Karlsruher Institut für Technologie

UNIVERSITÄT HEIDELBERG
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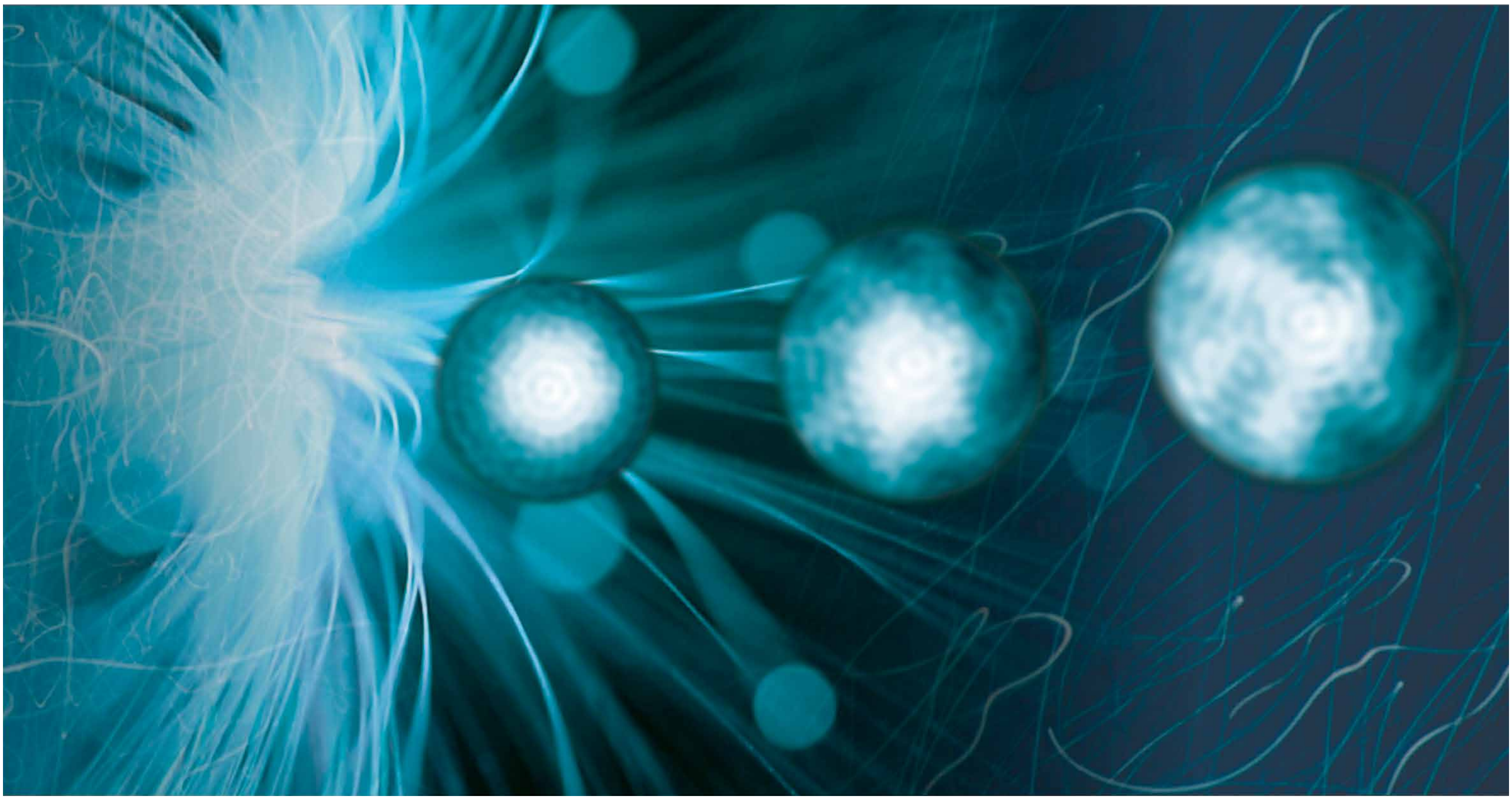
AccelerateRT

