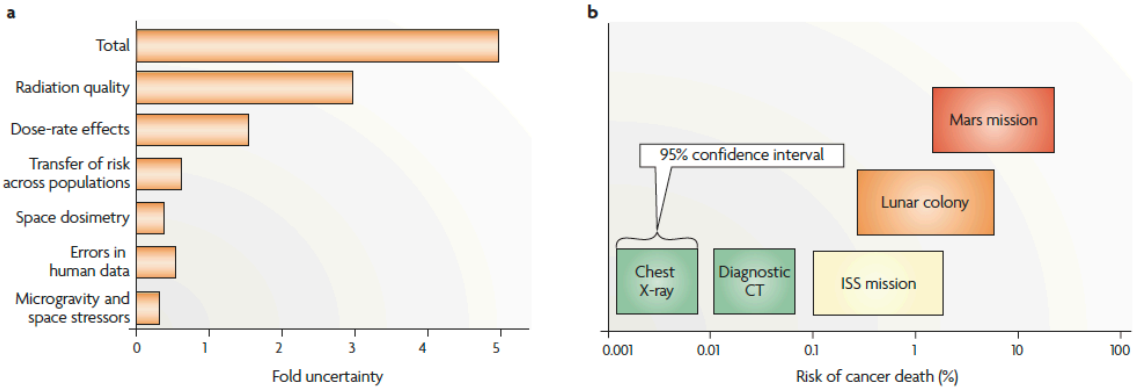


Figure 2.9 Panel **a** presents estimates of uncertainties in projecting cancer risks for space and terrestrial exposures. Several factors such as radiation quality effects, space physics, and microgravity do not contribute on Earth and lead to large increases in risk projections. Predicting risks to individuals is difficult as there are very few quantitative measures of individual sensitivity. The extrapolation from experimental models to humans is perhaps the greatest challenge to cancer risk assessments. The uncertainties are larger for astronauts in space compared to typical exposures on Earth as illustrated in Panel **b**, which shows the current estimates of cancer risks and 95% confidence bands for adults of age 40-yr, the typical age of astronauts on space missions for several terrestrial exposures and missions on the International Space Station, a lunar colony, and the projections for a Mars mission. Image reproduced from Durante and Cucinotta, *Nat. Rev. Cancer* (2008).

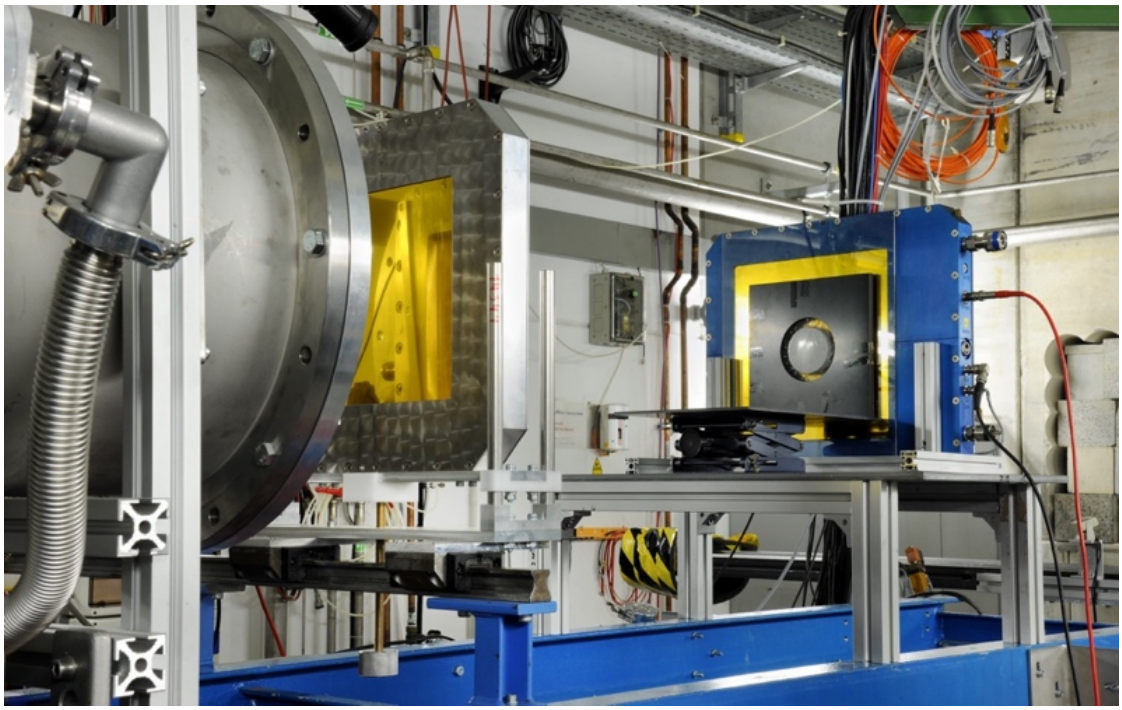


Figure 2.10 Setup in the GSI Cave A for the irradiation of LiH pellets with high-energy ^{56}Fe-ions. Lithium is a very promising light materials for shielding against cosmic rays, and relativistic iron ions are used as a proxy of GCR. The experiment was performed within the ROSSINI project funded by ESA. Image from GSI.

2.1.5 Risk of low-dose exposure

Exposure to ionizing radiation is unavoidable it is known to damage health at certain exposure levels. At very high doses radiation exposure can be lethal, while tissue damage can occur following more localized high dose exposures. Whole body exposures at these levels are very rare, but for localized exposures, severe tissue damage can be observed in some patients following radiotherapy for cancer.

Evidence accumulated over many decades demonstrates that radiation can cause **cancer** in humans following acute exposure in the dose range of a few Gy down to 100 mGy or less, with children often showing higher sensitivity. There are indications that these more moderate exposures may also be associated with other conditions such as circulatory diseases, cataracts, cognitive impairment, immunological effects (**non-cancer diseases**) and possibly effects on future generations (**hereditary or transgenerational effects**).

The risks to humans in terms of cancer are established down to around 100 mGy in adults, for circulatory diseases and lens opacities down to about 500 mGy and about 200 mGy for defects on brain development and cognition after prenatal exposure during neurogenesis. The risks to human health below these levels, especially following protracted or other non-homogenous exposures are less certain. Currently, the system of radiation protection aims to avoid tissue injury and minimize the risk of cancer and the possibility of hereditary disease. For radiation protection purposes, risks of cancer and possible hereditary effects below 100 mGy are regulated on the basis of an assumed LNT relationship between dose and incidence. However, there remains uncertainty about the exact dose-response relationship for such low-dose exposures, and the impact of protracting exposures over long periods such as during a working lifetime.

The main uncertainties in radiation health risk evaluation are in the magnitude of cancer risk at low and protracted doses below 100 mGy (see Figure 2.9b), the magnitude of non-cancer effects below 500 mGy, the variation in individual risk within the population, and the variation in risk with dose distribution in space and time. These are therefore the key areas requiring further exploration to provide better and more reliable evidence for appropriate decision making in all areas of radiation protection. Accurate and reliable low dose human health risk estimation is an essential foundation for a robust and acceptable system of radiation protection.

EU Member States involved in the EURATOM Programme set up in 2008 a ‘High Level and Expert Group on European Low Dose Risk Research’ (HLEG) aimed at identifying research needs and proposing a better integration of European efforts in

the field. The key policy issues defined by HLEG (Figure 2.11) that represent the main research topics suggested by the MELODI initiative are:

- The shape of the dose-response for cancer (Figure 1.1);
- Tissue sensitivities for cancer induction;
- Individual variability in cancer risk;
- The effects of radiation quality (type);
- Risks from internal radiation exposure;
- Risks of, and dose response relationships for, non-cancer diseases and hereditary effects.

Discussion of each key question is sub-divided below into two categories:

• Research to improve understanding of the mechanisms contributing to radiogenic diseases following low dose and dose-rate exposures.
• Epidemiological research that integrates, where possible and informative, biological approaches to improve health risk evaluation.

In the recent 2021 strategic research agenda, the MELODI group made an attempt to identify urgent priorities for the 2021-2025 funding period.
The following points provide more specific priorities within this overarching aim in light of recent developments:

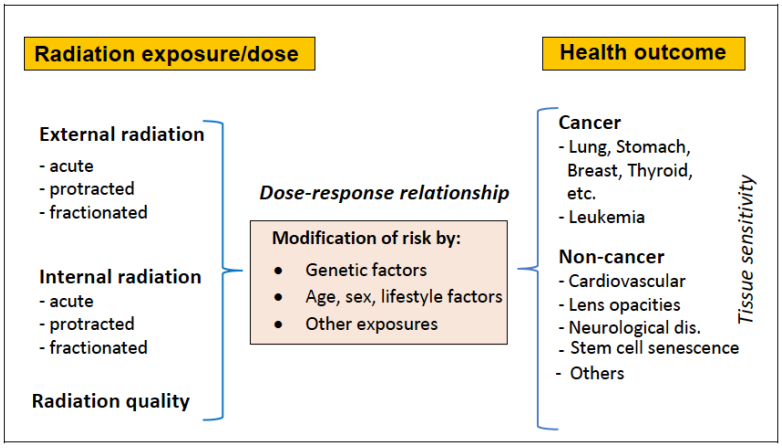


Figure 2.11 Key policy issues for low-dose European radiation research as defined by HLEG and recommended by MELODI.

• To understand the health effects of inhomogeneous exposures, various types of radiation including internal emitters and differences between risks from acute and chronic exposures through the integration of experimental and epidemiological data applying biologically-based risk models. To improve the understanding of the effects of intra-organ dose distribution through observations in patients exposed to inhomogeneous fields and experiments with organotypic tissue models.

• To evaluate the risks of, and dose-response/dose-rate response relationships for, non-cancer diseases at low and intermediate dose levels (100 - 500 mGy and below): in particular cardiovascular, cognitive, neurological and immunological effects.
• To define the processes contributing to cancer development in relevant target stem/progenitor cell populations after low-dose/low-dose-rate exposures; including for example the role of microenvironment, cell-to-cell interaction (as mentioned in ICRP 131), the role of epigenetics, metabolic status, ageing, and immuno-senescence amongst others, in single and multiple stressor exposure situations.
• To identify, develop, validate and implement the use of biomarkers of exposure, and for early and late effects for cancer or/and non-cancer diseases and variation in susceptibility. The relationship between these radiation biomarkers and those emerging biomarkers of various pathophysiological processes and health outcomes needs to be considered and explored.
• To continue to refine risk estimates for cancers after low-dose and low-dose-rate exposures in occupational, medical and other cohorts. Such quantitative risk estimations are required to inform judgements on risks from acute, chronic and inhomogeneous exposures, and will provide important input to the development of quantitative mechanistic risk models and adverse outcome pathways (AOPs), see below.
• To identify, explore and define AOPs for radiation-induced health effects, and determine if those operating at low doses and dose rates are the same as those at higher levels of exposure, and when the triggering of an AOP is sufficient to disrupt normal homeostasis and lead to pathologies.

2.2 RADIATION MEDICINE

Members of the HGF are world leaders in the advancement of radiotherapy technology and techniques as well as of radiopharmaceutical developments and applications. These include image-guided high-precision delivery modes using photons or charged particles and the development of highly innovative new radiation beams and their delivery methods. Moreover, the strengths of the centres is that the mainly physics aspects developed are interwoven with clinical partners, i.e. beyond state-of-the-art university hospitals and radiobiological research groups unravelling the effects of the changing imaging and radiation delivery techniques. Thus, when joining forces, Radiation Research at Helmholtz will significantly contribute to the early detection of cancer, its personalised treatment and ultimately to improved clinical outcome both in terms of local tumour control and low levels of normal tissue side-effects.

2.2.1 Imaging

Current status / Why is there need for new imaging techniques

Research performed on this topic provides important impact for cancer research on multiple levels. Through the National Cancer Prevention Center new imaging methods for early detection of cancer will be developed and transferred, which may increase the proportion of disease that can be cured with today's treatments. New imaging biomarkers will help to characterize more advanced cancers for selection of personalized treatment approaches and to monitor therapy response. Integration of imaging data with molecular markers and clinical information will further increase the power of these approaches. Novel image-guided high-precision radiotherapy or surgery techniques as well as new theranostic radiotracers promise improved disease detection, higher cure rates through effective treatment, and better sparing of healthy tissues. These approaches will be translated into clinical applications via NCT, DKTK and the national and international networks established with university medical centres and other hospital physicians.

The aims of Imaging in Radiation Research can be summarized as:

- *Develop and clinically validate new imaging methodologies for personalized early cancer detection*

Detection of tumours at an early stage is of central importance for **further increasing cure rates of cancer**. Medical imaging research is indispensable for establishing the new National Cancer Prevention Center at DKFZ. Here, novel personalized early detection strategies will be developed and validated. The strategies focus on new magnetic resonance (MR)-based technologies, preferentially without contrast agents, and ultrasound to reduce radiation exposure, which is currently often limiting structured early detection programs based on imaging in Germany and other countries. **Genomic and liquid biopsy studies** will be performed alongside to discover and validate biomarkers indicating the presence of cancer and potentially even provide hints on the affected organ. Corresponding to the research strengths of Helmholtz centres, the comprehensive and integrated early detection imaging programs will cover the major malignant diseases, such as breast, lung and prostate cancer. All developments will be validated in large prospective multicentre trials that will be performed using our existing network of hospital- and office-based diagnostic radiologists as well as the **National Center for Tumor Diseases (NCT)** and the **German Cancer Consortium (DKTK)**.

- *Precise characterization of the tumour and of its surrounding normal tissues and their response to treatment*

Among the Helmholtz Centres involved in Health, most centres hold an ion beam facility enabling the treatment of cancer patients in the context of clinical studies. In

those, the primary tumour control, but even more importantly, the toxicity encountered in normal tissues surrounding the tumour is part of the study endpoints on particle therapies. These possible toxicities can be scored clinically after an interval of months or years or by patient reported outcome measures. These parameters are somewhat subjective, and therefore more objective parameters, such as imaging biomarkers are strived for.

In 2016, the HZDR has started a prospective imaging study including **multiparametric magnetic resonance imaging** (MRI) in patients with primary tumours of the brain (gliomas, glioblastomas) undergoing photon or proton beam radiotherapy at the University Hospital Carl Gustav Carus Dresden. These patients underwent an MRI scan for radiation treatment planning and following radio(chemo)therapy in three-monthly intervals. Based on these studies, numerous possible imaging-biomarkers have been unravelled: volumetric changes of the cerebrum and cerebellum, changes in diffusion-weighted imaging, in diffusion-tensor imaging. The clinical relevance of these alterations of normal-appearing brain needs to be unravelled by **correlating the findings with functional parameters of patient tests**, such as neurocognitive function tests. Objective outcome measures are strived for in ever increasing numbers of patients treated with protons or heavy ions and will thus be studied in collaboration with clinical partners of national, i.e. NCT, and international networks (European Particle Therapy Network).
Moreover, scientists at DKFZ and HZDR have embarked on identifying the incidence and occurrence of **MR image changes** in (low-grade) glioma patients having undergone proton beam therapy (in combination with temozolomide chemotherapy). They have described the lesions to predominantly occur in the periventricular zone and to putatively be associated with a **variable relative biological effectiveness (RBE)**.

With the support of DESY, a group of the institute of experimental physics at the University of Hamburg (UHH) has advanced the so-called X-ray Fluorescence Imaging (XFI) method. XFI allows detecting and tracking of medical agents such as drug compounds, nanoparticles for drug delivery, immune cells, and antibodies, if those entities are labelled with XFI-markers which emit X-ray fluorescence photons when excited by a scanning X-ray pencil beam, e.g. from the DESY PETRA-synchrotron. The UHH-team achieved the first-ever tracking of labelled macrophages in a living mouse - a major milestone on which the future research on XFI can build on. XFI shows a substantially higher detection sensitivity than X-ray absorption imaging, with a spatial resolution of sub-millimeter, it can be applied over arbitrarily long-time windows (in contrast to PET/SPECT) and it offers multi-tracking, i.e. the simultaneous imaging of different agents, e.g. different types of immune cells. This will also contribute to personalized medicine, for instance, in cell therapy. Up to now the tumor tissue is marked by nanoparticles and the XFI signal is generated by synchrotron radiation. In the coming years it is planned that the XFI imaging technique

is extended for the case that the required fluorescence excitation is provided by a low intensity electron beam hitting the tumor area. This concept is developed by Prof. Grüner, Hamburg University, and will allow an online localization of the tumor and immediate treatment of the tumor tissue with a high intensity electron beam.

With increasing particle facilities offering treatment to patients with solid tumours and with ever changing medical indications, the necessity of Helmholtz Centers collaborating with medical centres in order to prospectively collect clinical parameters and imaging data in an attempt to identify treatment toxicity early on and thereafter prevent its occurrence is of utmost importance.

- *Accurate prediction of treatment outcome using advanced software tools unravelling imaging biomarkers - Radiomics*

The analysis of medical imaging in an automated, high-throughput manner is termed radiomics. During this analysis, machine-learning algorithms create an artificial intelligence (AI) model to associate imaging characteristics with the endpoint of interest, such as tumour recurrence after radiotherapy. Since the first milestone publication on radiomics analysis of lung cancer in 2014, a plethora of research has demonstrated the proof-of-concept of using **AI-based image analysis for the pathological or molecular characterization of tissues** (e.g. cancer), detection of disease, prediction of patient outcomes and therapy response, or automatic segmentation of defined regions of interest (e.g. organs or tumours). Besides classical feature-based machine learning predictions (radiomics), **deep learning techniques** are increasingly applied on a brought scale in applied research studies in medical imaging (Figure 2.9).

Many studies that employ radiomics do so using retrospectively obtained data. Some striking results have been produced, such as the use of radiomics to identify patients for immunotherapy. However, the move to prospective studies is hampered by the lack of reproducibility of retrospective studies. There are several aspects that play a role: the inherent variability induced by analysing imaging acquired in different centres; differences in the software used to perform the high-throughput analysis; and incomplete reporting.

Consequently, scientists at HZDR have founded the Image Biomarker Standardisation Initiative (IBSI) to improve the last two issues. This effort significantly reduced differences between software packages by offering a reference standard for software verification. The IBSI also produced reporting guidelines for radiomics studies, which is now being used in peer-review. Radiomics studies focus on prognosticating treatment success after radio(chemo)therapy, as well as radiation-induced toxicity, in patients with locally advanced head-and-neck squamous cell carcinoma, glioblastoma or colorectal carcinoma. The central aim is to identify those

patients that may benefit from treatment alterations to improve local tumour control or reduce the risk of side-effects. Many of these studies were conducted within the DKTK – Radiation Oncology Group (DKTK-ROG) with the aim to prospectively validate the obtained results and if successful apply them in randomized clinical trials.

We expect that digitisation will propel the field forward in the coming years. Digitisation will help achieve acquisition, analysis, and exchange of increasingly large datasets; integrated analysis of medical imaging with environmental, genomic and other data; and accelerated validation of imaging-based AI models in external and prospective settings. However, with larger and more diverse datasets, the analysis, including machine learning processes, become a bottleneck. We are developing a key tool to automate this analysis. It carries out end-to-end machine learning, which greatly reduces the amount of user input and handling required, automatically evaluates the models and provides explanations for them. We are currently preparing this tool for public release.

However, only a few AI solutions have made it into medical products approved for daily clinical practice. In the next decade, the following seven scientific challenges need to be addressed to increase the yield of AI-based solutions in daily clinical management.

1) **Development of the best possible prediction models for specific unmet clinical needs.** AI prediction models need to outperform existent clinical, pathological, or molecular-biological predictors. Research results have shown that the samples size used for the training of AI systems constitutes a major limiting factor for the effectiveness of prediction models. Hence, to achieve the best possible AI models large patient numbers need to be combined into training cohorts by extending multi-centre collaboration between medical centres in Germany and internationally, e.g. within the NCT and DKTK networks. At the same time, transfer learning or data augmentation need to be combined with novel modelling techniques to develop the best possible models despite limited medical datasets.

2) **Improve reproducibility and robustness of AI models.** Before the broad application of AI-based image analysis, it needs to be assured that AI models are robust against technical and differences between medical centres. Novel methods will need to be developed to 1) develop robust prediction models against such technical variations, and 2) allow calibration of developed models to specific local environments using novel AI techniques.

3) **Extracting complementary information by longitudinal image analysis.** Most existing evidence on AI-based prediction models is based on single time point imaging data. However, longitudinal changes seen on medical imaging over the course of treatment may harbour valuable information that could be used for therapy

individualization. Future studies should evaluate potential use cases and develop effective modelling techniques such as “Delta-Radiomics” or specialized deep learning networks to leverage this information.

4) **Integration of radiation dose distribution (“Dosiomics”) and medical imaging for outcome prediction in radiation oncology.** On top of current radiomic and deep learning models mainly exploiting imaging data, the radiotherapy dose distribution, needs to be integrated as “dosiomics” in order to improve predictions of therapy response or radiation-dependent side effects.