INNOVATIVE ACCELERATOR SYSTEMS AND TECHNOLOGIES FOR NEXT-GENERATION RADIATION MEDICINE



Excellence Strategy of the German Federal and State Governments
Joint Draft Proposal for a Cluster of Excellence
1 January 2026 – 31 December 2032

Content

List of abbreviations

ADL	ASIC and Detector Laboratory
AI	artificial intelligence
AICOR	Artificial Intelligence and Cognitive Robotics
ARRTI	Academy for Responsible Research, Teaching, and Innovation
ATP	Accelerator Technology Platform
BZH	Heidelberg University Biochemistry Center
CAF	cancer-associated fibroblast
CCU	Clinical Cooperation Unit
CNAO	Centro Nazionale di Adroterapia Oncologica, Pavia
CRUK	Cancer Research UK
cSTART	compact electron storage ring for accelerator science and technology
DAQ	data acquisition
DC	dendritic cells
DDR	DNA-damage repair
DESY	Deutsches Elektronen-Synchrotron
DKFZ	German Cancer Research Center
DKTK	German Consortium for Translational Tumor Research Therapy
DRs	doctoral researchers
DZG	German Centers for Health Research
EB	Executive Board
ECM	extracellular matrix
ECRs	early career researchers
EMBL	European Molecular Biology Laboratory
EuPRAXIA	European Plasma Research Accelerator with Excellence in Applications
ExC	Cluster of Excellence
FAIR	Findable, Accessible, Interoperable, Reusable
FAP	fibroblast activation protein
FAPi	fibroblast-activated protein 1 alpha inhibitor
FAU	Friedrich-Alexander University Erlangen-Nuremberg
FC	Finance Committee
FI EMS	Flagship-Initiative Engineering Molecular Systems
FLUTE	Ferninfrarot Linac- und Test-Experiment
FoF	Fields of Focus
FPGA	field programmable gate array
FRoG	Fast dose Recalculation on GPU

GSI	GSI Helmholtzzentrum für Schwerionenforschung, Darmstadt
HCLA	Heidelberg Center Latin America
He	Helium
He-CT	computed tomography with helium ions
HEiKA	Heidelberg Karlsruhe Strategic Partnership
HeKKSaGOn	Heidelberg University, Kyoto University, KIT, Tohoku University Sendai, University of Göttingen and Osaka University network
HGSFP	Heidelberg Graduate School for Physics
HIDSS4Health	Helmholtz Information & Data Science School for Health
HIRO	Heidelberg Institute for Radiation Oncology
HIT	Heidelberg Ion Beam Therapy Center
HTS	high temperature superconductor
HV-CMOS	High Voltage-Complementary Metal-Oxide-Semiconductor
HZDR	Helmholtz-Zentrum Dresden-Rossendorf
IAB	International Advisory Board
IAR-HERA	Institute for Anthropomatics and Robotics-Health Robotics and Automation
IB	Innovation Board
IORT	intraoperative, in-body RT
IP	intellectual property
(J)RGL	(Junior) Research Group Leader
KARA	Karlsruhe Research Accelerator
KCETA	KIT Center Elementary Particle and Astroparticle Physics
KCOP	Karlsruhe Center for Optics and Photonics
KHYS	Karlsruhe House of Young Scientists
KIT	Karlsruhe Institute of Technology
KNMFi	Karlsruhe Nano Micro Facility for information-driven structuring and characterization at the micro- and nanoscale
KSETA	Karlsruhe School of Particle and Astroparticle Physics: Science and Technology
LBL	Lawrence Berkeley National Laboratory
LET	linear energy transfer
MC	Monte Carlo
MITK	Medical Imaging Interaction Toolkit
MoA	mechanism of action
MPIMR	Max Planck Institute for Medical Research
MR / MRI	magnetic resonance / magnetic resonance imaging
NCRO	National Center for Radiation Oncology
NCT	National Center for Tumor Diseases
NFDI	National Research Data Infrastructure Germany
NHR	National High-Performance Computing Center

NKC	natural killer cell
NTCP	normal tissue complication probability
PSI	Paul Scherrer Institut
PSMA	prostate-specific membrane antigen
R&D	research and development
RDM	research data management
RF, RFs	Research focus, research foci
RT	Radiotherapy
SCC	Steinbuch Center for Computing
SMART	Smart Miniaturized Accelerators and Robotics for targeted Tumor Radio Therapy
SSC	Scientific Software Center
STEM	science, technology, engineering, and mathematics
TAC	Thesis Advisory Committee
TB	Translation Board
TCP	tumor control probability
THz	terahertz
TIME	tumor-immune microenvironment
TT	tenure track
UCSF	University of California San Francisco
UHD	Heidelberg University
uHDR	ultra-high dose rates
UKHD	Heidelberg University Hospital
UNIVERSE	UNIfied and Versatile bio-Response Engine
W1 TT	Junior professorship with tenure track
W3	Full professorship
YIN	Young Investigator Network
ZI	Central Institute of Mental Health
3DMM2O	3D Matter Made to Order

1. General data

1.1. Title in German and English

AccelerateRT – Innovative Beschleunigersysteme und Technologien für die Strahlenmedizin von morgen

AccelerateRT – Innovative accelerator systems and technologies for next-generation radiation medicine

1.2. Applicant universities

Managing University
Heidelberg University (UHD)

Further applicant universities
Karlsruhe Institute of Technology (KIT)

1.3. Spokespersons

Authorised spokesperson of the Managing University
Jürgen Debus

Further spokesperson	Institution
Anke-Susanne Müller	Karlsruhe Institute of Technology

1.4. Participating institutions

Participating institutions	Location
German Cancer Research Center (DKFZ)	Heidelberg (HD)

1.5. Principal investigators

No.	Principal investigators	Location/ Institution	Field of expertise	Position
1	Abdollahi, Amir	UHD, *Translational Radiation Oncology* and NCT	Tumor immune microenvironment, Particle Radiotherapy, personalized medicine	W3
2	Arndt, Tabea	KIT, *Institute for Technical Physics*	Superconducting magnet technology	W3
3	Asfour, Tamim	KIT, *Institute for Anthropomatics and Robotics*	Robotics, artificial intelligence	W3
4	Becker, Jürgen	KIT, *Institute for Information Processing Technologies*	Embedded electronic systems, sensors engineering	W3
5	Bründermann, Erik	KIT, *Institute for Beam Physics and Technology*	Lasers, semiconductors, terahertz techniques, accelerator technologies	RGL
6	Debus, Jürgen	UHD, *Department of Radiation* Oncology and NCT and HIRO/NCRO	Radiation oncology, ion beam therapy, image-guided high precision therapies, medicine	W3
7	De Carne, Giovanni	KIT, *Institute for Technical Physics*	Energy systems, digital twins	W1 TT