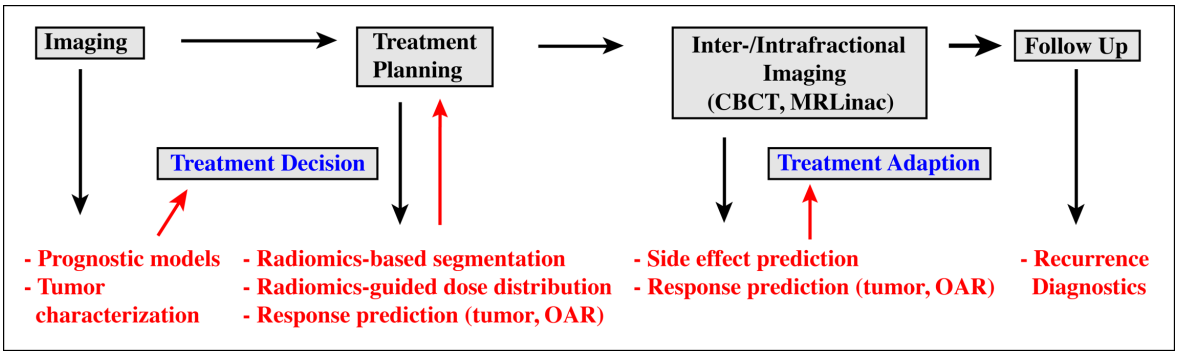


Figure 2.12 Potential applications (in red) of AI techniques (“radiomics” or deep learning) within the radiation oncology workflow. Blue: Potential consequences. Image from Peeken *et al., Strahlenther. Onkol.* (2017).

5) **Identification of spatial risk volumes for individualized treatment planning.** Recent developments in radiomic feature visualization, capable of displaying spatially resolved radiomic feature maps, as well as class activation maps (Figure 2.12) of deep learning models need to be applied to identify high-risk regions inside of tumour volumes. Such information may then be used for individual radiation therapy dose prescriptions (dose painting) in the future.

6) **Prospective validation of AI models.** In particular in use cases, in which treatment decisions are based on AI-based image analysis, prospective validation is warranted to demonstrate superiority above the current standard procedure and to provide the maximal possible level of validation. Prospective trials will need to be carried out by the clinical collaboration partners of Helmholtz, i.e. within the NCT and DKTK partner sites.

7) To achieve approval by international regulatory institutions (e.g. FDA or EMA) and to be able to provide technical support and maintenance, **commercialization** will need to be performed through the funding of spin-off companies or collaborations with industrial partners.

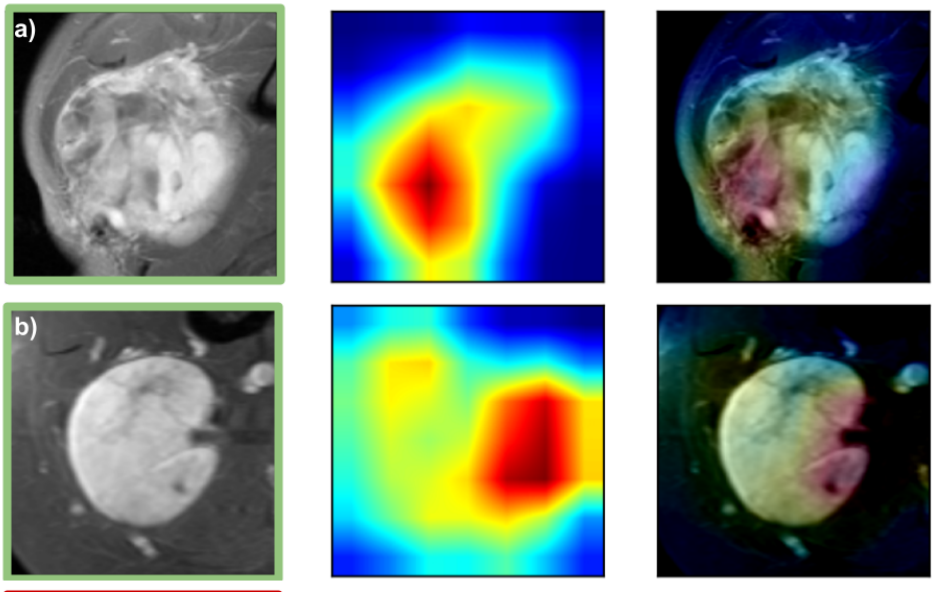


Figure 2.13 Exemplary class activation maps for deep learning based tumor grading prediction based on magnetic resonance imaging scans in patients with soft-tissue sarcomas using a DenseNet 161convolutional network architecture. Image from Navarro *et al., Cancers* (2021).

- *Develop radiological imaging strategies for immunotherapy*

Immunotherapy has recently evolved as an important treatment option in a broad range of cancers. However, despite its enormous potency, only a fraction of cancer patients shows durable responses and several cancer types do so far not benefit at all. The mechanisms underlying resistance against checkpoint inhibition or other immunotherapeutic approaches are not well understood and the study of predictive biomarkers is still in its infancy. The development of novel imaging methodologies, which can be used repeatedly before and during treatment, bears considerable promise to gain **new insights on cancer-specific adaptive immune responses** and their interaction with the tumour microenvironment. For this, MR-based imaging techniques in appropriate preclinical models will be designed and translate these into clinical studies. Multiparametric imaging will be performed to unravel further associations, for example microenvironmental factors such as perfusion, hypoxia and lactate gradients, which have been suggested to importantly modulate immune responses. All studies will be accompanied by **blood-based immune-monitoring** and, if possible, biopsy based assays to obtain a comprehensive understanding of the mechanisms governing anti-tumour immune responses in individual patients over time.

2.2.2 Image-guided adaptive radiotherapy

Adaptive radiotherapy (ART) has the potential to increase the clinical benefit of fractionated radiotherapy, as the therapy is not relying anymore on the assumption of a non-changing anatomy between pre-treatment imaging and the treatment course

and therefore allows for better target conformity and sparing of normal tissue. Anatomical changes can be sub-divided into inter-fractional changes, such as tumor shrinkage (systematic) or rectum filling (random) and intra-fractional changes like respiration-induced motion (mostly regular) or gut motility (irregular). Hence, different speed of adaption is needed to react to either inter- or intra-fractional changes. Whereas for inter-fractional changes an adaption before each treatment fraction (e.g., within a few minutes) is sufficient, so-called daily adaptation, for intra-fractional changes adaptations even within a single fraction are desirable.

With the availability of 3D imaging at the treatment units (mostly cone-beam CT), the speed up of dose calculation and the increasing capability of AI driven automatic contouring, **ART is coming into broad use for routine clinical application** (Figure 2.14). Nevertheless, **inefficient workflows** and the need for patient-specific quality assurance (QA) currently **limit the adaptation speed** in most cases to several days between recognizing the need for an adaptation until it is actually applied.

While in photon therapy with integrated MR-LINAC machines daily or even during-treatment adaptations are becoming feasible now or in the near future, **particle therapy (PT) is lagging far behind**. Many different entities are currently not treated with PT due to high likelihood of anatomical variations or motion (e.g., lung tumours with large motion amplitude). If they are treated, then with relatively large safety margins (oesophagus, liver). Hence, part of the benefit of PT due to the superior dose deposition is currently hampered by the inability of fast adaptations and the resulting increased safety margins.

Independent of the treatment modality, the following components are needed for a near-real-time adaptive radiotherapy in general: (1) 3D imaging in treatment position allowing sufficient accurate dose calculations; (2) fast decision support systems identifying the need of adaption; (3) fast and automated plan adaption including contouring; (4) quality assurance of the adapted plan without performing additional QA measurements with phantoms; (5) direct treatment verification or online imaging during delivery; (6) a closed feedback loop between the elements (1-5).

Radiation research within Helmholtz is active in the translation of fast, near-real-time adaptations into clinical application in both photon and proton therapy. While in photon therapy the focus is on workflow developments and improvements for the already existing state-of-the-art MR-LINAC hardware, in particle therapy the research includes hardware development as well as software/workflow development.

Towards near-real-time adaptive photon therapy

Two different MR-LINAC realizations are currently available as medical product, both combining a compact linear accelerator for photon therapy with an MR tomographic imaging unit allowing MR imaging in treatment position, before and during treatment. Both systems, ViewRay's MRIdian and ELEKTA's Unity, are available at the clinics in Heidelberg (since 2018) and Dresden (in 2022), respectively.

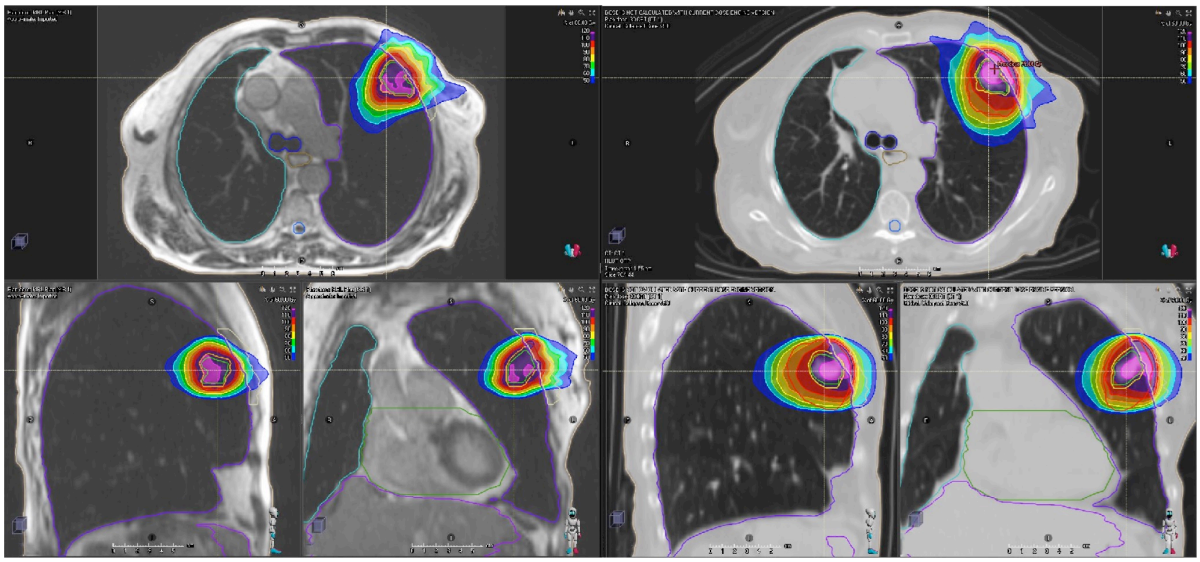


Figure 2.14 Benefit of MR-LINAC controlled treatment in breath hold (left) compared to a standard treatment (right) for a patient with a lung metastasis. With the gated treatment a smaller target volume and hence a more conformal treatment is possible, relevantly sparing healthy lung tissue from high dose deposition. Image from: Spindeldreier *et al., Der Radiologe* (2021).

The research carried out within Helmholtz, always in close collaboration with the clinical partners, e.g. under the umbrella of the NCT, covers the following aspects:

- Development of image processing tools: fast and reliable **non-rigid image registration**, **automated segmentation** based on state-of-the-art data science methods;
- **Pseudo-CT generation** for treatment planning from MR-images;
- **Automated QA** procedures for adapted plans;
- Exploring the potential of **functional MRI for treatment adaption**;
- **Comparison of online vs. offline MRI approaches** and development of **efficient adaption strategies and workflows**;
- Investigation of **changes in the clinical target volume (CTV) during the treatment** as basis for advanced adaptation strategies not only addressing geometrical changes.

Towards near-real-time adaptive particle therapy

Due to the very high sensitivity of the particle dose deposition against any type of anatomical changes, the **need for treatment adaptations is even higher in particle therapy than in photon therapy**. At the same time, ART is by far more challenging

in PT due to several reasons, one of them being the steep dose gradient in beam direction. Nevertheless, **to achieve the physically and clinically best possible radiation therapy, the benefit of an advantageous tissue-sparing dose distribution of particles needs to be combined with the advantages of an online adaptation capability of the treatment**, currently not available in PT. This will result in a radio-oncological treatment with maximized clinical benefit, namely improved patient survival and/or reduced side effects, and will consequently enlarge the advantage of PT. Patients with highly changing anatomy or moving tumours, who might today not be eligible for PT, could benefit much better from particle therapy. While this is a huge undertaking, it perfectly fits the profile of the HGF, whose researchers at different centres (GSI, DKFZ, HZDR) have already a world-renowned track record in the field of particle therapy innovations and are currently pushing the field forward towards near-real-time adaptive PT and foster collaboration with other leading centres, e.g. within the European ITN RAPTOR.

The components needed for a near-real-time adaptive PT are very similar to photon therapy. But, although certain aspects can be used and taken over from photon therapy (e.g. automated contouring for plan adaptation), the majority of the components need to be developed and adapted specifically for particle therapy.

One example is the independent **treatment verification**, which is capable to detect new or not-recognized deviations from the planned treatment, e.g. due to anatomical variations. Several groups within Helmholtz are active in this field using prompt gamma rays produced from the nuclear reactions of the particles with the patient's tissue. Different approaches, all investigated in Dresden or Heidelberg, use either the spatial, temporal or spectral distribution of the prompt gammas, named **Prompt Gamma Imaging, Prompt Gamma Timing** and **Prompt Gamma Spectroscopy**, respectively. Recently, it was also proposed to combine all the different characteristics simultaneously with the so-called **Multi-Feature Treatment verification**. With heavier ions (like ^{12}C-ions), also **secondary charged particles**, that, contrary to the primary ions, can leave the patient, can be used to verify the particle range as investigated in Heidelberg. Within the EU project **BARB**, researchers from GSI proposed using **radioactive ion beams**, namely positron emitters, which can be measured with positron emission tomography (PET). In contrast to prompt emission imaging, the signal is emitted after deposition in the tissue, with a potential for complementing information on otherwise not visible deformations or perfusion in the irradiated tissue.

Following the approach of the MR-LINACs, the integration of Magnetic Resonance Imaging at the treatment position of the particle therapy system (**MR-PT**) is investigated in parallel projects in Dresden and Heidelberg. Independently, also the potential of offline MRI before or after treatment is studied. In Dresden, the **world's first MRI imaging during proton irradiation** of a phantom was performed in 2018. Still, major technical hurdles – all PT-specific – need to be solved and are currently under research, e.g. interferences between imaging and beam delivery system,

treatment planning, beam monitoring and dosimetry in the presence of the magnetic field of the MRI. Furthermore, the imaging system and MRI sequences need to be optimized for treatment adaptation purposes. For the **first in-human application of MR-PT,** treatments at horizontal scanning beamlines are envisioned rather than integration of MR imaging at a gantry PT system, which is judged too complex at the current stage.

Despite the described progress, so far, research in the field of near-real-time adaptive PT is focused primarily on isolated component development rather than on integrated workflow solutions (similar to the pre-MR-LINAC era). Hence, the interaction and automated decision-making of the different needed components is nowhere integrally tested and thus made ready for actual application. Therefore, the goal of the **PT2030** project (Figure 2.15), which is also embedded in the Helmholtz research infrastructure roadmap, is the **first realization of near-real-time adaptive PT at a full gantry system** – enabled by a **closed, fully automated and AI supported feedback loop of imaging, treatment verification, adaptation and QA** in (almost) real-time (see Section 3.2.3).

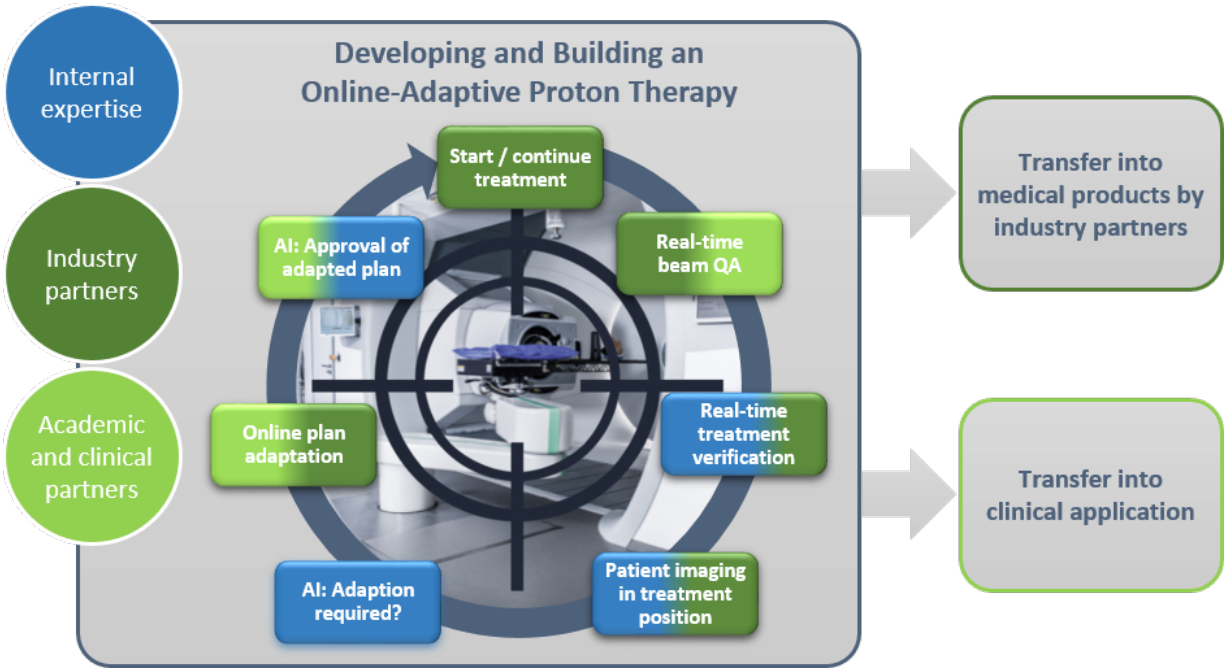


Figure 2.15 Overview of the PT2030 project of the Helmholtz Research Infrastructure Roadmap to realize near-real-time adaptive proton therapy in a clinical prototype PT system (adapted from "Helmholtz-Roadmap für Forschungsinfrastrukturen 2021").

With PT2030, a worldwide unique research-clinic hybrid proton facility will be built. Here, the innovative software and hardware components and their interaction will be integrally tested, further developed and finally enabled for clinical application for the first time, in close cooperation between the Helmholtz centre, the University Hospital in Dresden and the medical technology industry as well as other clinical and academic

partners. The long-term aim is to **develop the physically best possible radiation therapy for application on patients.**

For the treatment of regularly moving targets, especially due to respiratory motion, specific solutions are developed, as in principle no adaptation is mandatorily required. The focus within Helmholtz is on **4D treatment planning and delivery** as well as **4D logfile-based dose reconstruction**, both at GSI and in Dresden. These approaches are important to optimally include the motion in the planning process and to estimate the actual delivered dose distribution in the patient, respectively. Their clinical implementation and routine use is pushed forward (at CNAO and UPTD), as these approaches are also important prerequisites for adaptive PT. For example, the developed 4D-dose reconstruction system can in principle include online range measurements and/or recently acquired image data.

An alternative approach is studied in cooperation between DESY and the Hamburg university. Due to the capability of the Photo Injector Test facility at DESY in Zeuthen (PITZ) to produce bunch trains with a bunch repetition rate of currently 1 MHz and a total train length of up to 1 ms together with a kicker system which is capable of kicking each of the 1000 bunches to a different transverse location, it is possible to "paint" the whole tumor area with small pencil beams within 1 ms. Together with the X-ray Fluorescence Imaging (XFI) technology as described in section 2.2.1 it would be possible to locate the exact tumor region for XFI-guided electron beam irradiation. If for example the first part of the bunch train with low charge per bunch is used to locate the actual position of the tumor (e.g. by targeting gold nanoparticles which are able to emit x-ray fluorescence photons when excited by the scanning electron beam) and the second part of the bunch train with much higher charge per bunch is used to apply ultra-high dose rate, short treatment time (so called 'FLASH') radiation therapy, the control of the tumor localization and treatment of the tumor could be done within 1 ms. At such short time scales organ motion (e.g. by breathing, …) does not play a role anymore. This all has not been done yet but is planned to be studied in the next years. First simulations have shown the feasibility of this XFI-guided electron beam therapy concept.

2.2.3 New beam delivery methods

The Helmholtz centres are world-renowned for their research and clinical translational work on ion beam radiotherapy, where GSI was the first European center to treat patients from Heidelberg University Hospital in 1997 with ions. Novel beam delivery and beam monitoring technology are vital to improve the clinical outcome of ion beam radiotherapy. Novel beam delivery methods can improve ion beam radiotherapy in three main areas:

- Reducing Treatment toxicity;

- Improving Tumor Control;
- In-vivo beam monitoring to guarantee accurate delivery of particle beam dose.

- *Reducing Treatment Toxicity*

Reducing radiotherapy treatment toxicity is one of the major reasons for the development and clinical translation of new beam delivery methods. FLASH and spatially fractionated radiotherapy (SFRT) with particle beams are novel beam delivery methods that can potentially reduce radiation treatment toxicity, while maintaining approximately the same level of tumor control. In the case of FLASH, the radiation is delivered at significantly higher average dose rates >40Gy/s when compared to standard radiotherapy of 6 Gy/min. Healthy organs in the radiation path of the FLASH particle beam, behave as if they are hypoxic during the delivery of the radiation dose. Animal studies comparing FLASH dose-rates to standard dose-rates have shown a significant reduction in radiation toxicity, in the order of 40%-70% for healthy organs in radiation path. In the case of SFRT, the radiation to the cancer is given via narrow strips known as peaks, which are separated from each other by valley region of low dose, with approximately 10 to 50 times less dose than the peak. Consequently healthy organs in the radiation path of SFRT beams, receive less dose than a uniform beam, because of the lower dose delivered by the valley regions. Currently the Helmholtz centres GSI, DKFZ, HZDR, DESY and HZB (protons only) are actively researching FLASH (i) to investigate the mechanism behind the FLASH protection of healthy organs and (ii) to establish how-to best translate FLASH into a clinical environment. In the case of SFRT delivery methods, HMGU, DESY, and DKFZ are actively studying the mechanism of SFRT and how to translate SFRT into a clinical environment.