8	Dokic, Ivana	UHD, HIT and NCT *Particle Radiobiology*	Particle radiobiology, FLASH, ion-beam therapy, neuro-toxicity and oncology	JRGL
9	Fischer, Peer	UHD, *Institute for Molecular Systems Engineering and Advanced Materials* and MPIMR	Molecular systems engineering, micro- and nano robotics.	W3
10	Haberkorn, Uwe	UHD, *Department of Nuclear Medicine* and CCU Nuclear Medicine	High throughput ligand screening and proteomics, nuclear medicine, molecular imaging, theranostics	W3
11	Herold-Mende, Christel	UHD, *Experimental Neurosurgery* and NCT	Patient derived 2D/3D organoid models, immunobiology, biobanking, tumor microenvironment	W3
12	Hochbruck, Marlis	KIT, *Institute for Applied and Numerical Mathematics*	Numerical mathematics and computational physics, laser-plasma simulations	W3
13	Holzapfel, Bernhard	KIT, *Institute for Technical Physics*	Superconducting materials and High Temperature Superconducting (HTS) wires	W3
14	Husemann, Ulrich	KIT, *Institute of Experimental Particle Physics*	Fast radiation-hard silicon detectors, particle tracking, large-scale data analysis	W3
15	Jäger, Dirk	UHD and NCT, *Medical Oncology and Applied Tumor-Immunity*	Immunology, medical oncology, immune-oncology, personalized medicine	W3
16	Jäkel, Oliver	DKFZ, *Department of Medical Physics in Radiation Oncology* and UHD and HIRO, NCRO	Medical physics in radiotherapy, ion beam therapy, detector physics, dosimetry	W3
17	Jelonnek, John	KIT, *Institute for Pulsed Power and Microwave Technology*	Pulsed power and microwave technology, vacuum electronics	W3
18	Korvink, Jan G.	KIT, *Institute of Micro-structure Technology*	MEMS, added manufacturing, nuclear magnetic resonance	W3
19	Ladd, Mark E.	DKFZ, *Division of Medical Physics in Radiology* and UHD	MR imaging and spectroscopy, ultra-high magnetic fields, MR-guided radiotherapy	W3
20	Maier-Hein, Lena	DKFZ, *Division of Intelligent Medical Systems and NCT*	Data science, biomedical image analysis, machine learning validation	W3
21	Mairani, Andrea	UHD and HIT, NCT *Biophysics in Particle Therapy*	Biophysical modeling, MC simulation, ion beam therapy	JRGL
22	Mathis-Ullrich, Franziska	FAU Erlangen, *Dept. Artificial Intelligence in Biomedical Engineering*	Surgical robots, cognitive robotics, minimally invasive surgical instruments, micro-robotics	W3
23	Müller, Anke-Susanne	KIT, *Institute for Beam Physics and Technology*	Accelerator physics and technology, ultra-short pulse dynamics, precision metrology	W3
24	Paulino, Cristina	UHD, *Heidelberg University Biochemistry Center (BZH)*	Biophysics, structural biology, single-particle cryo-EM	W3
25	Simon, Frank	KIT, *Institute for Data Processing and Electronics*	Detector technology and data-acquisition systems	W3

8 principal investigators are women; equivalent to a share of 32%.

1.6. Cooperation partners

No	Institutional cooperation partners	Location
1	CERN	Geneva, Switzerland
2	Harvard University	Boston, USA
3	Paul Scherrer Institute (PSI)	Villigen, Switzerland
4	GSI Helmholtzzentrum für Schwerionenforschung	Darmstadt, Germany
5	Helmholtz-Zentrum Dresden-Rossendorf (HZDR)	Dresden, Germany

2. Summary of the proposal

Cancer is a leading cause of death globally. Radiotherapy (RT) – tumor treatment with ionizing radiation – is a cornerstone of cancer therapy. Advances in basic science and technology have substantially contributed to the success of radiotherapy. The improved outcome for many cancer types has increased survival and enhanced quality of life for many patients. Major improvements will now require fundamentally novel concepts, integrating know-how from a spectrum of scientific disciplines.

AccelerateRT is a multidisciplinary alliance of expert partners from physics, engineering, life sciences and biomedicine. Recent advances in these disciplines mark a new era for the development of novel strategies to eradicate tumor cells more efficiently and selectively while preserving healthy tissue. We plan to build the scientific foundations of a new generation of radiotherapy with the goal to substantially improve cancer cure rates. Our long-term vision is to translate this basic research into more effective, efficient and widely available radiotherapy.

The basic research in *AccelerateRT* will focus on three major areas: (A) tailored compact accelerators, (B) beam control, dosimetry and visualization of irradiation efficacy, and (C) exploration of bio-medical effects and optimization of novel radiotherapy qualities. The high level of interconnectedness across these research foci will, e.g., enable comprehensive investigation of irradiation with ultra-high dose rates and its selective sparing effect on healthy tissue. Moreover, by engineering novel miniaturized accelerator technologies, detectors and robotics, optimal beam characteristics will be discovered for next-generation intracorporeal irradiation.

Embedded in one of Germany's leading healthcare and technology regions, *AccelerateRT* is especially well positioned to discover new therapeutic opportunities in radiation medicine: We have at our disposal a unique technology portfolio, providing access to accelerators with an unprecedented spectrum of beam features, high-resolution radiation detectors and imaging devices as well as large-scale data processing. We host state-of-the-art biomedical facilities to systematically study molecular, cellular and tissue-level effects of irradiation.

We expect *AccelerateRT* to shape the future research directions of the partner institutions and to attract the best talents at all levels. Our *AccelerateCareers* program for early independence and plannable career paths comprises funding for trailblazing research proposals and professorships with the goal to recruit outstanding women.

In the longer term, we will translate *AccelerateRT's* research results into innovative medical devices and therapies. To ensure sustainability of this unique combination of basic research and translation to the clinic, our plan is to transform *AccelerateRT* into a permanent HeiKA-*Center for Innovative Biomedical and Radiation Technologies,* supported by both partner universities.

Zusammenfassung

Krebs ist weltweit eine der führenden Todesursachen. Die Behandlung von Tumoren mit ionisierender Strahlung (Strahlentherapie, engl.: radiotherapy, RT) ist ein zentraler Bestandteil der Krebstherapie. Viele Erfolge der Strahlentherapie entstammen Fortschritten in Grundlagenforschung und Technologie; sie haben die Überlebenswahrscheinlichkeit und Lebensqualität vieler Patientinnen und Patienten deutlich verbessert. Um weitere erhebliche Verbesserungen zu erreichen, sind nun grundlegend neue Konzepte aus einer Vielzahl wissenschaftlicher Disziplinen erforderlich.

AccelerateRT ist ein multidisziplinärer Verbund aus Physik, Ingenieur- und Lebenswissenschaften und Biomedizin. Fortschritte in diesen Fächern werden zu einer neuen Ära der effektiveren und selektiveren Vernichtung von Tumorzellen bei gleichzeitiger Schonung des gesunden Gewebes führen. Wir möchten die wissenschaftlichen Grundlagen für eine neue Generation der Strahlentherapie legen, die effektiver, effizienter und breiter verfügbar ist und somit deutlich verbesserte Heilungsraten bietet.

Die Forschung in *AccelerateRT* gliedert sich in drei Themenblöcke: (A) kompakte Beschleuniger, (B) Strahlkontrolle, Dosimetrie und Visualisierung, und (C) biomedizinische Effekte und Optimierung neuer strahlentherapeutischer Ansätze. Aufgrund der engen Verzahnung dieser Schwerpunkte können wir u. a. die Bestrahlung mit ultrahohen Dosisraten umfassend untersuchen. Außerdem werden aus der Kombination von miniaturisierten Beschleunigern, Detektoren und Robotern neuartige Systeme zur Bestrahlung von Tumoren im Körper entwickelt.

AccelerateRT findet in einer der führenden Gesundheits- und Technologieregionen Deutschlands ein exzellentes Umfeld für die Entdeckung neuer strahlenmedizinischer Therapien: Wir verfügen über ein einzigartiges Technologieportfolio mit Zugang zu Beschleunigern mit einem außergewöhnlich breiten Spektrum an Strahleigenschaften sowie zu hochauflösenden Geräten für Strahlungsnachweis und Bildgebung. Mit unseren hochmodernen biomedizinischen Laboren können Strahleneffekte systematisch auf dem Niveau von Molekülen, Zellen und Gewebe untersucht werden.

Wir erwarten, dass *AccelerateRT* die zukünftige Ausrichtung der Forschung an den Partnerinstitutionen prägen und die besten Köpfe des Feldes anziehen wird. Mit unserem Programm *AccelerateCareers* fördern wir die frühe Unabhängigkeit und planbare Karrierewege junger Forschender, u. a. durch die Finanzierung neuartiger Ideen und durch Professuren mit dem Ziel, herausragende Frauen anzuwerben.