- *Improving Tumor Control*

Improving radiotherapy tumour control is another major reason for the development and clinical translation of new beam delivery methods. SFRT was shown to achieve improved tumour control for an extremely aggressive and deadly brain cancer (gliosarcoma), where animal studies were performed at the Brookhaven National Laboratory (BNL, New York) and at the European Synchrotron Radiation Facility (ESRF, Grenoble). Follow-up studies done at Experimental Radiotherapy Platform of Curie Institute in Orsay with protons also demonstrated excellent tumour control in the case of high-grade gliomas in rats. Currently the Helmholtz centres HMGU and DKFZ are developing in-vitro and in-vivo tumour models to investigate the mechanism by which SFRT beams achieve tumour control.

- *In-vivo beam monitoring to guarantee accurate delivery of particle beam dose*

Accurate delivery of the particle beam dose to the tumour is critical to achieve tumour control. Therefore, in-vivo beam monitoring is vital to guarantee that the ion beam dose is delivered to the cancer and not to the surrounding healthy organs. A variety of novel beam delivery and beam monitoring technologies are being developed at the Helmholtz centres such as radioactive ion beams (RIB), prompt gamma imaging (PGI) and mixed ion beams (see Figure 2.16). RIB are being developed at GSI to allow real-time monitoring of the ion beam Bragg peak within the patient with the use of positron emission tomography (PET).

RIB and mixed ion beams technology would allow for simultaneous treatment and imaging (theranostics) with ion beams. Prompt gamma imaging (PGI) is being developed at DKFZ and HZDR, to allow real-time imaging of the ion-beam Bragg peak within the patient. PGI also provides an in-vivo spectroscopic analysis of the chemical composition of the tumour. Both RIB and PGI offer the capability of theranostics for ion-beam therapy, with PGS also providing in-vivo spectroscopic chemical analysis. Mixed ion beams are also being developed at the DKFZ and GSI to allow monitoring of ion beam delivery to moving tumours in the lung. Moving lung tumours are extremely hard to treat with Carbon ions, because the motion makes it very hard to accurately deliver the Carbon ion dose.

Also the in-vivo monitoring of cancer tissue with the help of nanomarkers and XFI detection as described in the previous section should allow the online localization of tumor tissue and immediate treatment with particle beams within 1 ms so that tumor motion e.g. during breathing does not play a role anymore. In addition, the treatment volume can be restricted to the tumor tissue and when the radiation treatment is done with high energy electrons also the depth dose profile is not so strongly depending on tissue density variations before the tumor area as it is for radiation treatment with ions. The online control of the transverse dose distribution during the treatment could be monitored using a fluorescence layer on the beam exit window and a beam imaging system to the phantom/patient/sample as it is currently planned for FLASH*lab*@PITZ.

The development of novel beam delivery and beam monitoring technology are vital to improve the clinical outcome of particle beam radiotherapy. However, in order to optimize the development of novel beam delivery methods, cross-platform studies at the Helmholtz are needed and should focus on two main areas:

- Fundamental research: focused on understanding the mechanism that allows for (i) reduced treatment toxicity and (ii) improved tumour control for the novel delivery technologies such as FLASH and SFRT;
- Translational research focused on pre-clinical studies in animals and phantoms to establish the best methodology for applying the novel technologies to patients such as FLASH, SFRT, RIB, PGI and mixed ion beams.

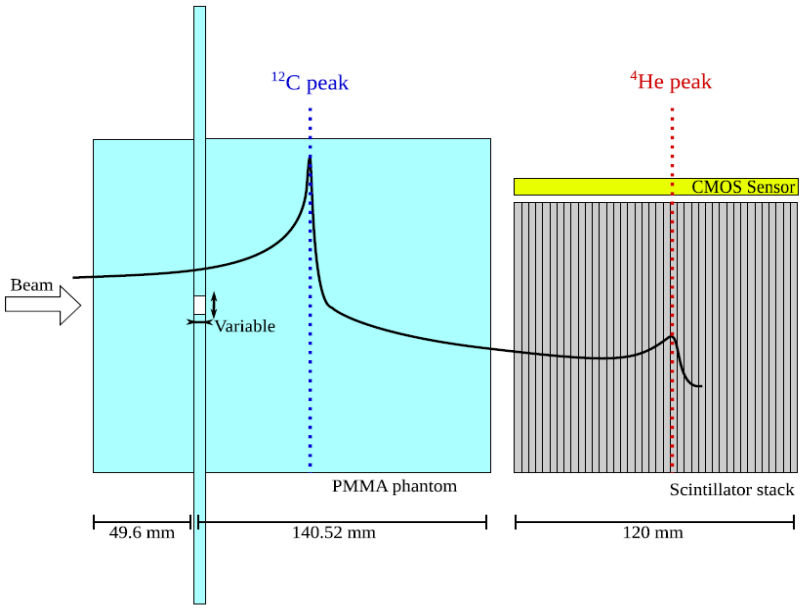


Figure 2.16 Schematic depiction of mixed Helium/Carbon ions delivered simultaneously to allow range monitoring in-vivo. Image from: Volz *et al., Phys. Med. Biol.* (2020).

- *Fundamental research*

The FLASH studies are being performed at the DKFZ and GSI primarily use in-vitro and computational models to study the underlying mechanisms. DKFZ has developed a novel Oxygen sensor that allows direct measurement of the total amount of Oxygen present in the extracellular matrix before and after FLASH irradiation of water and cells. GSI has developed a computational model of the radiochemistry of FLASH using the “step-by-step” tracking of all chemical species produced during irradiation of water (TRAX-CHEM). In order to develop an accurate computational model of the FLASH effects in cells, a cross-platform activity between DKFZ and GSI is needed to bring together both expertise in FLASH radiation. The know-how on FLASH in-vitro irradiations (DKFZ) needs to be combined with the computational modelling expertise of chemical species in water (GSI). In addition, recent experimental studies on lung cell lines using FLASH radiation with Helium ions, where performed jointly between GSI and DKFZ/HIT. Experimental cross-platform studies are needed to improve the understanding of the FLASH mechanisms and to investigate which ion beam is best suited for FLASH irradiation.

At the Photo Injector Test facility at DESY in Zeuthen (PITZ) a worldwide unique parameter range of electron beams is available for studies on FLASH radiation therapy and SFRT. This beam parameter range does not only cover currently found beam conditions which show the FLASH effect but also widely extends into the yet unexplored and unexploited range of even higher dose rates and shorter treatment times. This holds the perspective for even further opening the therapeutic window for

FLASH therapy. The first aim of the research at PITZ is to define the optimum beam parameter conditions which offer the best treatment of different types of tumors. Cooperation with DKFZ, HZDR, HMGU and other Helmholtz centres is being pushed forward to exploit the potential of the HGF.

The SFRT research is being performed at the DKFZ, GSI and HMGU centres using primarily in-vitro models. The DKFZ is performing SFRT irradiation using X-rays and ions at standard dose rates. The HMGU is actively developing a novel X-ray machine capable of delivering SFRT at FLASH rates. GSI is working together with a French group (ERC grant awardee on the topic) for using very heavy ions (such as Ne or even Ar) in SFRT. The DKFZ has presently developed an in-vitro model for studying the mechanism of SFRT on lung (H460) and pancreatic (PANC01) cancer cells. A cross-platform study is needed to investigate the mechanism of tumour control using SFRT delivered at both standard and FLASH rates with X-rays and particle beams. In addition, the development of combined technology capable of delivering simultaneously FLASH and SFRT can have a major impact in radiation therapy. A cross-platform program is needed that also focuses on technological developments for combined FLASH-SFRT.

The high electron beam quality available at PITZ allows to study mircrobeams with electrons. Together with the capability to produce long bunch trains of such beams and the usage of a kicker system to distribute the bunches of a train over the tumor area it will be possible to do SFRT with electrons. Currently a beam energy of 22 MeV is available but for FLASH*lab*@PITZ a beam energy upgrade to 250 MeV is planned. Since the bunch train length is 1 ms which is much shorter than the currently known treatment time limit for FLASH therapy this not only allows to study SFRT stand-alone but also in combination with FLASH radiation therapy which can have a major impact in radiation therapy.

In the context of FLASH, also the development and characterization of novel radiation sources delivering the ionizing radiation in ultra-short pulse durations (sub-ns down to few fs) seems interesting. Here, HI-Jena is preparing novel sources of electrons, protons as well as heavier ions, and x-ray radiation to allow for investigating the potential for their future application in radiation therapy. These pulsed sources are generated during the interaction of the high-power laser pulses operated at HI-Jena with matter. Here, the ultra-short pulse duration of the driving high-power laser (several 10s of fs) is responsible for the ultra-short pulse duration of the ionizing radiation pulses. For their characterization, not only the controlled generation of the different particle and radiation pulses with variable parameters (particle flux, energy distribution, angular divergence) is crucial but also their exact detection and diagnostic with respect to these parameters. Here, HI-Jena carries out – in collaboration with partners from GSI, HZDR, national universities and other international partners – experiments to generate such pulses. The diagnosis and characterization can be carried out building upon Jena's long-standing expertise in x-

ray optics and x-ray detectors. Developing and characterizing these detectors also suitable for radiation pulses with ultra-short duration reaching extreme intensities will also be beneficial for all other activities within this CCA towards the application of the FLASH delivery method.

- *Translational research*

Translational animal studies are being performed in FLASH and SFRT. In the case of FLASH, HZB, GSI and HZDR are investigating FLASH in mice and zebrafish. In the case of SFRT, HZDR is performing in-vivo studies of tumours transplanted into the mouse ear. DESY is very actively trying to acquire the necessary resources to be able to perform own in-vivo experiments. External partners are already welcome to perform their in-vivo experiments at the DESY infrastructure since very recently the DESY directorate opened with research direction.

A cross-platform program is needed to investigate the methodology of using both FLASH and SFRT beams independently and also in combination. Currently, multi-directional FLASH irradiation is not possible due to the high dose needed to achieve protection of the healthy organs and due to the poor understanding of the level of FLASH protection per organ within the human body. In addition, a fractionation study is needed for FLASH to understand the optimal number of fractionations that maintain tumour control and yield reduced organ toxicity. In the case of SFRT, this novel beam delivery will also benefit from cross-platform projects that study (i) the optimal particle type that achieves best tumour control for SFRT beam delivery, (ii) the fractionation needed to achieve optimal tumour control, with SFRT and (iii) the impact of high dose-rate delivery of SFRT on the time the patient is on the couch during radiation delivery.

Translational phantom studies are being performed with RIB, PGI and mixed ion beams at GSI, DKFZ and HZDR. Phantom studies are ideally suited to investigate how to use this novel technology in a clinical environment. Future cross-platform studies are needed to assess this novel technology in animal models for RIB, PGI and mixed ion beams. Cross-platform animal studies could focus on inter-comparing all the range monitoring technology (RIB, PGI and mixed ion beams) under in-vivo conditions. In-vivo range monitoring is vital to guarantee the accurate delivery of ion beam dose. In the case of RIB, a small animal PET imaging system is being developed specifically for imaging RIB in-vivo.

2.2.4 Translational radiotherapy and radiobiology

Translational radiotherapy and radiobiology provide the pipeline for the development of precision cancer medicine. Precision cancer medicine arises from the improvement and individualization of the clinical treatment consisting of different

schedules of combined therapeutic approaches. Within the Helmholtz centers (DKFZ, HZB, GSI, HZDR, HMGU, DESY), various optimized cell culture models (including more physiological 3D models and tumour organoids) as well as *in vivo* animal models of zebrafish, mice and rats are established. Different beam qualities and techniques beyond standard photon or electron 2D/3D preclinical irradiation machines are available, including proton or heavier ion irradiation, FLASH with electrons or protons, microbeam radiation therapy and proton minibeam radiation therapy. Preclinical models are established for 3D (including organoids) and in vivo subcutaneous or orthotopic irradiation with or without simultaneous systemic treatment as well as for in vivo normal tissue irradiation with photons, protons or heavy ions. While the technology of clinical radiotherapy has been rapidly improved over the last decades from 2D over 3D, intensity modulated radiotherapy, image-guided radiotherapy including bioimaging to particle radiotherapy with increasingly better dose distributions, the inclusion of biological knowledge could hardly keep up this pace. Simultaneous combined treatments of radiotherapy with systemic treatments in e.g. head and neck cancer or brain tumours have been improved only to a small extent over the last 15 years. Proton therapy is used in clinical routine or clinical trials for thousands of patients profiting from the better physical dose distribution. However, so far no path is defined to validate and integrate the preclinical knowledge of a heterogeneous radiobiological efficacy of particle beams into clinical application. A substantial lack of knowledge exists for the efficacy of standard combined systemic treatments applied during proton radiotherapy compared to the simultaneous use with photons. Immunotherapy approaches are increasingly developed for palliative or systemic-therapy-only settings, however the combination with radiotherapy is more complex and thus lagging behind. Today, no single molecular or genetic biomarker is established in clinical routine that would lead to treatment adaptation or personalisation of radiotherapy.

Preclinical radiotherapy and radiobiology aims to optimize and personalize radiotherapy using new biomarkers and novel combined treatments as well as new beam qualities and imaging technology in order to improve tumour curability while minimizing side effects. Three major pillars have been defined within the Radiation Oncology and Imaging program of Helmholtz POFIV, which can be further enhanced by joining forces with other Helmholtz centers and other research areas:

- *Biomarker definition and evaluation of resistance mechanisms for personalised radiotherapy or combined treatments*

Biomarkers are either identified from patient tumour material out of either clinical routine or clinical studies or are coming from preclinical experiments on mechanisms of radioresistance. In both cases, pathway evaluations and knowledge of mechanisms and functions of the biomarkers are of high importance for an efficient clinical use for patient stratification as well as for development of novel treatment approaches, e.g. evaluation of targetability of the biomarkers during radiotherapy. Thus, in close

collaboration with clinical partners and with DKTK and NCT sites, backwards translational experiments are performed on the role of clinical radiotherapy biomarkers for radio(chemo)resistance and on ways to influence these mechanisms and to utilize them for improved treatment concepts.

- *Development of novel combined treatments*

Existing or newly identified targets are evaluated for their value for combined treatment approaches, e.g. by re-purposing of existing drugs or by novel targeting approaches or immunotherapy. Major tumour entities with a high need for such improvement include glioblastoma as well as head and neck, lung and esophageal cancer. Preclinically, organoid and other 3D models are used to identify the best candidates for combinations, which require further evaluation in clinically relevant animal models using clinically relevant curative endpoints. In parallel, biomarkers have to be developed to assess the success of such novel treatment approaches. The final aim consists of a subsequent clinical study applying both the novel therapeutic approach and a biomarker-based patient stratification and selection for improving patient cure rates.

- *Integration of biological knowledge on radiobiological efficacy into clinical radiotherapy*

Preclinical experiments will evaluate the efficacy of combined particle irradiation with standard and experimental systemic treatments in comparison to the same combinations with photons. Functional 3D in vitro experiments with some validation in animal experiments and evaluation of mechanisms will help to answer the question on transferability of such treatment approaches between different beam modalities. The knowledge of a heterogeneous radiobiological efficacy, coming mainly from cell culture and some normal tissue (intestine) in vivo experiments, will be further specified with complex in vivo normal tissue experiments e.g. in brain (Figure 2.17) or other normal tissues with definition of regional effects dependent on the depth of the beam, but also on substructures of the normal tissues. Modelling of these data will help to improve assumptions for clinical treatment planning with particles and sets a basis for clinical trials on further reduction of normal tissue toxicity of particle radiotherapy.

At the Helmholtz centers (DKFZ, HZB, GSI, HZDR, HMGU), the various departments cover a very wide spectrum of tumor and normal tissue associated factors mediating resistance and toxicity, respectively. The jointly declared goals are target and biomarker identification, assessment and integration into clinical routine via relevant and focused preclinical and clinical studies. The spectrum of research areas spans from the tumor microenvironment (hypoxia, angiogenesis, extracellular matrix) over therapy resistance mechanisms (target and biomarker identification),omics (genome, epigenome, transcriptome, proteome, metabolome, etc.) and bioinformatics to multimodal imaging for normal tissue toxicities.

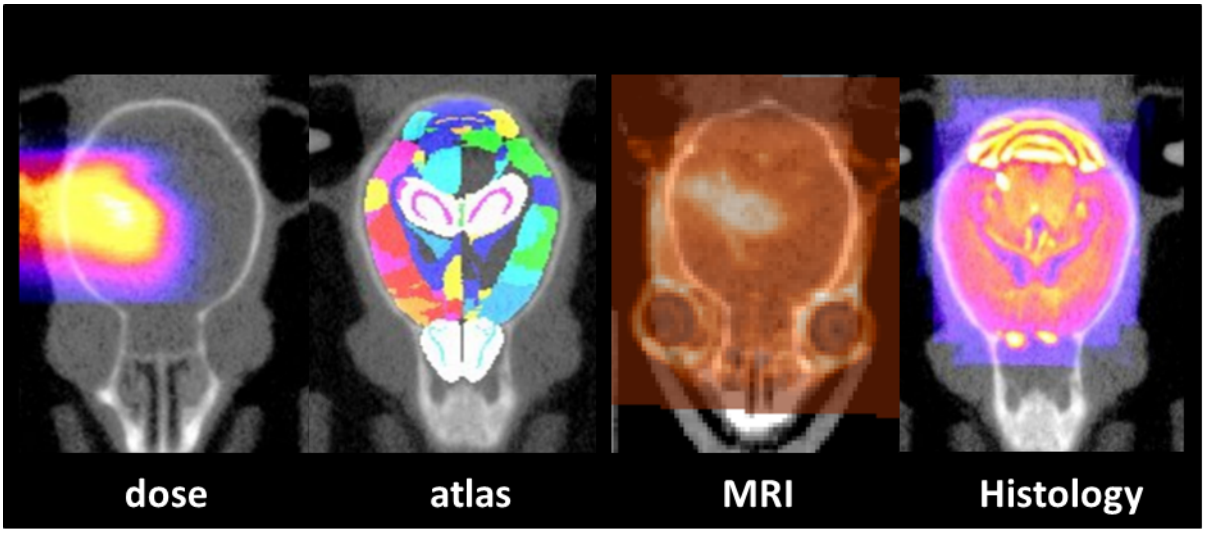


Figure 2.17. Precise irradiation of mouse brain subvolumes with protons as a prerequisite to define beam-depth- and anatomy dependent differences in radiobiological efficacy. Irradiation dose distribution, a brain atlas defining subregions, follow-up MRI identifying necrotic regions and histological whole-brain section are 3D-co-registered for detailed evaluation of regional, dose- and anatomy-dependence of toxicity of protons. ©Antje Dietrich, Mechthild Krause, HZDR, DKTK

The wealth of preclinical models (different 3D cell models such as organoids; different subcutaneous and orthotopic animal models) provides state-of-the-art tools to address the most important questions:

1. How does a tumor facilitate its resistance to therapy?
2. What is the most effective way to sensitize tumors and impair their adaptive response?
3. Which biomarkers are most reliable, predictive and/or prognostic and applicable for patient stratification for a specific treatment approach and schedule?
4. What are the tumor and normal tissue effects and effectiveness of proton irradiation as well as novel promising radiation approaches such as microbeam, FLASH and ions?
5. Which cell subpopulations in the heterogeneity of the tumor is how much affected/eradicated by the different combined treatment approaches and how can we deduce the concept of personalization from this knowledge?
6. What do the various solid tumors have in common to minimize the panel of effective combined therapy options and schedules with regards to infrastructural and ecological reasons?

At the DLR, the Radiation Biology Department at the Institute of Aerospace Medicine currently investigates the role of tumor hypoxia in the radioresistance of non-small-cell lung cancer. The response of tumor cell lines towards X-rays and carbon ions is compared under different hypoxia conditions.