Längerfristig werden wir unsere Forschungsergebnisse in innovative Medizingeräte und Therapien umsetzen. Zur nachhaltigen Sicherung unserer einzigartigen Kombination aus Grundlagenforschung und Translation in die Klinik planen wir, *AccelerateRT* in ein permanentes *HEiKA-Zentrum für innovative Technologien in Biomedizin und Strahlentherapie* zu überführen, das von beiden Universitäten getragen wird.

3. Research concept

Radiotherapy (RT) is an important therapeutic weapon in the fight against cancer. Accelerator-based external beam RT, the most common type of RT, delivers radiation – primarily photons, but also protons or carbon ions – to the tumor from outside the body. Internal RT such as brachytherapy delivers the therapeutic dose by temporarily introducing radiation sources next to the target area. In the EU, more than 3,000 medical accelerators are in use for RT, and in Germany, more than 250,000 patients receive RT as part of their cancer treatment each year. RT has rapidly evolved into highly individualized, high-precision cancer medicine. However, factors like motion of target structures during treatment, biological resistance of tumors to RT, and side effects of radiation limit the outcome in cancer patients. Rethinking RT has the potential to significantly impact survival and quality of life for many cancer patients. In *AccelerateRT*, we aim to build the physical, technological, and biomedical foundations to substantially improve the cancer cure rates via development of novel concepts to eradicate tumor cells more efficiently and selectively while exploiting the biophysical boundaries to preserve healthy tissue. Many state-of-the-art techniques of personalized high-precision RT have been pioneered in Heidelberg. KIT, on the other hand, provides a world-leading broad portfolio of technologies highly relevant to further advancing RT.

Joining forces in *AccelerateRT*, we will pave the way to make RT more effective against tumor cells, more efficient with fewer or shorter treatments, safer with fewer side effects, and more affordable with compact highly available solutions. To this end, *AccelerateRT* aims to discover sources of radiation with superior characteristics, combined with deep understanding of tissue interaction, to develop fast therapy control that enables novel (molecular) imaging with a large dynamic range, and to exploit cross-discipline synergies within the cluster to create efficient modular treatment approaches. The scientific long-term vision of *AccelerateRT* is to create effective therapies with affordable devices, tailored to the anatomical and biophysical constraints of each individual.

With today's technological advances, radical improvements in radiation medicine are imminent. At UHD and KIT, we address all key technologies: non-equilibrium particle beams; sensors and detectors; superconducting magnets; energy, high-power pulse, microwave, laser and terahertz technologies; robotics; data processing; artificial intelligence (AI) and more. These have experienced recent breakthroughs and/or have become significantly faster, smaller, and much more powerful and efficient. Building on these advances, we will lay the groundwork for novel radiation delivery systems. *AccelerateRT* will combine compact particle accelerators providing innovative temporal and spatial radiation patterns and ultra-fast delivery of high dose with precise dosimetry and imaging. This will allow exploitation of novel biological effects for RT, such as the selective sparing of healthy tissue at ultra-high dose rates (uHDR), called the FLASH effect, which was discovered recently for a variety of beam modalities. We will also pursue novel imaging techniques, such as computed tomography with helium ions (He-CT) and next-generation magnetic resonance imaging (MRI).

Enabling these advances for RT requires basic research and innovations in all fields of physics and engineering involved. In *AccelerateRT* we will link these technologies with basic radiation research, aiming at deep molecular, cellular and tissue-level understanding of the radiochemical and radiobiological effects. This unique combination will provide novel opportunities to observe unprecedented biological phenomena and will guide the design of innovative therapies. *AccelerateRT* will build on excellent existing infrastructures (Section 5.2), most prominently the medical accelerator facility HIT (Heidelberg Ion Beam Therapy Center) – Europe's first RT center operated with light ions, the synchrotron light source KARA (Karlsruhe Research Accelerator), as well as the accelerator test facility FLUTE (Ferninfrarot Linac- Und Test-Experiment) at KIT. This infrastructure is complemented with high-throughput

AI-assisted multiscale omics laboratories that provide know-how to decipher the radiobiological landscape and advance the understanding of radiobiological effect space.