DESY just very recently noticed that the high brightness photo injector at DESY in Zeuthen PITZ can provide worldwide uniquely capabilities for particle radiation

therapy due to its 2 decades long work for high brightness, high repetition rate, high charge electron sources for European XFEL. Together with the neighbouring TH Wildau and other national and international partners a proposal for an R&D platform for FLASH and VHEE radiation therapy and radiation biology was developed (FLASH*lab*@PITZ). Now the existing accelerator at PITZ has been extended by a basic version of an R&D beamline where first experiments are possible since November 2022. In addition, activities on high dose rate dosimetry, simulation of radiation effects and involvement in the international radiation and oncology community are ongoing

2.2.5 Radiopharmaceuticals and theranostics

Radiopharmaceuticals have become indispensable tools for the detection and treatment of malignancies in many fields of clinical practice and remain an important part of basic, preclinical and clinical research. For example, **β^+- or γ-emitting diagnostic radionuclides** bound to a targeting vector are frequently used as probes for diagnostic purposes, as their distribution and local concentration can be determined by non-invasive **positron emission tomography (PET)** or **single photon emission computed tomography (SPECT)** imaging, respectively (Figure 2.18). In addition, studies with such probes have made essential contributions to our current understanding of many (patho)physiological processes, both at the cellular and molecular level. In the research field “information” within the framework of PoF-IV, the development of novel radiolabeled probes is envisaged to facilitate **decoding of the human brain** and understanding of the mechanisms underlying its ability to encode, maintain and retrieve information. Besides normal function, various forms of human brain dysfunction will be addressed by development of specific radiotracers to visualize neurological, cognitive and psychiatric disorders. In this regard, the search for novel selective tracers, which target neurotoxic protein aggregates associated with neurodegenerative diseases like Alzheimer’s or Parkinson’s disease will be another research goal. The development of neurotracers is associated with several challenges and potential bottlenecks, as they have to fulfil many requirements like an altered expression of the molecular target in the diseased state; a high binding affinity to the molecular target to achieve high target-to-background ratios and an efficient penetration of the blood brain barrier to actually reach the central nervous system. For the treatment of malignant disorders, the same targeting vectors are frequently used in combination with **therapeutic radionuclides (α-, β^-- or Auger electron-emitters)** to selectively destroy tumour cells (Figure 2.19). In this case, a high tumour-to-background ratio and a high “receptor” capacity of the malignant tissues is mandatory to spare healthy tissue. Although a range of different particle emitters (e.g. ^{177}Lu, ^{223}Ra and ^{225}Ac) are already used in clinical practice, there is an urgent need for additional radionuclides with suitable decay properties, ease of production and amenable chemistry. Apart from additional β^- particle emitters such as ^{67}Cu or ^{47}Sc and mixed β^- / Auger electron emitters such as ^{161}Tb, especially α-particle emitting radionuclides are

expected to play an important role for future therapeutic approaches, as their high LET in tissues offers the capability to deliver higher and more targeted radiation doses to malignant cells. However, only a small number of α-particle emitting radionuclides like ^{149}Tb, ^{211}At, ^{212}Bi, ^{213}Bi, ^{223}Ra, and ^{225}Ac with suitable decay properties have been proposed and their availability is limited. Therefore, a future goal is to optimize production methods and enhance production capacities for these radionuclides. Likewise, while application of efficient Auger electron emitters for therapeutic purposes is just at the beginning, it has tremendous potential for future applications.

In general, the process of radiopharmaceutical drug development can be divided into different steps. It typically starts with identification of a molecular target followed by the search for lead structures with a high affinity for this target. In recent years, computer-aided approaches have significantly accelerated discovery and optimization of lead structures for conventional drug development. As such, implementation of *in silico* methods into the radiopharmaceutical design process promises to boost future developments in this field as well. Other important steps consist of radionuclide production and development of suitable radiolabeling strategies (Figure 2.19A). Beyond routinely produced PET nuclides like ^{18}F, ^{13}N, ^{11}C, ^{15}O or ^{99m}Tc there is increasing demand for radionuclides that can be used for special applications like endoradiotherapy, as mentioned above. Besides the targetry for irradiation, separation techniques based on novel extraction approaches or chromatography for radionuclide isolation will have to be established. A very attractive and relatively new concept is the **theranostic approach**, which uses a pair of radionuclides from the same element to combine diagnostic (PET/SPECT imaging) and therapeutic (endoradiotherapy) applications.

For this purpose, the targeting vector is usually coupled to a chelator that enables chelation of both, the diagnostic and the therapeutic radiometal (Figure 2.19B). Examples for theranostic radionuclide pairs include ^{44g}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{83}Sr/^{89}Sr, ^{86}Y/^{90}Y, ^{124}I/^{131}I, ^{152}Tb/^{161}Tb and ^{152}Tb/^{149}Tb. While the first six pairs each consist of one β^+- and one β^--emitter, the seventh pair consists of one β^+- and one α-particle emitter. The distinct advantage of the theranostic approach is that it provides pairs of diagnostic and therapeutic radiopharmaceuticals with identical physicochemical and biological properties. This in turn means that PET imaging with the diagnostic counterpart can be used for individualized dosimetry (i.e. estimation of the dose absorbed by different organs/tissues in a specific patient), facilitating therapy planning as well as prediction of whether a patient will actually benefit from treatment with the corresponding therapeutic radiopharmaceutical. As such, this new approach constitutes a form of **personalized and precision medicine** that is attracting tremendous attention today, but the availability of clinically used theranostic radiopharmaceuticals is still very limited. Development of radiopharmaceuticals for theranostic applications is therefore another important goal of the research field “Information” at the Institute for Neuroscience and Medicine of the FZJ. The same approach of radiopharmaceutical sciences is in the focus of the research field “Health” at the HZDR. Thus, the Institute of Radiopharmaceutical Cancer Research develops

novel theranostic radiotracers that can be used for both, non-invasive cancer imaging by means of PET/CT, PET/MRI and SPECT/CT and subsequent treatment of cancer patients with the same compounds bearing a therapeutic radionuclide.

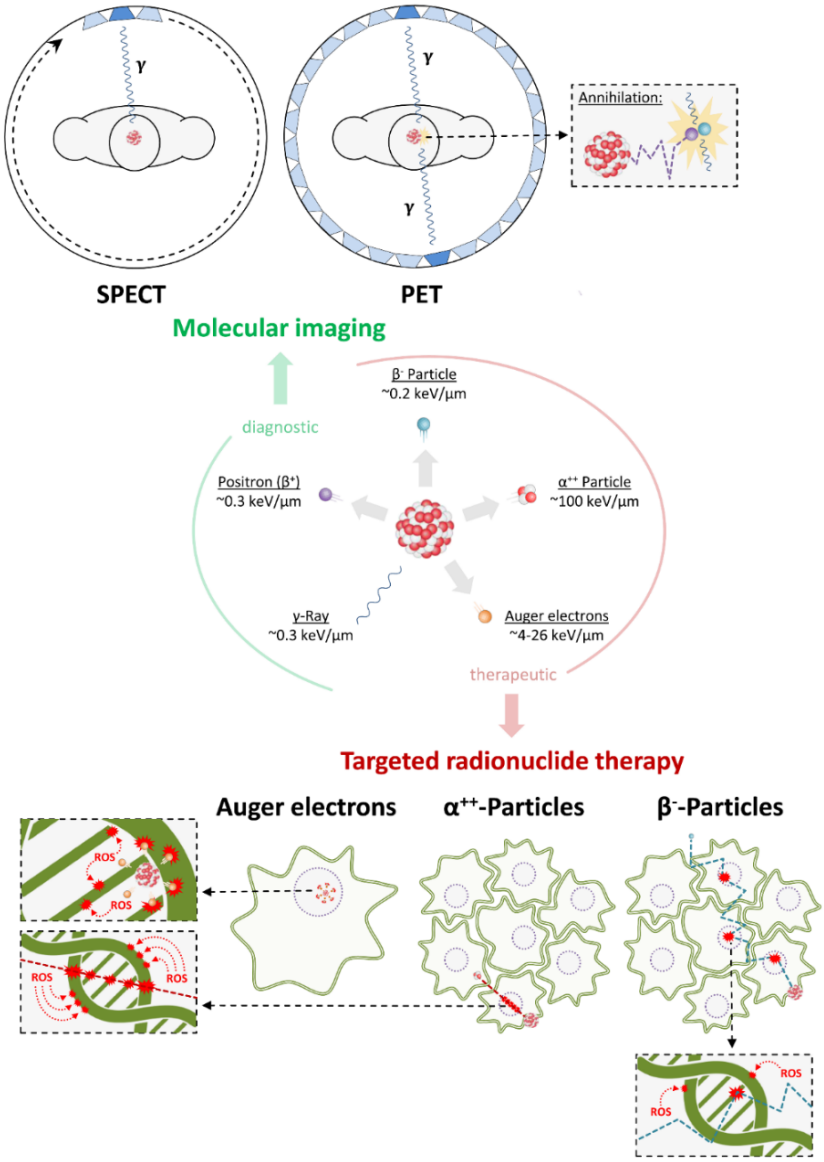


Figure 2.18 Types of radiation and their use for diagnostic and therapeutic radiopharmaceuticals. While diagnostic radiopharmaceuticals that contain β^+- or γ-emitting radionuclides can be used for molecular imaging by PET or SPECT (top), therapeutic radiopharmaceuticals that contain β^--, α-, or Auger electron-emitting radionuclides can be used for endoradiotherapy (bottom). Reprinted from Neumaier *et al.*,*Pharmaceutics* (2020).

Another obstacle to the more widespread use of PET techniques is the limited number of available molecular probes, which can at least in parts be attributed to a lack of simple labelling methods for their preparation. Owing to the favourable properties of ^{18}F, radiofluorination plays a dominant role for current PET radiochemistry and recent introduction of novel labelling strategies based on transition metal mediated fluorination reactions has changed the field dramatically. Although this

has helped to expand the radiochemical space, all of these methods have inherent limitations and novel labelling strategies that enable fast and easy access to new radiotracers are still highly sought after.

A further challenge is the sustainable and cost-efficient availability of the diagnostic and theranostic radiopharmaceuticals. As far as the radio nuclide production via cyclotrons is possible constant timely and local supply can be offered which is less the case on nuclides produced via fission reactors. Here alternative production methods have to be explored as considered at FZJ within the HBS project.

With regard to the development of therapeutic and theranostic radiopharmaceuticals, novel chelator system for thermodynamically stable and kinetically inert **complexation of radiometals** remain in the spotlight of current research. In addition, there is increasing interest regarding potential therapeutic applications of the pure α-emitter ^{211}At. However, due to its poor accessibility and incompletely understood chemistry as well as the lack of a stable isotope, endotherapeutic applications of ^{211}At remain underexplored.

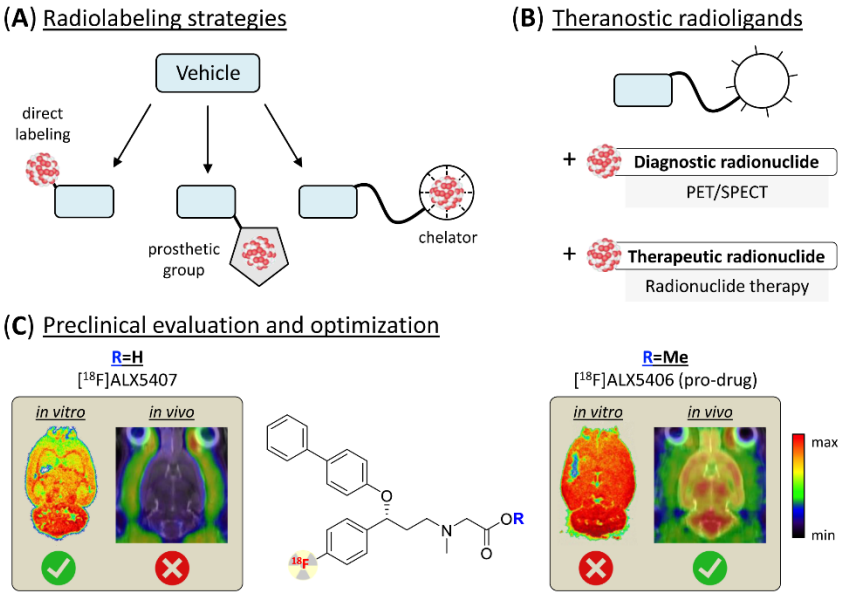


Figure 2.19 Radiolabeling strategies and preclinical evaluation of radiopharmaceuticals. (**A**) Radiolabeling of a targeting vector (vehicle) can be achieved by direct introduction of the radionuclide (left), by conjugation with a radiolabeled building block (middle) or by conjugation with a chelator for radiometal complexation (right). (**B**) Theranostic radioligands are typically based on conjugation of a vehicle with a chelator for complexation of either diagnostic or therapeutic radiometals, allowing for imaging and radionuclide therapy with the same compounds. (**C**) Example for the preclinical evaluation and optimization of a candidate neurotracer. Brain penetration of the radiolabeled lead structure [^{18}F]ALX5407 (R=H, left) was too slow for *in vivo* PET imaging, which could be overcome by development of the brain-penetrating pro-drug [^{18}F]ALX5406 (R=Me, right). A & B reprinted from Neumaier *et al. Pharmaceutics* (2020). C modified from Hoffmann *et al. ACS Chemical Neuroscience* (2021).

Following their successful preparation, candidate radiopharmaceuticals have to be exhaustively evaluated in *in vitro* and *in vivo* model systems to demonstrate their

diagnostic or therapeutic potential, exclude e.g. accumulation in radiation-sensitive tissues and potentially tune important properties like brain penetration (Figure 2.19C). For this step, suitable *in vitro* and preclinical animal models have to be established, validated and used. Subsequently, successful candidates have to pass first in man studies before they can be transferred into clinical practice, where their preparation has to be carried out in accordance with strict regulations to ensure that all radiopharmaceuticals administered to patients meet certain approved quality requirements.

In conclusion, the development of radiopharmaceuticals is a complex process comprising a multitude of research areas that include, among others, nuclear chemistry, radiochemistry, radiopharmaceutical chemistry, nuclear medicine, biology and computational medicine. In the clinic, **radiation** emitted by these radiotracers is used to non-invasively detect or selectively destroy diseased tissues. Research applications include the visualization of (patho)physiological processes on the cellular or molecular level to decode mechanisms that are otherwise difficult or impossible to study *in vivo* like e.g. information processing in the human brain. Future challenges in this research field include the identification of novel molecular targets, the development of novel radionuclide production methods and the establishment of novel labelling strategies.

3

LARGE HELMHOLTZ INFRASTRUCTURES IN RADIATION RESEARCH

The Helmholtz association builds and operates unique research infrastructures and large-scale facilities, such as particle accelerators, research vessels, supercomputer and aircraft. The research infrastructures of the HGF exemplify the division of tasks in the German science system and the cooperation with German as well as foreign universities and research institutions. More than ten thousand external scientists from more than thirty nations work at the research facilities of the HGF every year. In 2011, the HGF presented for the first time a roadmap coordinated across research fields on possible lines of development for its research facilities. The new Helmholtz roadmap on research infrastructures for the current decade has been published in 2021.

In this section we will deal with the current and future infrastructures in radiation research in the Helmholtz centers participating to the CA RR.

3.1 CURRENT INFRASTRUCTURES

Current infrastructures in operation are summarized in Table 3.1 and described in detail below.

Infrastructure	Helmholtz Center	Topics
JCNS	FZJ	neutron irradiation systems, neutron analytics
INM-5 Cyclotron	FZJ	radioisotope production, low current irradiation
INE	KIT	radionuclide/actinide research, analytics
Irradiation Facility	KIT	irradiation with photons, electrons, neutrons, x-rays
ABYSS	DLR	space simulation facility
IRE	HZDR	Biological (safety level 1) and radiochemical laboratories for radioecological and radiochemical research; analytics, spectroscopy, microscopy
ROBL-II	HZDR	radiochemical beamline, synchrotron radiation
ELBE	HZDR	accelerator and laser-driven radiation sources; electron beams, radiobiological experiments, high intensity superradiant THz radiation, laser-driven ion acceleration
OncoRay	HZDR	clinical and translational oncology, radiotherapy, imaging techniques, particle therapy
ZRT	HZDR	radiopharmaceuticals, radionuclides, radiochemistry, imaging, immunotherapeutics
GSI Accelerator Complex	GSI	cancer therapy, space radiation research, carbon ion therapy, radiobiology, FLASH radiation therapy

PITZ	DESY	high brightness electron beams, high intensity THz radiation, FLASH radiation therapy, radiation biology
ARES	DESY	ultrashort electron beams, VHEE radiation therapy, radiation biology
Cyclotron	HZB	Proton therapy, dosimetry, FLASH radiation therapy, radiation hardness tests
REZ	DKFZ	radiological imaging, radiation oncology, radiation chemistry
HI-Jena high-power lasers	HI-Jena	Generation and characterization of laser-based particle and radiation sources with ultra-short pulse duration and extreme intensities

Table 3.1. Radiation infrastructure in operation within HGF at April 2022.

3.1.1 JCNS

The Jülich Centre for Neutron Science (JCNS)[27] (Figure 3.1) operates instruments at leading national and international sources: at the Heinz Maier-Leibnitz Zentrum (MLZ)[28] in Garching, Germany, at the high-flux reactor at the Institut Laue-Langevin in Grenoble, France, and till recently at the first megawatt-class spallation source, SNS, in Oak Ridge, Tennessee, USA. These instruments are made available for external users to conduct experiments by means of a procedure whereby proposals are reviewed by an independent group of experts. Thus, JCNS offers a large international user community access to state-of-the-art neutron instruments under consistent conditions at the neutron source, affording the best conditions for each individual experiment undertaken. In addition, JCNS serves as the organizational framework for FZJ globally-recognized development programme for neutron methods and instruments, as well as for its own research programs in the areas of soft condensed and biological matter, as well as on nanomagnetism and highly correlated electron systems.

In collaboration with the MLZ various irradiation facilities exists at the research reactor FRM II which cover a wide range of applications including rabbit and capsule irradiation systems, mechanical irradiation systems, a silicon doping facility, irradiation with fast neutrons at the instruments MEDAPP, NECTAR and FaNGaS and with cold neutrons at the instrument PGAA[29].

3.1.2 INM-5 cyclotron

The Cyclone 30 XP from IBA (Ion Beam Applications, Louvain-la-Neuve, Belgium) in INM-5[30] is an isochronous three particle beam cyclotron with high intensity beam currents (Figure 3.2). It has variable energy extraction for protons and deuterons up to 30 MeV and 15 MeV particle energy, respectively. Alpha particles are extracted

[27] https://www.fz-juelich.de/jcns/EN/Home/home_node.html
[28] https://mlz-garching.de/englisch.html
[29] https://www.frm2.tum.de/en/frm2/the-neutron-source/irradiation-facilities/
[30] https://www.fz-juelich.de/inm/inm-5/DE/Home/home_node.html

at a fixed energy of 30 MeV. With proton (350µA), deuteron (50µA) and alpha (50µA), it is the perfect tool to combine the field of diagnosis and therapy as well as research works.

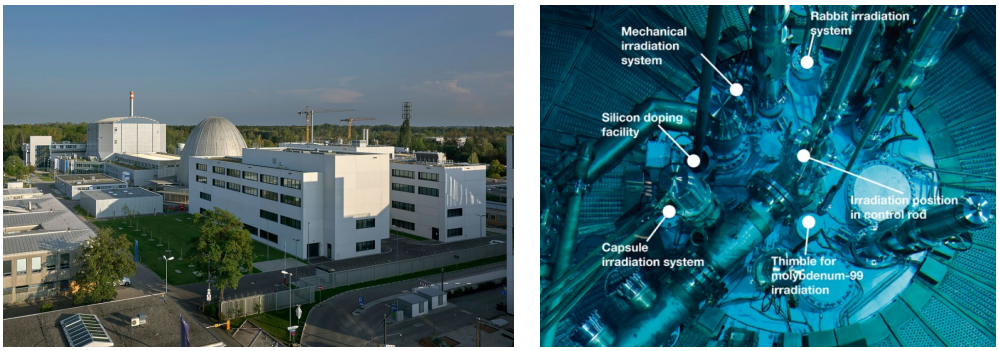


Figure 3.1. The JNCS facility

While protons and deuterons are accelerated in a negative ion mode and extracted with a stripping system, the positive 30 MeV $^{4}He^{2+}$ beam is accelerated and extracted in positive ion mode using an electrostatic deflector (Table 3.2) . The ions to be accelerated are produced with two ion sources installed below the cyclotron, i.e. a multicusp source for proton and deuteron and an electron-cyclotron-resonance ion source for alpha particles. The cyclotron is equipped with two exit ports for beam extraction, which can be fed with protons or deuterons of different beam energy simultaneously due to the implemented Dual-Beam mode. One exit port is connected via a short beamline to a switching magnet which is able to provide beam to up to five targets. Currently, there are 4 target systems installed, namely two liquid targets for ^{18}F production as well as an oxygen and a nitrogen gas target for the production of ^{15}O and ^{11}C, respectively. The 30 MeV alpha beam can only be delivered to the other exit port which is connected to two beamlines. One beamline is connected to the IBA solid target station for high-current irradiations, and the second beamline is able to mount a variety of experimental target systems for nuclear data measurements and low-current irradiations.

	Protons	Deuterons	Alpha particle
Energy	15-30 MeV	9-15 MeV	30 MeV (fix)
Type of particle	H^-	D^-	$^{4}He^{2+}$
Maximum beam current	350 µA	50 µA	50 µA
Exit ports	A and B	A and B	only B
Dual-Beam	Yes	Yes	No

Table 3.2. Beam parameters of the Cyclone 30XP in FZJ

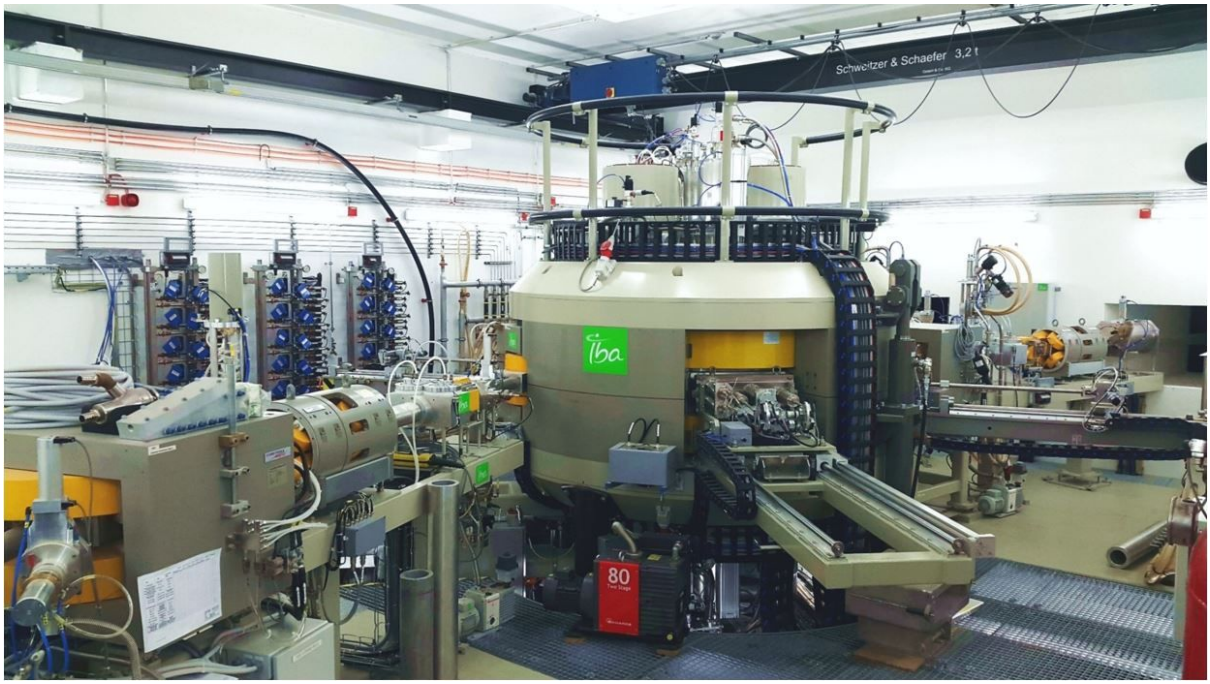


Figure 3.2 A picture of the INM-5 cyclotron.

3.1.3 KIT-INE

INE laboratories are equipped with all necessary infrastructures to perform radionuclide/actinide research, including a shielded box line/hot cells enabling the investigation of highly radioactive materials such as spent nuclear fuel and nuclear waste glass, alpha glove boxes, inert gas alpha glove boxes and radionuclide laboratories (Figure 3.3). State-of-the-art analytical instruments and methods are applied for analysis and speciation of radionuclides and radioactive materials. Advanced spectroscopic tools are available for the sensitive detection and analysis of radionuclides.

Figure 3.3 Infrastructure of the shielded box line/hot cells at INE

3.1.4 KIT- Irradiation facility

The irradiation facility (accredited according to the ISO/IEC 17025:2018 standard) originally designed for the irradiation and calibration of active and passive dosimeters is also used for research and development. It offers different irradiation installations:

- **Photons**: The calibration facility performs irradiations with Cs-137-photons (Figure 3.4) in a range from 0,5 µSv/h up to 2 Sv/h H*(10). For this purpose, collimated radiation fields are available according to ISO 4037 using 6 Cs-137 sources. In addition to H*(10) the measurement quantities Hp(10), Hp(3), Hp(0,07) or Kair can be provided.
- **Electrons:** A Beta Secondary Standard (BSS2) with Sources of Kr-85 and Sr-90/ Y-90 (activities in the E+08 Bq range) provides irradiations in Hp(0,07) and Hp(3)
- **Neutrons:** An installation including Cf-252 source provides defined neutron fields
- **X-Rays:** There are two X-Ray tubes (soft X-Rays with voltages up to 60 kV, hard X-Rays up to 320 kV), in combination with different filters to generate radiation qualities of the N-series

Figure 3.4 Irradiation bench for 137Cs photons

3.1.5 Space Simulation Facilities

Research in the space simulation facility[31] in the Institute for Aerospace Medicine of DLR in Cologne expands our knowledge of the limits of life on Earth and of resistance mechanisms towards environmental stressors including ionizing radiation. This enables statements to be made about habitability, i.e. the possible existence of a life-friendly environment on other planets and moons as well as the effects of a naturally changing or artificially changed environment on Earth.

In the approximately 93 m^2 simulation facility with associated biological laboratories (Figure 3.5), it is investigated whether and how terrestrial organisms, sometimes from extreme regions on Earth, survive or even multiply under the

[31] https://www.dlr.de/content/de/grossforschungsanlagen/biophysikalische-weltraumsimulationsanlage.html

simulated conditions of space or other planets, but also changed environmental conditions on Earth. From this, knowledge about the origin, evolution and distribution of life on Earth and beyond can be gained. The analyses also serve as an experimental basis for international standards for the protection of other planets and the icy moons of the outer solar system (ECSS standards) - “Planetary Protection”.

In addition, astrobiological space missions are prepared in the facilities and space hardware and materials are tested[32]. In this context the fully equipped and monitored Planetary and Space Simulation facilities allow a broad range of tests with biological and chemical material individually or integrated into space hardware. In the focus of interest are defined and controlled conditions like ultra-high vacuum, gas compositions, low and high temperature limits, temperature oscillations, extraterrestrial UV radiation and X-rays. Furthermore, adjacent cell culture laboratories enable also the investigation of the effects of non-ionizing and ionizing radiation on mammalian cells and tissues.

Figure 3.5 Astrobiology Space Simulation facilities (ABYSS) at DLR.

3.1.6 Radiochemical Laboratories and Rossendorf-Beamline at ESRF

Handling radionuclides and studying their behavior in the environment require several types of unique large infrastructures. First of all, the HZDR operates state-of-the-art **radiochemical laboratories** approved for working with biological systems (biological safety level 1) and **hot cells** for radiochemical work and radioecological research. The associated Institute of Resource Ecology (IRE) has the allowance to handle all types of radionuclides. The high level of approval in the radiochemistry laboratory with $6 \cdot 10^7$ times the exemption limit enables work with up to 10^{11} Bq per handling. In the radiation safety controlled labs modern spectroscopic, microscopic and diffraction techniques, as well as systembiology are combined for molecular characterization. This is accompanied with, numerical simulation and quantum chemistry. This infrastructure is completed by the Rossendorf Beamline (**ROBL**-II) at

[32] https://www.dlr.de/me/de/desktopdefault.aspx/tabid-7207/

the world's first 4th generation synchrotron at the ESRF in Grenoble (Figure 3.6). Here, two experimental stations for synchrotron spectroscopy and diffraction techniques are provided and the HZDR is engaged in detecting the molecular and electronic structures of actinides and other radionuclides with detection limits and resolutions at the limits of what is currently technically feasible.

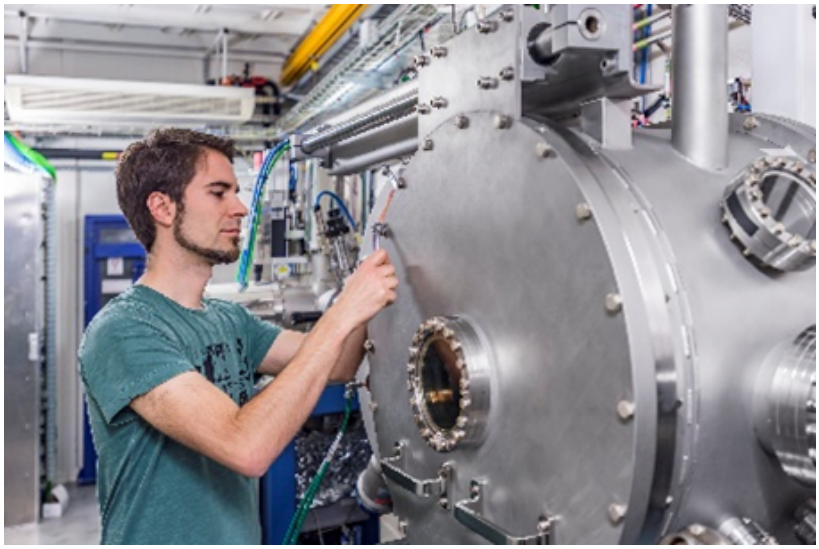


Figure 3.6 Beamline scientist in the preparation of an experiment

3.1.7 ELBE

The ELBE – Center for High-Power Radiation Sources at HZDR (Figure 3.7) operated by the Institute of Radiation Physics is a worldwide unique user facility combining a superconducting linear accelerator (ELBE) with ultraintense PW lasers (DRACO and PENELOPE). Its mission is to develop and operate accelerator- and laser-driven sources of radiation and particles like neutrons, positrons, gamma rays, single electron bunches as well as IR- and (superradiant) beams. These sources are utilized by a broad international community of users coming from nuclear, astro, high-energy-density and strong-field physics to materials and life sciences as well as medicine. Moreover, ELBE is a testbed for advanced technology developments within the Research Field Matter as well as for applications in radiotherapy in the Research Field Health. The leading high-power laser platform provided at ELBE is dedicated to advanced plasma accelerator and radiation source development with emphasis on low repetition rate but ultimate peak current and a very high stability. It is a well-suited base for the development of compact laser plasma accelerators as alternative to present conventional accelerator systems for radiotherapy. In order to characterize the effect of the intense pulsed radiation on biological systems, interdisciplinary radiobiological studies are conducted together with OncoRay. The principle suitability of the laser plasma source can be demonstrated using the dose-controlled irradiation of living cells or tissues.

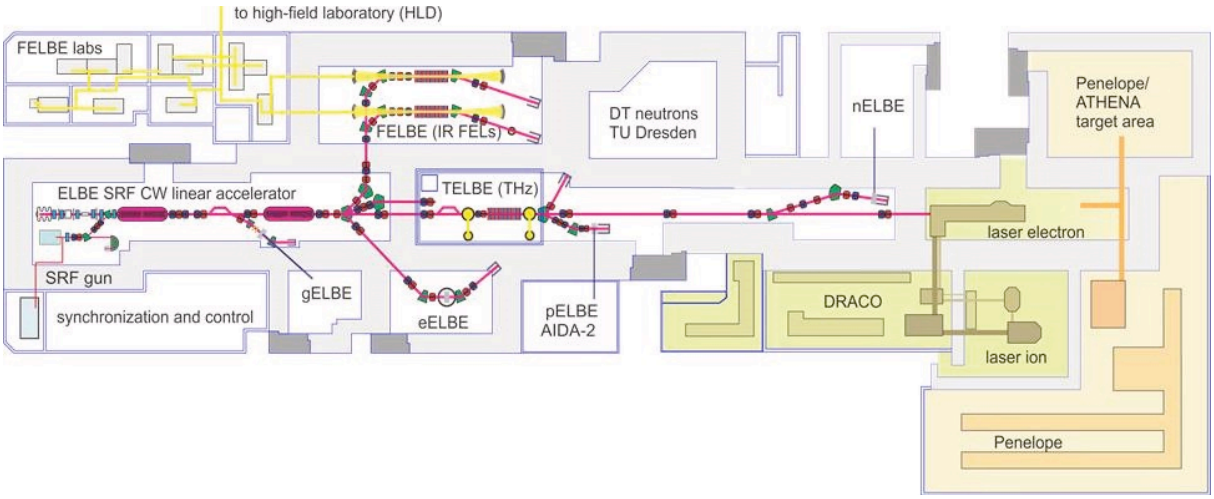


Figure 3.7 Layout of ELBE accelerator and beamlines: IR FELs (FELBE), superradiant THz (TELBE), positrons (pELBE), Bremsstrahlung, (gELBE), neutrons (nELBE), and PW lasers (DRACO and PENELOPE)

Moreover, detectors and electronics for radiation therapy (e.g. based on prompt gamma ray timing), which are developed in collaboration of the Institute of Radiation Physics and the OncoRay can be tested at ELBE. HZDR works on the concept for a successor of ELBE named DALI, the Dresden Advanced Light Infrastructure (operations planned for 2031). This facility, mainly focusing on the application of THz, ultrafast electron radiation and positrons will open up new possibilities, also in life science and medicine. A full conceptual design report will be finished in the summer 2023.

3.1.8 Proton therapy Dresden

HZDR's Institute of Radiooncology – OncoRay is situated at the campus of the Faculty of Medicine of the University Hospital Carl Gustav Carus, in one building with the proton therapy facility (University Proton Therapy Dresden) and the Department of Radiotherapy and Radiation Oncology of the university hospital. This enables the institute to effectively conduct translational research from laboratory and into clinical application. In detail, the research in clinical and translational radiation oncology at HZDR focuses on:

- the development of biologically individualized radiotherapy using modern imaging technologies and the definition of tumor-specific biomarkers for prediction of treatment response and future individualized treatment decisions;
- image-based adaptive radiotherapy as well as biology-based target volume definition, including the investigation of 3D/4D imaging techniques for high-precision radiation therapy in moving tumors and development of new concepts in the field of MRI-based radiation therapy planning and delivery;

- the development and scientific evaluation of high-precision methods for proton therapy in preclinical/translational as well as in clinical studies with the aim of a fast transfer into clinical application;
- the exploration of novel methods such as prompt gamma ray timing and development of clinically applicable instruments for precisely assessing the range of proton beams in the patient's body during radio-oncological treatments;
- the further development of laser-accelerated particle therapy concepts together with HZDR's Institute of Radiation Physics and understanding of the consequences of laser-driven, ultrashort-pulse particle beams with respect to detection, dosimetry, radiobiological effects and delivery as therapeutic beams.

For these goals, next to the clinical proton therapy facility the scientists have access to a large proton experimental room, dedicated animal breeding and animal experiment areas including a preclinical platform for imaging (ultrasound, X-ray, CT, optical imaging, PET/MRI) and an in-house developed 3D image-guided small animal irradiation device (Figure 3.8). Moreover, fully equipped radiobiological laboratories and a clinical-preclinical structure for the storage of biomaterial from patients.

Figure 3.8 Picture of treatment room of the University Proton Therapy Dresden (left) and the experimental proton room with two horizontal beam lines (right).

3.1.9 ZRT

The Center for Radiopharmaceutical Tumor Research (Zentrum für Radiopharmazeutische Tumorforschung, **ZRT**) at HZDR is part of the Institute of Radiopharmaceutical Cancer Research, which works on an interdisciplinary basis to develop and evaluate radioactive drugs (in short: radiopharmaceuticals) both for diagnostic applications in molecular imaging and for targeted endoradiotherapy, also called radioligand therapy. For this work, the ZRT provides its unique research infrastructure (Figure 3.9).

Figure 3.9 Impressions of the ZRT at HZDR

In particular, the following facilities are located here under one roof:

- a 30 MeV high-current proton cyclotron, which makes non-standard radionuclides accessible for tracer development;
- state-of-the-art laboratories for work in the fields of radiochemistry, non-radioactive and medicinal chemistry, biochemistry and biology;
- laboratories for tomographic and optical imaging of small animals (PET/CT, PET/MR, SPECT, OI, MR);
- a laboratory animal facility designed according to the latest standards;
- a radiopharmaceutical production unit in accordance with GMP (Good Manufacturing Practice) standards for the provision of radiopharmaceuticals for clinical use;
- a high-performance IT infrastructure for processing computationally intensive tasks in the field of quantitative molecular small animal and human imaging.

Complementary to the ZRT, there is an 18.5 MeV cyclotron and laboratory areas for tracer development and evaluation in the (neuro)oncological field at HZDR's campus in Leipzig. In addition, exclusive access is granted to corresponding laboratories on the campus of the University Hospital Dresden for the development of immunotherapeutics via its Department of Radioimmunology.

The concentration of a very efficient, multidisciplinary infrastructure represented by the ZRT is an essential basis for the research focused on translational research in the field of theranostics, where radiotracers for diagnostics and non-invasive imaging as well as novel combined endoradio- and immunotherapeutics for the treatment of tumor diseases are developed and evaluated.

3.1.10 GSI accelerator complex

The GSI Helmholtzzentrum für Schwerionenforschung in Darmstadt operates a unique set of accelerators for heavy ions. Researchers from around the world use this facility for experiments that help them make fascinating discoveries in basic research. In addition, they continually develop new applications. The current accelerator complex is shown in Figure 3.10, where it is visible the ion source, the low- (UNILAC) and high- (SIS18) energy accelerators, the storage ring ESR, and the fragment separator (FRS).

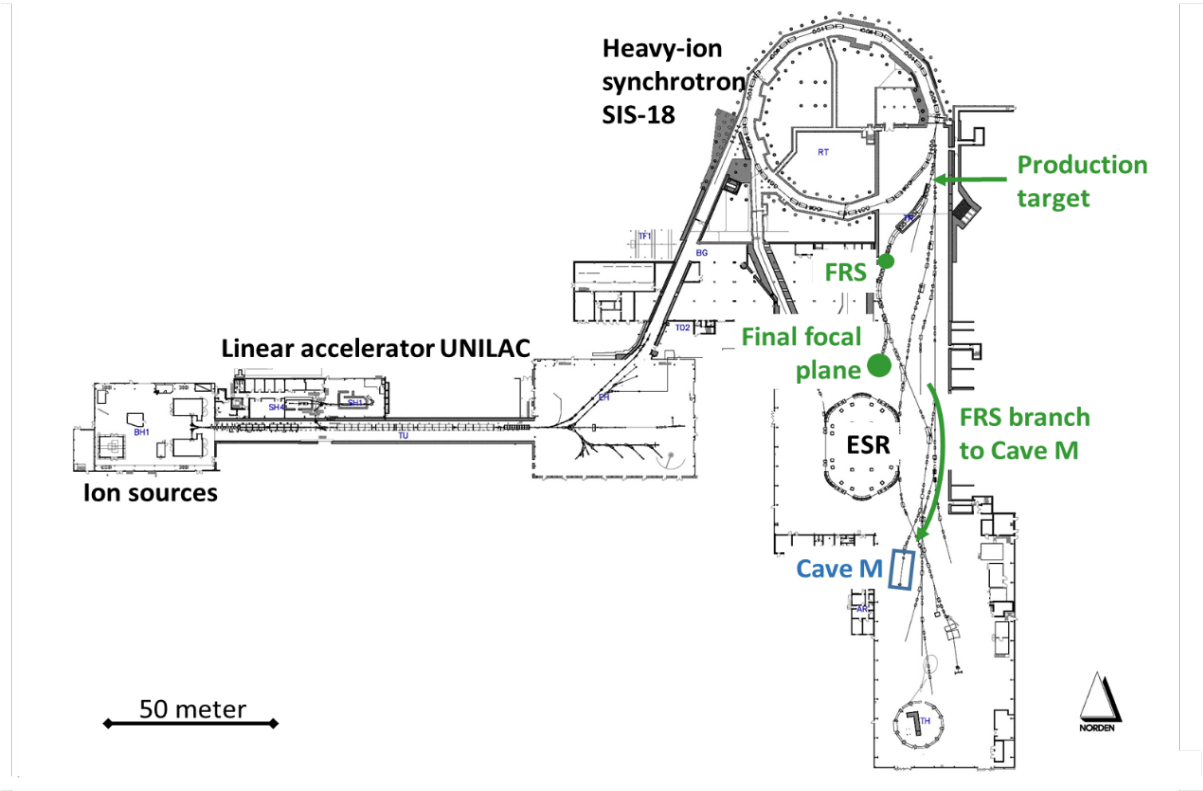


Figure 3.10 The GSI accelerator complex in Darmstadt

While the primary goal of the facilities is nuclear physics basic research, target station dedicated to biological effects of heavy ion radiation are present at UNILAC (X6) and SIS18 (Cave A and M). Cancer therapy and space radiation research are mostly using the high energies branch of the SIS18 synchrotron (Figure 3.11), whose numbers are summarized below.

- 216 m: The SIS18 has a circumference of 216 meters.
- 18 Tm: magnetic rigidity of the accelerator is 18 Tm, which allows accelerations of protons up to 4.5 GeV and heavy ions up to ~1 GeV/n
- 92 elements: The SIS18 can accelerate ions of all natural chemical elements of the periodic table – from hydrogen to uranium.

- 270,000 km/s: Ions coming from linear accelerator UNILAC can be accelerated to up to 90 percent speed of light with the SIS18.
- 80,000 V: Ions in the SIS18 are accelerated by a voltage of 80,000 volts in the accelerator structures during every circulation.
- 416,000 circulations: The ions are accelerated in one second and cover a distance of 90,000 kilometers, that corresponds to 416,000 circulations in the ring.
- 32 billion particles: At no other accelerator as much medium-charged uranium ions can be accelerated as at the SIS18.
- One billionth Pascal: An ultra-high vacuum is a prerequisite for the acceleration. So ions almost never collide with particles in the air.
- Four experiments: With the beam coming from the SIS18 up to four experiments can be supplied in parallel in different target stations.

Figure 3.11 The GSI ring accelerator SIS18.

GSI has pioneered carbon ion therapy in Europe, with the pilot project when 440 patients were treated 1997-2008 under the medical supervision of the University of Heidelberg. The patients were treated in Cave M (Figure 3.12), which is now used for research in heavy ion therapy with a multi-scale model system approach (cells, tissues, organoids, animals). The former patient visit rooms were re-converted in 2008 in tissue culture laboratories with ESA funding to support the IBER project (see Section 2.1.4) and a new large animal facility is currently under construction to expand the use of rodents as model system in pre-clinical and space radiobiology. Most space-related experiments are performed in the Cave A (Figure 2.8), where generally Fe-ions at 1 GeV/n are used for simulation of the GCR. SIS18 is the only European accelerator able to reach this high-energy and therefore an irreplaceable tool for simulation of cosmic rays for ESA.

Figure 3.12 The GSI medical vault (Cave M) receives the heavy ion beams from the SIS18 synchrotron.

The GSI complex is currently operating on the so called FAIR-phase-0, i.e. in preparation for the opening of the new FAIR ring SIS100 (see Section 3.2.4). This includes an upgrade in the intensity that has already allowed to perform experiments with heavy ions in FLASH condition (see Section 2.2.3) and to reach intensity of secondary, radioactive beams high enough to treat a tumor in an animal, which is the main motivation of the ERC BARB AdG (see Section 1.3). In the framework of the BARB experiment, in July 2021 had been commissioned a new line connecting the FRS to Cave M: Figure 3.10 shows the position of the line in the GSI map, and Figure 3.13 the details of the line. With the new line, biological experiments can be performed in the medical cave with the beam coming directly from the fragment separator.

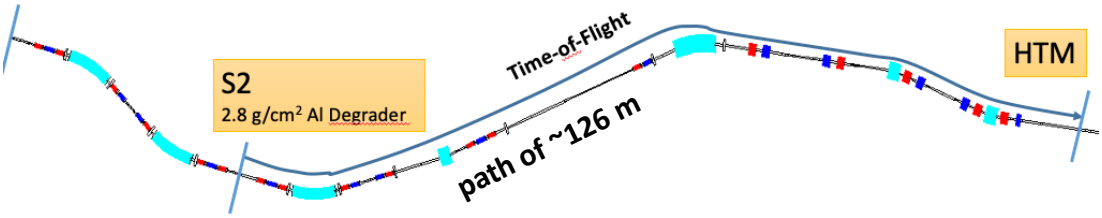


Figure 3.13 The new beamline connecting the FRS to Cave M (HTM). Separation of the isotopes is done by the Brho-dE-TOF method at S2. The secondary beam has then to be directed into Cave M. This gives the unique possibility to irradiate biological samples and animals with high-intensity radioactive ion beams.

3.1.11 PITZ

The Photo Injector Test facility at DESY in Zeuthen (PITZ) was originally built for the development and optimization of high brightness electron sources for high duty cycle, short wavelength, high power free electron lasers (FELs) like the European XFEL and its precursor, the Free electron LAS in Hamburg. Both FEL facilities are equipped with electron sources from PITZ (see Figure 3.14) and provide reliable user

operation with unique research capabilities for a wide spectrum of research directions, including also structural dynamics which for example is also important for drug and vaccine developments. Through the 2 decades long accelerator R&D work at PITZ for the benefit of the users of these FEL facilities, the beam parameter range for high brightness electron beams that is available at PITZ is worldwide unique.

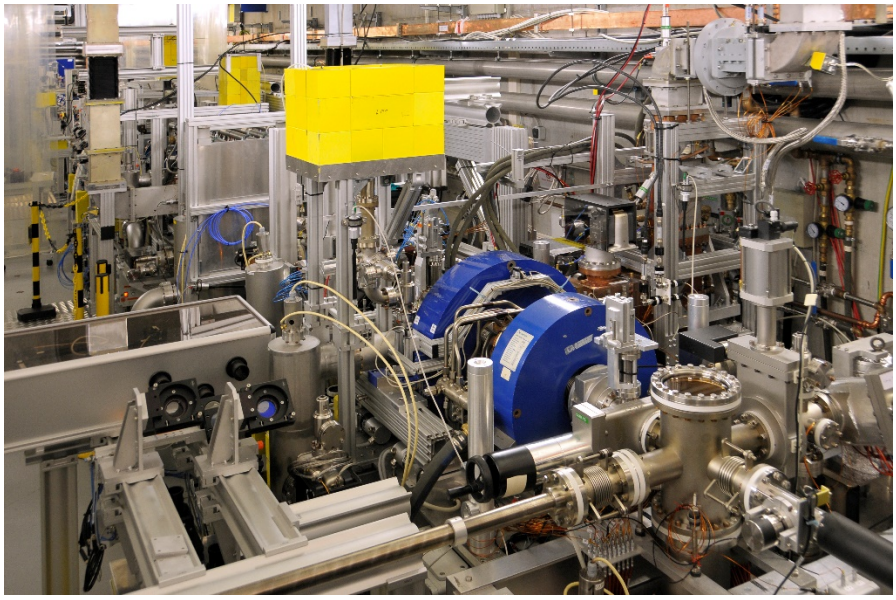


Figure 3.14 The high brightness electron beam source at PITZ surrounded by 2 blue solenoid magnets. Upstream in the foreground on the right there the photo cathode exchange system is shown and downstream of the electron source lots of beam diagnostics and a further accelerating cavity are installed which allow a detailed characterization of the beam with a total beam energy of 22 MeV.

Recently it became clear that the electron beam parameters available at PITZ would also be a great opportunity for worldwide unique R&D on FLASH radiation therapy and radiation biology. The PITZ capabilities can be summarized as follows:

- trains of electron bunches where the bunch trains can have a length of up to 1 ms and the repetition rate of the bunches in the train is up to 4.5 MHz, i.e. up to 4500 electron bunches can be provided in 1 ms
- the bunch trains can be repeated with up to 10 Hz
- the individual bunches in the bunch trains can have
    - a bunch charge from <fC up to 5 nC
    - a bunch length of 0.1 to 60 ps
    - a spot size down to ~100µm (depending on bunch charge, e.g. below 100pC)
- In addition, a kicker system can be used to distribute the up to 4500 bunches within 1 ms over the tumor area, thus ‘painting’ the tumor within 1 ms.
- Focusing and defocusing magnets can be used to change the spot size of the bunches and to image the beam distribution from the beam exit window to the sample/phantom/patient. When the exit window is covered with a luminescence layer this would allow an online monitoring of the transverse beam distribution which corresponds to the transverse dose distribution at the sample entrance.

To illustrate the beam parameter range available at PITZ it can be compared with those beam parameter combinations which have shown a successful FLASH treatment experimentally (see Figure 3.15).

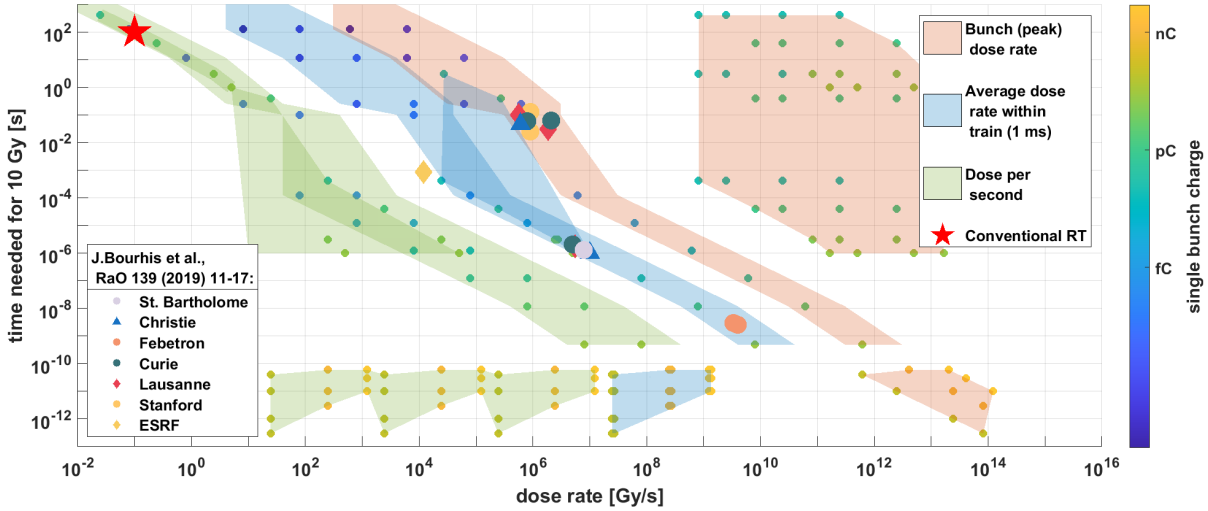


Figure 3.15 The worldwide unique parameter space available at PITZ in comparison with state-of-the-art FLASH radiation therapy and conventional radiation therapy. The vertical axis shows the time needed to deliver 10 Gray and the horizontal axis shows the dose rate. The conditions to obtain reproducible FLASH effects as summarized by the publication (Bourhis et al. RaO 139 (2019) 11-17) are included as big markers in the center of the plot and a star is added to represent conventional radiation therapy in the upper left corner. The colored areas in red, blue and green show the parameter space available at PITZ: The red area shows the bunch or peak dose rates, the blues area shows the average dose rates within the bunch trains and the green area shows the dose rate averaged over a full second. The color of individual dots represents the bunch charge that was assumed for the individual PITZ operation parameter set. The dose was estimated for 20 MeV electron beam in water and a 1mm³ irradiation volume.

From Figure 3.15 it gets clear that a worldwide unique beam parameter range for FLASH radiation therapy and radiation biology is available at PITZ. The parameter space available on the right and lower part of the plot is yet unexplored and unexploited territory and gives potential for further improvement of FLASH radiation therapy in future.

Currently the existing beamline in PITZ is extended by a switchyard magnet to install a very basic version of an R&D beamline for FLASH radiation therapy and radiation biology at PITZ. In 2022 first experimental tests started, including tests of dosimeters at high dose rates. A design for a full R&D beamline as a basis for an R&D platform for FLASH and VHEE radiation therapy and radiation biology has been done but requires external resources for its realization (see FLASH*lab*@PITZ in section 3.2.5).

3.1.12 ARES

At the Accelerator Research Experiment at SINBAD (ARES) at DESY in Hamburg also beam experiments with short electron bunches are possible. The ARES

linac currently can provide single electron bunches with a repetition rate of 50 Hz and a beam energy of up to 160 MeV. Each bunch can have a bunch charge up to 200pC and a bunch length in the range of <fs to few ps. Upgrades for higher bunch charges and the generation of multiple bunches are planned. The beam energy of up to 160 MeV already now allows to study the dose delivery in tissue at larger depths under VHEE conditions.

3.1.13 DKFZ facilities

For radiology and radiotherapy developments, DKFZ has recently completed a new 5 story building for research and developments in radiology and radiation oncology (Radiologisches Forschungs – und Entwicklungszentrum, REZ). Within REZ, several hundred researchers are working in the divisions for radiology, radiation oncology, as well as for radiation biology, medical physics and radiation chemistry and data sciences.

Within REZ, DKFZ operates a variety of radiological imaging devices for diagnostics of cancer patients. Among them are single and dual energy, as well as spectral X-ray CT scanners, MRI scanners with 1.5, 3 and 7T field strength, an MRI hyperpolarization unit and several hybrid devices, like a PET-CT and the latest high sensitivity, full-body PET-MR scanner.

For radiation oncology applications, a 200m^2 bunker exists in the REZ building, which is about to be completed in the first quarter of 2022. Here, a novel treatment device for AI-guided adaptive radiotherapy will be located next door to a 3T MRI of latest technology, to investigate the potential of off-line MRI guided radiotherapy with a special focus on biology guided RT, i.e. treatment plan adaption based on repeated functional MRI and PET during the course of therapy.

DKFZ together with KIT also hosts the Helmholtz Information and Data Science School for Health (HISDDSS4Health), which aims at the training of young data scientists in the area of medical applications, esp. in cancer diagnosis and therapy. This field is currently undergoing a tremendous growth and becomes more and more important for radiology and radiotherapy, in order to make full use of the potential of the additional image information available today with modern diagnostics and IGRT approaches.

Together with the department for radiation oncology of the university medical center (UMC) Heidelberg and the Heidelberg Ion Beam therapy center (HIT), the research divisions focusing on radiation oncology at DKFZ form the Heidelberg Institute for Radiation Oncology (HIRO). Within HIRO, the researchers at DKFZ also have access to the HIT facility for research purposes. HIT is the first European ion beam therapy center and was established by joint efforts of the three Helmholtz centers GSI, DKFZ and HZDR under the lead of the UMC Heidelberg, to transfer the pilot project at GSI into the clinic. HIT has a dedicated research area, including labs for dosimetry and radiation biology as well as animal facilities. Beams of protons and carbon ions are used for routine treatments, while recently the first patient worldwide has been treated

here with a scanned beam of Helium ions. For research purposes, also Oxygen ions are available. The HIT facility is a focus point of many joint research projects of HIRO and DKFZ researchers.

Within HIRO, the Heidelberg consortium for MR-guided therapy has been established, which acquired the first hybrid device for MR-guided radiotherapy (an MR-Linac) in Germany through competitive funding. Recently, the Heidelberg consortium for MR-guided radiotherapy obtained additional funds and installed an in-beam MRI at the fixed experimental beam-line of the Heidelberg ion beam therapy center (HIT) and an additional off-line MRI scanner (3T) next to one of the patient treatment rooms. Here, the research teams of the UMC Heidelberg, HIT and DKFZ are performing basic research for MR-guided radiotherapy with proton and ion beams and prepare the translation of techniques needed for MRI-guided treatments from X-rays to particles.

3.1.14 HZB cyclotron

The Helmholtz-Zentrum Berlin für Materialien und Energie operates two accelerator complexes: on one site the electron storage ring BESSY II in Adlershof and the cyclotron accelerator complex in Wannsee (Figure 3.16), primary used for the treatment of uveal melanoma as well as accompanying research and development. Experiments for, among others, dosimetry, beam delivery, radiation hardness tests, and geology are performed. The main accelerator is a k=130 isochronous separated-sector cyclotron which acts as an energy multiplicator with a fixed factor of 17. There are two electrostatic accelerators as injectors available, and they are chosen in dependence of the requirements.

The highly adjustable high-frequency system and the variable magnetic configuration of the cyclotron permit a kinetic energy ranging from 1 MeV/u up to 72 MeV/u. The cyclotron provides a pulsed beam with a repetition rate between 10 MHz and 20 MHz (cyclotron frequency) and a pulse width of less than 5 ns. In respect to the treatment of uveal melanoma the high repetition rate can be seen as quasi-DC beam. Adding a pulser to the cyclotron allows to manipulate the time structure of the beam over a wide region down to single pulses with a maximum repetition rate of 2 MHz. Thus, experiments with different time structures can be carried out. Three target stations are available:

- treatment room: The standard beam here is 68 MeV protons with beam intensities below 3 nA. The beam size is 38 mm in diameter with an excellent homogeneity of 97% over the irradiated area.
- experimental station: On this station either a broad or a focused beam may be used. The time structure of the beam ranges from singles pulses over variable pulse trains to quasi-DC. The intensity can be varied between 0.1 pA to 1.5 µA. Protons or other light ions are available.
- for high beam intensities a station in the cyclotron vault is available.

About 85% of the beam time are used for the treatment of uveal melanoma, 8% for accelerator R&D, 5% for medical physics and dosimetry, and 2% for radiation hardness tests.

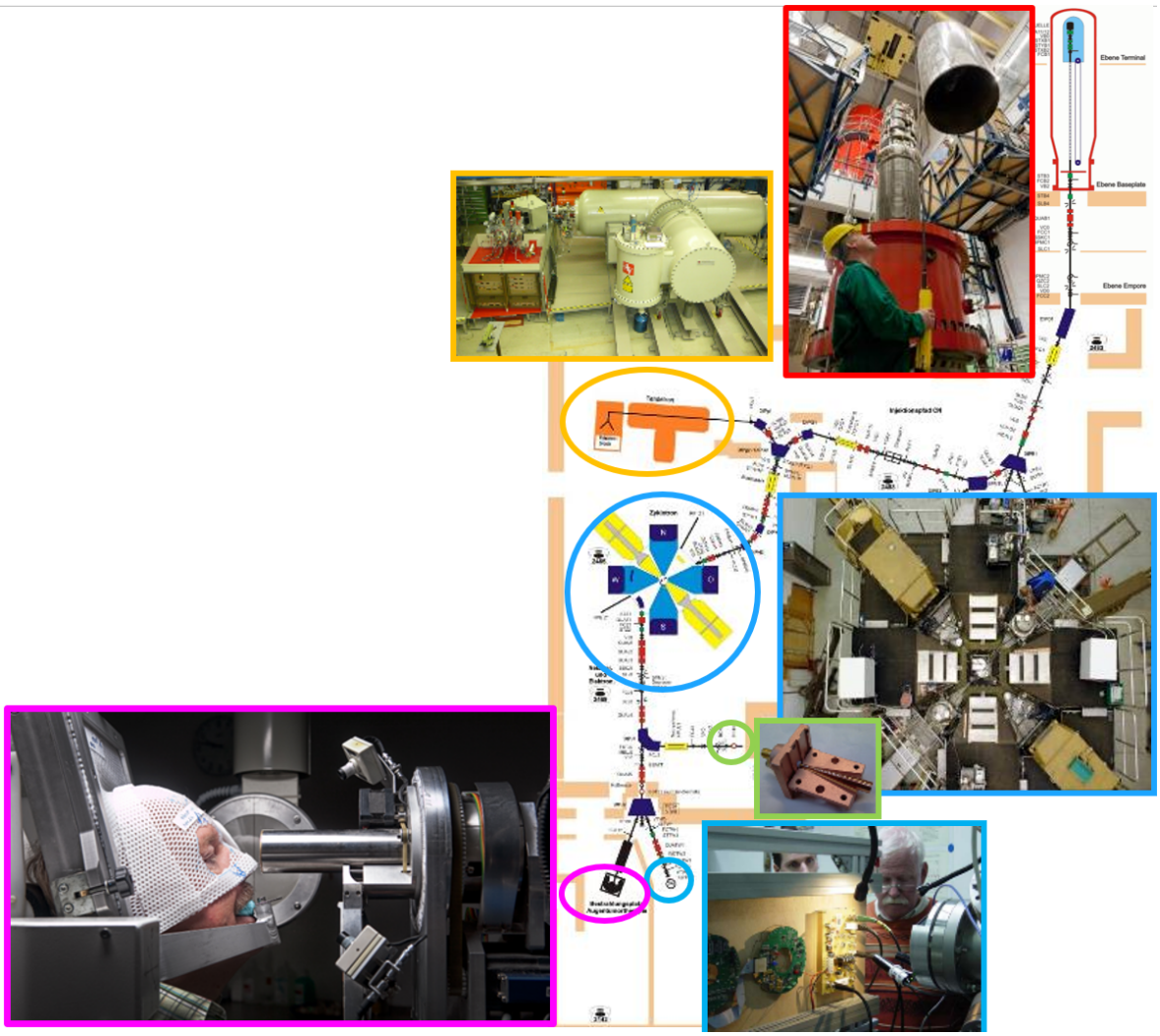


Figure 3.16 The HZB cyclotron accelerator complex and its target stations. Red: 6 MV Van-de-Graaff injector; orange: 2 MV Tandetron injector; blue: k=130 cyclotron; green: target station in cyclotron vault; cyan: flexible target station for dosimetry and radiation hardness tests; magenta: treatment room.

HZB is Germany's first proton therapy facility (since 06/98) and unique in its technical capabilities. Over the past years, more than 230 patients per year have been treated in 12 therapy blocks. Experiments include, among others, the study of side effects of proton therapy. A set-up for the irradiation of single mice eyes under FLASH conditions has been installed. Thus, the second eye of the individual animal may serve as reference. Furthermore, high dose rate dosimetry is investigated (Figure 3.17).
Radiation hardness tests are performed for the German aerospace center DLR, universities, research institutes, and industry. A cobalt-60 source is also available on site, enabling additionally irradiations with gamma rays with an energy of 1.17 MeV and 1.33 MeV up to 100 Gy/h, without inducing nuclear reactions in the samples.

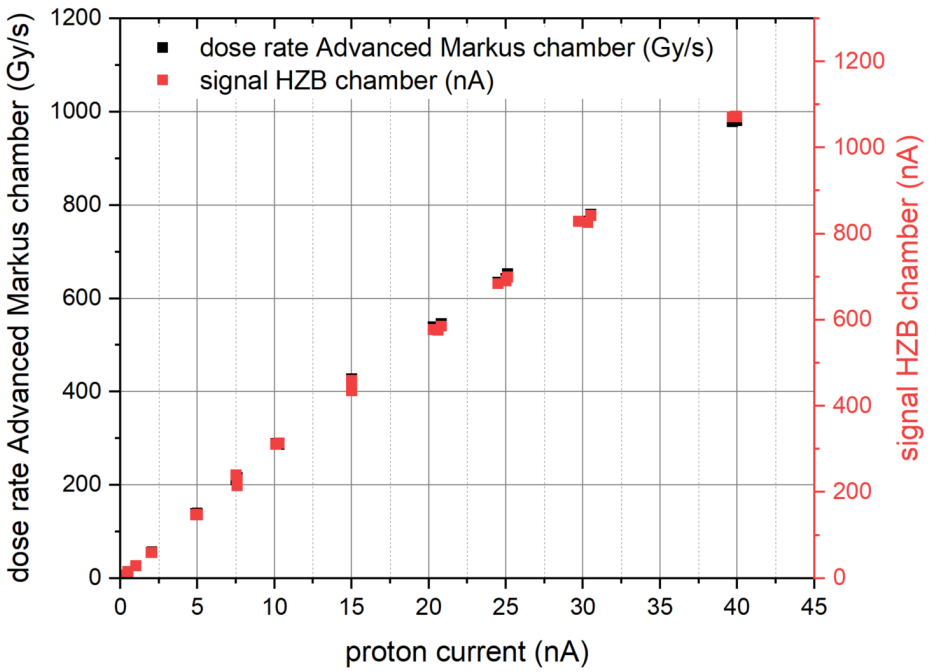


Figure 3.17. Signal from the HZB transmission ionization chamber as a function of proton beam current in comparison to an Advanced Markus chamber (non transmission). Both chambers are working linearly up to 400 Gy/s.

3.1.15 High-Power Laser Systems at HI-Jena

The Helmholtz-Institute Jena operates two high-power laser systems, JETI200 and POLARIS, which deliver laser pulses with durations of several 10s of fs reaching peak intensities of several 100 TW (Figure 3.18). The laser pulses generated by these systems are sent into two specially assigned, radiation shielded target areas equipped with all necessary diagnostics. By focusing the laser pulses delivered by the JETI200 or POLARIS systems on different type of matter, several novel scenarios for particle accelerators are investigated and characterized. The generation of ultra-short (several fs), high-charge (up to several 100 pC) electron pulses with energies in the range from several MeV to more than 1 GeV is routinely possible. Furthermore, the generation of ultra-short (fs to 10 s of ps) high-charge (pC) proton pulses with kinetic energies up to 50 MeV is investigated. Through secondary processes, ultra-intense x-ray pulses with photon energies up to several 10s of keV and few-fs pulse duration can be generated. The experimental research program is supported by multi-dimensional numerical simulation tools, which can model the relevant physical phenomena of the interaction. Building upon a long-standing expertise in Jena, the generated pulses of ionizing radiation can be characterized with respect to their spectrum, angular distribution, delivered dose, etc. using a suite of carefully adapted detectors and diagnostics.

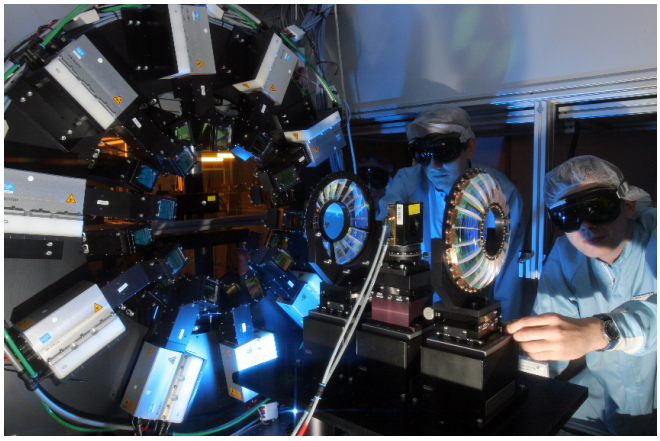


Figure 3.18 The two high-power laser systems JETI200 (left) and POLARIS (right) operated by HI-Jena. The laser pulses generated by these systems are then delivered to two different target areas equipped with diagnostics and detectors for the generated ionizing radiation (electrons, ions, x-rays).

3.2 NEW INFRASTRUCTURES IN THE COMING 5-10 YEARS

New radiation research infrastructure are summarized in Table 3.3 and described in detail below.

Infrastructure	Helmholtz Center	Start of operation	Topics
ZRS**	HZDR	2031	radioecology, radionuclides, radiation
HOVER*	HZDR/KIT/FZJ	2026	decommissioning technologies, behaviour of materials in interim storage, behaviour of radionuclides in final repositories and ecosphere
PT2030**	HZDR	2031	proton therapy
FER*	DKFZ	2024	radiopharmaceutics, imaging, theranostics
FAIR*	GSI	2026	heavy ion therapy, space radiation research, high energy particle radiography, FLASH irradiation, radioactive ion beams therapy, theranostics
FLASH*lab*@ PITZ **	DESY	2023	R&D platform for FLASH irradiation studies, FLASH and VHEE radiation therapy, radiation biology
HBS**	FZJ	2028	neutron irradiation, radioisotope production
DALI**	HZDR	2031	accelerator and laser-driven radiation sources; electron and positron beams, radiobiological experiments, high intensity superradiant THz radiation, laser-driven ion acceleration

Table 3.3 Facilities under construction (*) or in planning stage (**) in HGF at April 2022.

3.2.1 ZRS

The new Center for Radioecology and Radiation Research (Zentrum für Radioökologie und Strahlenforschung, **ZRS**) at HZDR planned for realization from 2027 to 2031 is dedicated to the research on the effects of radionuclides on the environment (Figure 3.19); a field of great social relevance that has not been represented in the Helmholtz association so far.
Core concerns of radioecology and radiation research are the detection, explanation and health-relevant evaluation of the effects of radionuclides on biological process chains. Experimental data obtained on biomolecules are complemented by theoretical analyses using molecular dynamics. For even more complex systems, such as living organisms and microbial communities, innovative coupling techniques are needed to quantify radionuclide effects on their metabolism. Here, the immune system of plant cells will be used as a model system to understand the stress responses of cells to radionuclides (e.g. formation of metabolites) at the molecular and cellular level. Instead of mainly using statistical methods to investigate the effects of radionuclides (RN) on the environment, ZRS, with its radioactive control area with biological safety level and its molecular biological and chemical equipment, will open up the topic through basic scientific research and by elucidating processes at the molecular and cellular level.

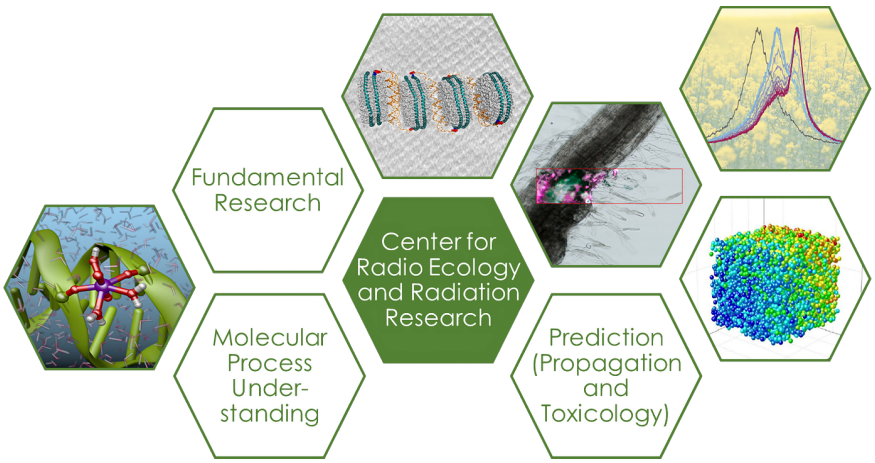


Figure 3.19 The ZRS approach

Complemented by the Rossendorf Beamline (**ROBL-II**) at ESRF, this approach can help to link radiation-research-related activities in the Research Fields Energy, Matter and Health. Moreover, intensive collaboration with the Helmholtz Center UFZ is planned to reveal synergies with the Research Field Earth and Environment. Therewith, the future-oriented work of the ZRS goes beyond reactor safety or repository research and represents a further development of the Helmholtz program NUSAFE.

3.2.2 HOVER

The Helmholtz Research and Technology Platform for the Decommissioning of Nuclear Facilities and the Disposal of Radioactive Waste (Helmholtz Forschungs- und Versuchsplattform zur Entsorgung radioaktiver Abfälle und zum Rückbau kerntechnischer Anlagen, **HOVER**) is a decentralized research infrastructure and is dedicated to advanced scientific investigations and technical developments in the context of the German phase out of nuclear energy. Three Helmholtz partners contribute to HOVER: KIT, FZJ and HZDR, complementing their expertise in different aspects of nuclear waste management under the conditions of extended interim storage and final disposal, for decommissioning of conventional and nuclear facilities and for waste reduction.

At HZDR, HOVER is already in the implementation phase, operations will start in 2026. The focus lies on processes potentially leading to the propagation of radionuclides in the ecosphere. Future research will concentrate on the so-called far field and mesoscale surroundings of a future deep geological repository. This includes, in particular, experiments on the migration and retention of radionuclides in potential host rocks (rock salt, clay rock and crystalline rock such as granite), with soils and within the biosphere. The facility will be equipped with advanced instrumentation to investigate radioactive samples relevant for investigations dedicated to the detailed scrutinization of radio/bio/geochemical processes in different nuclear waste disposal concepts discussed in Germany and internationally. It will comprises various – in their combination unique – characterization and analysis methods to analyze radioactive samples. The laboratory equipment and instrumentation will allow investigating radioactive material properties and radionuclide behavior at different scales and over a span of sensitivities.

At KIT the installation of the BIM Lab (Building Information Modelling) in a separate building and the construction design of a new building for spectroscopy devices have been started. Important research topics are the development and demonstration of decommissioning technologies for automated procedures to optimize radiation protection for workers and reduction of secondary waste, the long-term investigation of claddings behavior under storage conditions and the enhancement of analysis and quantification of processes for final storage.

At FZJ, HOVER is already in the planning phase, and operations will begin in 2026. The main focus of the Materials Science Laboratory (MSL) for Nuclear Waste Management in Jülich is aimed at the (chemical) behavior of nuclear waste forms and the radionuclides contained therein, addressing fundamental scientific aspects as well as application-oriented issues. The utmost aim of the MSL is the enhancement of the mechanistic process understanding of the stability and reactivity of nuclear waste materials and the behavior of radionuclides under interim storage conditions and conditions relevant to geological disposal, as well as during dismantling of nuclear installations –from the molecular level to the macro-scale.

3.2.3 PT2030

The basic idea of HZDR's **PT2030** at the University Hospital Dresden is to realize, for the first time, a real-time adaptive proton therapy – enabled by a closed, fully automated and AI supported feedback loop of imaging, treatment verification and adaptation in near real time (Figure 2.12). This will bring the clinical advantage of proton therapy to its physical maximum, improve patient survival and/or reduce side effects, and furthermore make proton therapy beneficial for more tumor entities and therefore more patients.

The aim is to develop the physically best possible radiation therapy for application on patients: the advantageous tissue-sparing dose distribution of protons will be combined for the first time with the advantages of online adaptation capability of the treatment, which currently exists to some extent only in dosimetrically inferior photon therapy. The research focus is on further development and integral translation of preclinical prototype-like innovations, techniques, algorithms with AI-enabled decision support into patient applications. This will ultimately result in relevantly improved clinical outcome. Patients with highly changing or moving tumors could better benefit from proton therapy. Currently, research is focused only on isolated component development in the laboratory – the interaction and automated decision-making is nowhere integrally tested and thus made ready for actual application. The implementation of AI-supported decision-making is of utmost importance to speed up the adaption process gradually from days to seconds.

Herewith, a worldwide unique research-clinic hybrid proton facility will be built from 2027 to 2031, where the innovative software and hardware components and their interaction will be integrally tested, further developed and finally enabled for clinical application for the first time. PT2030 will be developed, implemented and operated in close cooperation with the University Hospital Dresden, the medical technology industry and CASUS, the newly founded Center for Advanced System Understanding in Görlitz.

3.2.4 FAIR

The Facility for Anti-protons and Ion research (FAIR) is the new accelerator under construction at the GSI Helmholtzzentrum für Schwerionenforschung in Darmstadt. The current SIS18 synchrotron will become the injector of the new SIS100 accelerator, which at 100 Tm can push heavy ion energy around 10 GeV/n. Moreover, intensity will be up to x10,000 what currently available. The new plan of the facility in Darmstadt, which will go beyond Helmholtz to become fully International with the support of 11 countries, is shown in Figure 3.20. While the official opening of the SIS100 is slated for 2025, research is currently ongoing within the FAIR-phase-0. Research activity at FAIR is structured into four pillars: NuSTAR, CBM, PANDA and APPA. APPA deals with applied research (biophysics and materials research), atomic

and plasma physics. FAIR is a user facility and research is proposed by Collaborations. The Biophysics Collaboration is indeed based at FAIR[33] but, unlike the other pillar collaborations, includes other accelerator facilities and pursues a distributed research program. The biophysics research program at FAIR impose on the experience of the GSI Biophysics Department both in heavy ion therapy and space radiation research. Radiation research at FAIR will continue along the lines already established at GSI (heavy ion therapy and space radiation protection), according to the new opportunities that the SIS100 energies and the upgraded intensities offer (Figure 3.21). The new research programs include the construction of a galactic cosmic ray simulator, high-energy particle radiography, FLASH irradiations with heavy ions, and radioactive ion beams in therapy (BARB; see Section 1.3). The Biophysics Department will benefit in FAIR of a new experimental vault, the APPA cave (Figure 3.22), where especially high-energy space radiation protection experiments will be performed.

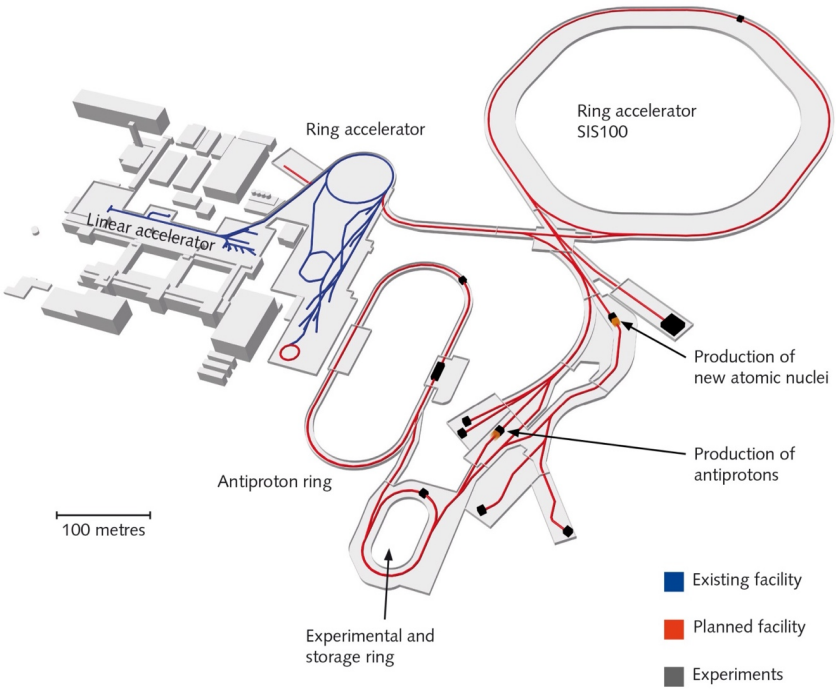


Figure 3.20 The plan of the FAIR facility under construction at the GSI Helmholtzzentrum für Schwerionenforschung in Darmstadt.

There are several facilities worldwide providing high-energy beams for biomedical research. Medical facilities are limited to protons and C-ions with energies up to 400 MeV/n. Higher energies are needed for space radiation protection studies, and currently these studies are limited to the NSRL at BNL in USA and the SIS18 at GSI in Germany. FAIR will be the first facility able to study heavy ions at energies above 1 GeV/n, an important component of the GCR. The development of efficient countermeasures for high-energy heavy ions in the GCR is a mandatory step toward

[33] www.gsi.de/bio-coll

the planned manned mission to the moon and Mars. Therefore, these studies are urgent and highly needed.

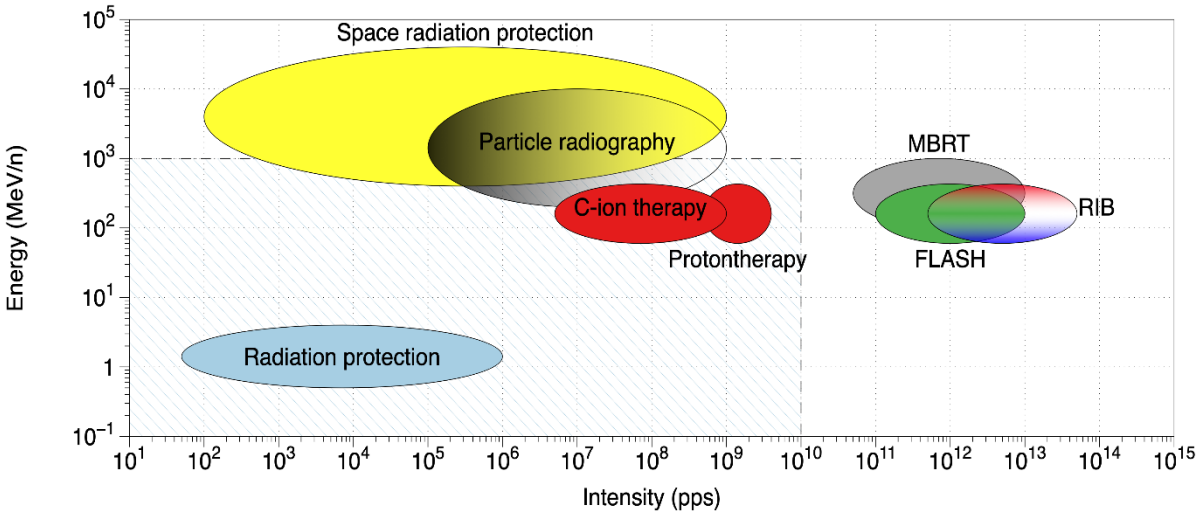


Figure 3.21 Radiation research at new accelerators. The shaded region includes values of energy and intensities covered by the present accelerators. The upgrade in energy and intensity at FAIR offers new opportunities. MBRT=minibeam radiotherapy; RIB=radioactive ion beams, FLASH= high dose-rate radiotherapy. Image from: Patera *et al., Front. Phys*. (2020).

In oncology, even if current facilities cover the range necessary to treat deep tumors in humans, higher energies can be beneficial for imaging. Using the same beam for imaging and treatment would bring therapy in the modern area of theranostics and could facilitate the treatment of moving targets. Theranostics is also an attractive possibility when using RIB for therapy, currently produced at intensity too low for practical treatments. The high intensity at FAIR will make possible to test RIB for simultaneous treatment and beam visualization by online PET. Finally, the high intensity at FAIR offers other unique opportunities. Will it be possible to treat tumors in seconds, thus making particle therapy cheaper and easier, especially when treating moving organs? Is this high dose rate beneficial in widening the therapeutic window, as suggested by FLASH experiments with electron beams? FAIR will give answers to these questions and more. Obviously the potential of the FAIR facilities cannot be translated elsewhere in the present days, but the results in this special facility will drive the technological developments in the next 20 years.

3.2.5 FLASH𝓁𝒶𝒷@PITZ

To provide a worldwide unique R&D platform for FLASH and very high energy electron (VHEE) radiation therapy and radiation biology on the basis of the beam parameter space that is already available at PITZ, DESY and the TH Wildau together with national and international partners have developed a common proposal which is called FLASH𝓁𝒶𝒷@PITZ. This proposal includes an upgrade of the PITZ facility with the installation of a dedicated R&D beamline containing all the necessary equipment

to allow an in-depth understanding of the recently discovered FLASH effect and the construction of an animal facility at the TH Wildau which is just 3.6 km apart. It also includes a local biology/animal laboratory at the DESY site in Zeuthen and in the second phase of the project a beam energy upgrade at PITZ from currently 22 MeV to 250 MeV which will allow to treat deep seated tumors.

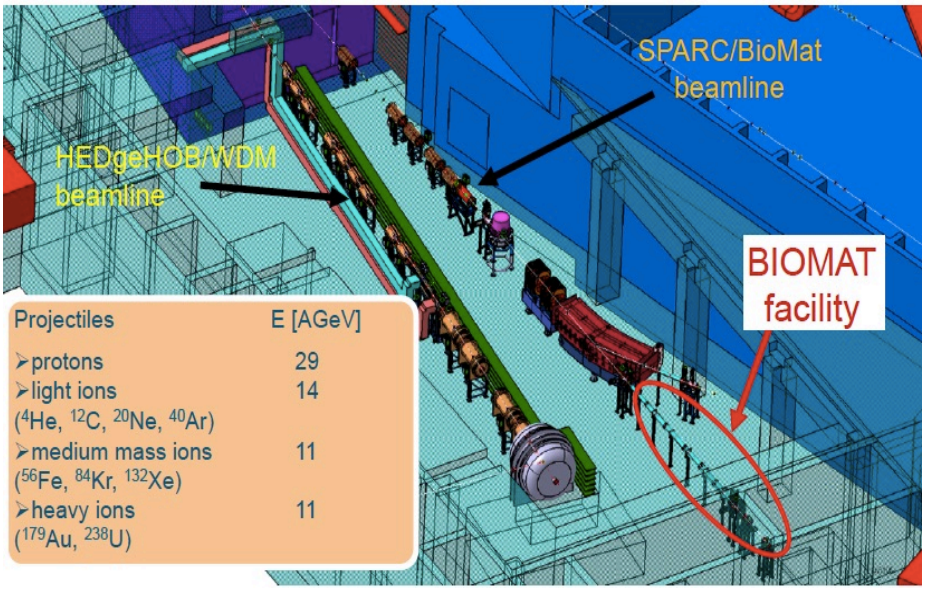


Figure 3.22 Layout of the future BIOMAT cave that will be used at FAIR for the biomedical applications within the APPA experiment. The vault includes the beamline for plasma physics and the SPARC experiment. Maximum energies of the beam that will be transported in BIOMAT are indicated in the insert. Image from: Durante *et al., Phys. Scr.* (2019).

Figure 3.23 shows a schematic timeline of the project which is organized in four work packages which are not sequential but overlappingly address different goals that are interdependent. The first work package is to build a first version of an FLASH R&D beamline at PITZ, and to perform the necessary beam dynamics and dosimetry experiments with phantoms and non-biological samples. Computer modelling generating in silico predictions of FLASH effects covering all stages of a radiation response is also part of this work package. In the second work package as preparation for the subsequent in vivo experiments, in vitro studies of the biological effects and mechanisms taking place during high dose rate irradiation will be studied using biological samples like organic molecules, cells, tissue and organoids. In the third work package, in vivo studies of biological effects of FLASH radiation therapy will be studied on simple and more complex animal models with beam energies up to 22 MeV. The overlapped addressing of these three work packages will allow a most effective use of the accelerator and to obtain progress as quick as possible. In the fourth work package which is planned to be started in parallel due to the long lead time of major accelerator components, a beam energy upgrade up to 250 MeV is realized at PITZ which allows irradiation of deep-seated tumors, better control of the irradiation volume and VHEE radiation therapy studies. The experiments here will be done with thicker samples like

body phantoms, biological tissue and animal models, and the preparation of applying the new technology for treating humans is started.

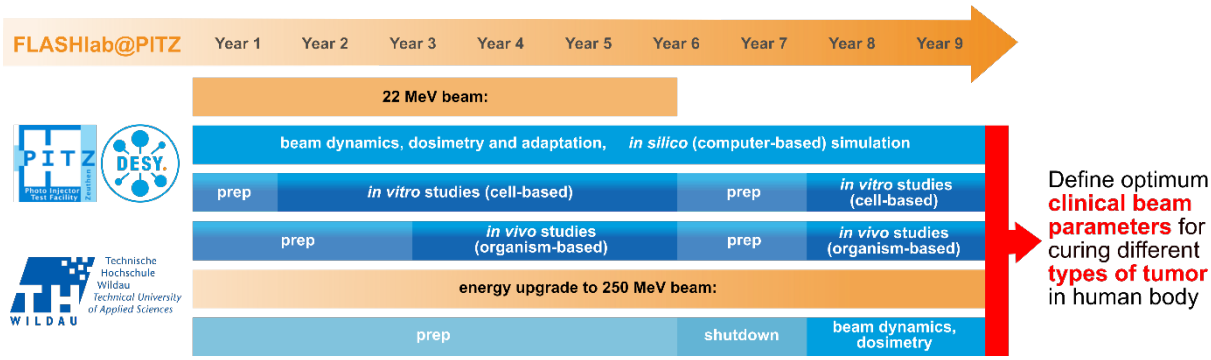


Figure 3.23 Schematic time structure of the four work packages of FLASH*lab*@PITZ. More details on the work packages is given in the text.

The goals of FLASH*lab*@PITZ are to significantly contribute to the understanding of the FLASH effect and to define the optimum beam parameter sets for clinically treating different types to tumor at different locations in the human body. Once these optimum beam parameters for specific therapies are known, the advances in accelerator technology can be used to shrink the needed accelerator infrastructure for the specific treatment so that handy systems can be developed that can be installed in hospital worldwide. This medical technology is an enormous economic market and the advances in laser plasma acceleration (LPA) technology can be a key in shrinking the system size. DESY is also one of the world leading players in LPA and therefore a strong synergy in the LPA developments and radiation biology can be expected.

To push this whole activity forward external resources are urgently needed to take benefit of these unique capabilities in Germany and put ourselves in a leading position in this enormous health market. This would allow to capitalize on the developments done in Germany and secure a world competitiveness for years. DESY is extremely open for extending its cooperation with all relevant partners in the HGF, the international FLASH and VHEE community and the medical partners in hospitals.

3.2.6 FER

At DKFZ a new Research and Development Center for Radiopharmaceutical Chemistry (FER) is scheduled to open in 2024, which aims at provision of innovative GMP grade substances for academic driven multicenter trials. Based on DKFZ's track record in developing effective PSMA theranostics which is now validated in several international clinical trials, new approaches in various cancer types will be developed. In this context, novel bimodal imaging tracers for PET, SPECT and fluorescence optical technologies will be developed for pre-operative staging of cancer but also for intraoperative image-guided surgery. In addition to directly targeting tumor cells also new classes of theranostic radiotracers will be explored, which address cells of the tumor microenvironment and show both high intratumoral uptake and high-contrast.

3.2.7 HBS

The project of Jülich Centre for Neutron Science (JCNS) at Forschungszentrum Jülich for a High Brilliance accelerator-driven neutron Source (HBS) aims to develop a unique infrastructure for neutron scattering, neutron analytics, irradiation, and isotope production[34]. The facility (Figure 3.24) could be used in a multitude of scientific disciplines such as physics, chemistry, biology, geology, engineering science and health. Optimized for brilliance, providing small, intensive beams for customized applications, the HBS neutron facility will facilitate the use of neutron scattering, neutron analytics and neutron irradiation for topical research on nanostructures via biological materials to energy materials systems and in radiation research and health applications.

A detailed Conceptual Design Report which outlines the capabilities and options of the HBS facility has been published recently. A Technical Design Report for the realization of this new infrastructure is in preparation and will be published in 2023. The HBS facility will offer access to new capabilities and will establish novel methods for the production and provision of radiodiagnostic isotopes as well as irradiation of materials.

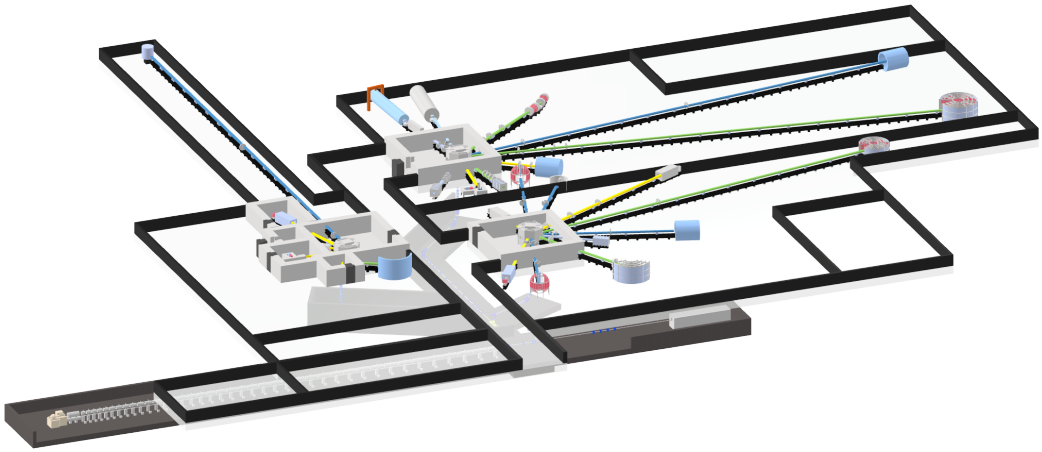


Figure 3.24 Basic layout of the accelerator-based high brilliance neutron source facility (HBS).

[34] https://www.fz-juelich.de/jcns/EN/Home/home_node.html
https://www.fz-juelich.de/jcns/jcns-2/EN/Leistungen/High-Brilliance-Neutron-Source/_node
https://www.fz-juelich.de/SharedDocs/Downloads/JCNS/JCNS-2/EN/Conceptual-Design-Report-HBS.pdf?__blob=publicationFile

3.2.8 DALI

The Dresden Advanced Light Infrastructure (DALI) is the infrastructure planned to become successor of ELBE (see Section 3.1.7). This facility, mainly focusing on the application of THz, ultrafast electron radiation and positrons will open up new possibilities, also in life science and medicine. Moreover, the DALI hall will also contain the high-power laser platform currently integrated into the ELBE center. Operations for DALI are foreseen from 2031 on. The concept of the facility is under fundamental review. A full conceptual design report based on this effort will be finished in the summer 2023.

4

THE FUTURE OF RADIATION RESEARCH IN HELMHOLTZ

Radiation on the one hand represents an unavoidable risk for the population and for the workers. On the other hand, it is a unique opportunity to exploit and advance diagnostics and treatment in medicine. Helmholtz has engaged its infrastructures and researchers on both topics for years (Figure 4.1). With the construction of new facilities (see Section 3) and the increasing commitment to radiation research, the Helmholtz community feels the urge to work more closely together to face the challenges in radiation research (see Section 2). The Helmholtz radiation research community recognizes that collaboration among the different HGF Research Fields (Figure 4.2) would be highly beneficial to face the many challenges described in Section 2, to exploit the opportunities of the existing and new infrastructures described in Section 3 as well as to participate in solving the current societal problems, such as the energy and climate crisis.

The CCA RR was already active in the POF-III funding period, but with very limited dedicated funding. With the start of the CCA RR in the POF-IV funding period, a list of topics with high societal relevance were readily identified by the participating centers that are listed below:

- accurate determination of exposures in different radiation environments and the development of solutions to keep the doses as low as reasonably achievable (ALARA principle)
- development of strategies to minimize potential risks from the decommissioning and long-term deposition of nuclear waste (including quantification of secondary radiation effects)
- dose estimations after radiation exposures accounting for physiological variation, personalization and microdosimetry.
- pathways into the food chain, proof and ideally live-cell quantification of low radiation dose effects distinguishing actual radiation effects from purely chemical radionuclide toxicity
- radiation protection in air and space travel matched by radiation simulations at particle accelerators
- optimizing cancer treatment with charged particle therapy
    - reduction of range uncertainty, organ motion management
    - biomarkers, treatment individualization, combination of particles with other treatments (e.g. immunotherapy)
- exploration of future breakthroughs in radiotherapy with novel, unique infrastructures, like
    - FAIR
    - laser-driven particle accelerators (ELBE)
    - PT2030

- FLASH*lab*@PITZ

This is a long list of topics, where in many cases already strong co-operations among different Helmholtz centers exist. They can broadly be divided into radiation protection and radiation medicine and impose on the HGF infrastructures as outlined below.

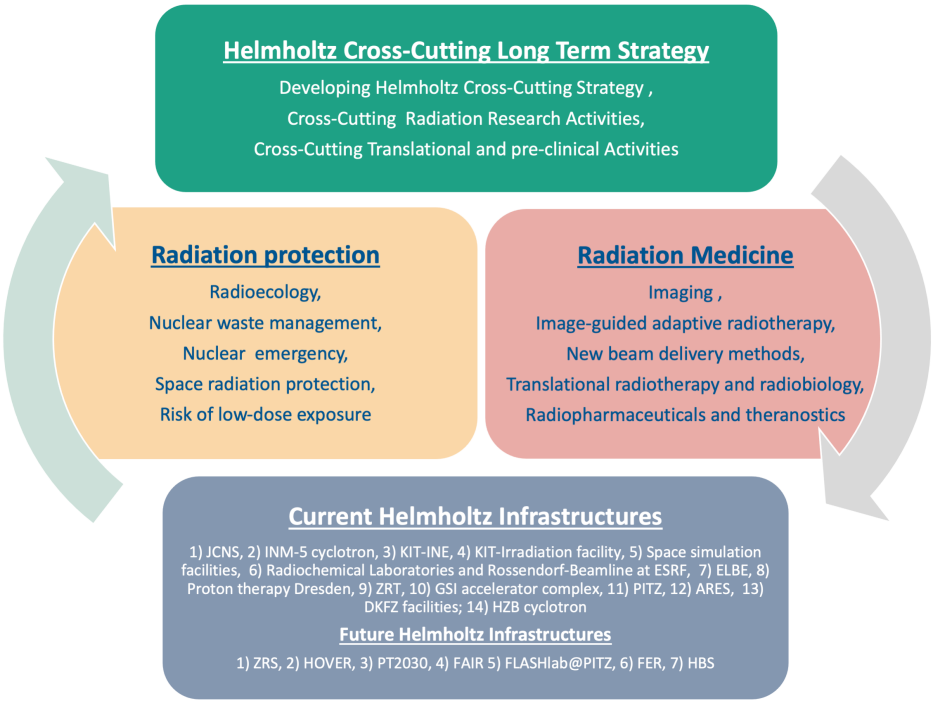


Figure 4.1 Intended linking of structural, thematic and strategic goals within CCA RR.

Research and development in the field of **radioecology and radiation protection** (Section 2.1) are now and in future indispensable for the protection of the population and the environment against the risks of ionizing radiation. These risks are posed in particular from the intentional use of radionuclides in medicine for diagnosis and treatment of cancer, from natural radiation and from the unintentional radiation during dismantling of nuclear power plants, the interim and final storage of radioactive waste, and reactor accidents such as those in Chernobyl and Fukushima. Radiation risk is indeed the main argument against a widespread use of nuclear energy. There is a need for future research due to the growing public awareness of radiological risks, existing knowledge gaps, and the need to educate and train the next generation of scientists. An accurate determination of exposures in different radiation environments and the development of solutions to keep doses as low as reasonably achievable (ALARA principle) needs, beside advancement in radiation measurement techniques, the in-depth understanding of the propagation and transfer of radionuclides in the

environment and the impact of ionizing radiation on materials and organisms. This includes a profound process understanding on a cellular and molecular level as well as its extension to larger space and time scales. CCA RR can pursue high-level interdisciplinary collaboration and provide unique infrastructures, such as HOVER, ZRS, various accelerators or neutron sources, which are ensured by the participating Helmholtz institutes.

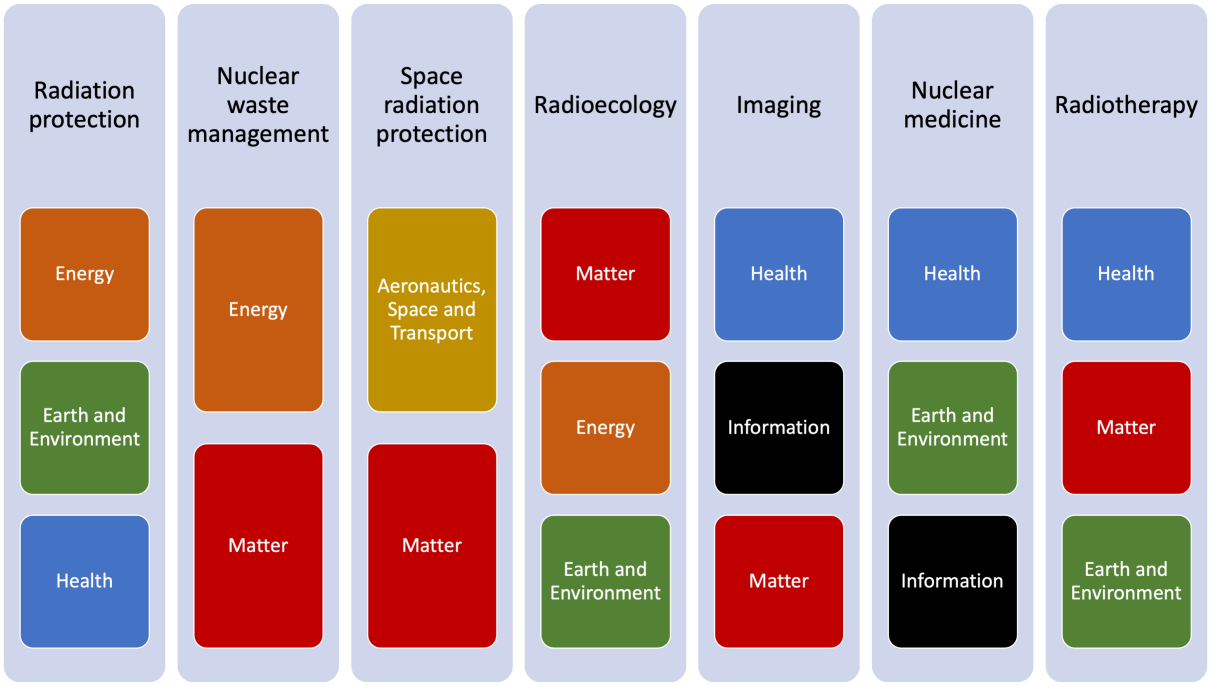


Figure 4.2 The cross-map between HGF Research Fields and radiation research topics.

The challenges in the field of **radiation medicine** have been widely described in Section 2.2. In HGF there are tremendous competences in image-guided radiotherapy, particle therapy, and theranostics. Several topics are actively pursued in different centers, belonging to different Helmholtz cross-centers research programs. The CCA RR is the ideal tool to promote collaborations among the different research programs that are supported by the current POF funding. Among the many challenges noted in Section 2.2, typical cross-program activities include radioimmunotherapy (combination of RT and in particular particle therapy with immunotherapy as well as targeted therapy with radioisotopes); and ultra-high dose-rate RT (FLASH), where many different HGF Research Fields are developing infrastructures and carrying out pre-clinical research studies.

Finally, an outstanding **multidisciplinary training of young scientists** should be maintained in order to preserve competencies for further generations. All centers are aware of this challenge, especially for young talents in the field. Besides the radiation protection professional training, there is a need for training in radiation research that Helmholtz tries to address also with specific measures for promoting young talents. Here, the CCA RR can work as a network to promote multidisciplinary

training e.g. enabling insight into the activities across disciplines and enabling exploitation of infrastructure capacities at other centers for their own work. To further promote synergy effects in the future, for example, a "cross-cutting" Master's student could study a multidisciplinary topic in one institution (discipline 1) in the first year and in another institution with a focus on discipline 2 in the second year. The entirety of these activities contributes to the development of sustainable strategies for the protection of humans and environment towards the risks of ionizing radiation.

In conclusion, radiation research is a hallmark of Helmholtz research. It is actively pursued in many different centers, and has led to outstanding results proving the power of the Helmholtz infrastructures and the translational potential of its research products. Future advances can be fostered by connecting the radiation research activities currently ongoing in separate research programs (Figure 4.2). Inter-program activities in radiation protection, radioecology, and radiation medicine can make HGF the leading radiation research organization in Europe. Recent events show how quickly the situation in Europe can change and how fast the risk of the release of radionuclides into the environment and the safeguarding of the energy supply come into focus. This underlines again the importance of conducting outstanding research and maintaining competence in the field of radiation research.

5

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6

List of abbreviations

AI = Artificial Intelligence
ALARA = As Low As Reasonably Achievable
AOP = Adverse Outcome Pathway
APPA = Atomic, Plasma Physics and Applications
ART = Adaptive radiotherapy
BARB = Biomedical Applications of Radioactive Ion Beams
BIM = Building Information Modelling
BMBF = Bundesministerium für Bildung und Forschung
BMUV= Bundesministerium für Umwelt, Naturschutz, nukleare Sicherheit und Verbraucherschutz
BNL = Brookhaven National Laboratory
CASUS = Center for Advanced System Understanding
CBM = Compressed Baryonic Matter.
CCA RR = Cross-cutting activity “Radiation Research”
CRT= Conformal radiotherapy
CT = Computerized Tomography
CTV = Clinical Target Volume
DALI = Dresden Advanced Light Infrastructure
DEGRO = Deutsche Gesellschaft für Radioonkologie
DFG = Deutsche Forschungsgemeinschaft
DLR = Deutsches Zentrum für Luft- und Raumfahrt
DKFZ = Deutsches Krebsforschungszentrum
DKTK = Deutschen Konsortium für Translationale Krebsforschung
DKTK-ROG = DKTK – Radiation Oncology Group
DSS = Decision Support System
ELBE = Elektronen Linearbeschleuniger für Strahlen hoher Brillanz und niedriger Emittanz
ECSS = European Cooperation for Space Standardization
EPTN = European Particle Therapy Network
ERC = European Research Council
ESA = European Space Agency
ESRF = European Synchrotron Radiation Facility
EU = European Union
FAIR = Facility for Anti-protons and Ion Research
FLASH = ultra-high dose rate radiotherapy
FLASH*lab*@PITZ = R&D platform for FLASH and VHEE radiation therapy and radiation biology at PITZ

FRS = Fragment Separator
FZJ = Forschungszentrum Jülich
GCR = Galactic Cosmic Radiation
GSI = GSI Helmholtzzentrum für Schwerionenforschung
HGF= Helmholtz-Gemeinschaft Deutscher Forschungszentren
HLEG = High Level and Expert Group on European Low Dose Risk Research
HMGU = Hemholtz-Zentrum München
HOVER = Helmholtz Forschungs- und Versuchsplattform zur Entsorgung radioaktiver Abfälle und zum Rückbau kerntechnischer Anlagen
HZB = Helmholtz-Zentrum Berlin
HZDR = Helmholtz-Zentrum Dresden-Rossendorf
IAEA = International Atomic Energy Agency
IBA = Ion Beam Applications
IBSI = Image Biomarker Standardisation Initiative
IMRT = Intensity Modulated Radiotherapy
INM = Institut für Neurowissenschaften und Medizin
IBER = Investigations of Biological Effects of Radiation
ICRP = International Commission on Radiological Protection
ISO = International Organization for Standardization
ISS = International Space Station
IT = Information Technology
JNCS = Jülich Centre for Neutron Science
JRodos = Java based Real-time On-line DecisiOn Support
KIT = Karlsruher Institut für Technologie
KVSF = Kompetenzverbund Strahlenforschung
LINAC = Linear accelerator
LEO = Low-Earth orbit
LNT = linear-no-threshold
MARE= MATROSHKA AstroRad Radiation Experiment
MBRT = Microbeam Radiotherapy
MELODI = Multidisciplinary European Low Dose Initiative
MLZ = Heinz Maier-Leibnitz Zentrum
MRI = Magnetic Resonance Imaging
NASA = National Aeronautics and Space Administration
NCT = National Center for Tumour Diseases
NORM = naturally occurring radioactive materials
NSRL = NASA Space Radiation Laboratory
NuSTAR = Nuclear Structure, Astrophysics and Reactions
OI = Optical Imaging
PANDA = Physics with High Energy Antiprotons
PET = Positron Emission Tomography
PITZ = Photo Injector Test facility at DESY in Zeuthen
PGI = Prompt Gamma Imaging

POF = Programmorientierte Förderung
POM = Program Owners and Managers
PT = Particle Therapy
PTCOG = Particle Therapy Co-Operative Group
QA = Quality Assurance
RBE = Relative Biological Effectiveness
RIB = Radioactive Ion beams
ROBL = Rossendorf Beamline
RT= Radiotherapy
SFRT = spatially fractionated radiotherapy
SIS = Schwerionensynchrotron
SNF = Spent Nuclear Fuel
SPE= Solar Particle Event
SPECT = single photon emission computed tomography
SRA = Strategic Research Agenda
SSK = Strahlenschutzkommission
UNILAC = Universal Linear Accelerator
VHEE = Very High Energy Electrons
WHO = World Health Organization
XFI = X-ray Fluorescence Imaging
ZRS = Zentrum für Radioökologie und Strahlenforschung
ZRT = Zentrum für Radiopharmazeutische Tumorforschung