In a highly multidisciplinary and integrative approach, *AccelerateRT* brings together scientists from UHD, KIT, and DKFZ, from medicine, biology, mathematics, physics, and engineering. We will develop novel diagnosis and therapy modalities in **joint, concerted research projects**, which we will approach from a scientific, a technological, and a clinical perspective from the start. The basic research in *AccelerateRT* is organized in three **research foci** (RFs) which reflect the three major scientific directions of the cluster: (A) Novel beams, tailored compact accelerators & systems, (B) Radiation control and visualization, and (C) Biophysics and radiobiology. Each RF contains several research and development (R&D) modules (A1 through C5, Tab. 1). This robust and flexible network of R&D modules combines high-risk with "guaranteed" approaches and technologies, which is also a measure of risk mitigation, as it provides the necessary redundancy and fallback solutions. Three **model cases** (Section 3.4) illustrate how we interconnect R&D modules from different RFs towards an overarching goal.

Table 1 *Research foci, R&D modules, and PIs within AccelerateRT (lead PIs: bold, otherwise: initials).*

Research Focus A	**Novel beams, tailored compact accelerators & systems**
A1 Light-to-electron systems	**PIs: Müller, Husemann,** TAr, EB, JD, ID, OJ, JJ, AM, CH
A2 Electrons-to-photon systems	**PIs: Bründermann, Debus,** ID, MH, OJ, BH, AM, CH
A3 Short-pulse dynamics	**PIs: Müller, Dokic,** TAr, JD, GDC, OJ, JD, JJ, AM
A4 Robotic systems for advanced therapy approaches	**PIs: Mathis-Ullrich, Fischer,** AA, TAr, ID, CH, LMH, DJ
Research Focus B	**Novel approaches to radiation control and visualization**
B1 Next-generation radiation control	**PIs: Husemann, Jäkel,** JD, PF, AM, FS
B2 Visualization of biochemical radiation effects	**PIs: Korvink, Ladd,** EB, JD, BH, OJ, JJ, AA, UHa
B3 Data processing and AI	**PIs: Simon, Maier-Hein,** JB, UHu, OJ, AM
Research Focus C	**Biophysics and radiobiology for translation into next-generation precision medicine**
C1 Systems Radiobiology	**PIs: Dokic, Bründermann,** AA, JD, CH, DJ, OJ, AM, ASM
C2 Integrative Biophysical Modeling	**PIs: Mairani, Hochbruck,** AA, ID, OJ, JD
C3 Intelligent molecular systems	**PIs: Abdollahi, Paulino,** JD, UHa, ID, PF, DJ, CH
C4 Biomedical functionalization of microrobots	**PIs: Fischer, Mathis-Ullrich,** AA, TAr, TAs, EB, JD, ID, UHa, UHu, JK, LMH, ASM, CP
C5 Tumor-immune micro-environment evolution	**PIs: Herold-Mende, Jäger,** AA, JD, ID, AM, FM, EB

The extraordinary dynamics we expect from *AccelerateRT* build on various established multidisciplinary projects among cluster PIs, associate PIs (defined in Section 5.2), and further scientists from UHD, KIT, and DKFZ: A joint project on particle therapy beam monitoring with HV-CMOS sensors (J. Debus, UHD, I. Perić, KIT) is preliminary work on next-generation beam control in RT (RF B). The UHD/KIT/DKFZ Transregio-Collaborative Research Center (DFG SFB-TRR 125 "Cognition-Guided Surgery") focus on AI and cognitive robotics for precision localized therapy has led to the formation of a sustainable joint research hub, which integrates the KIT Health Robotics and Automation (HERA) laboratory (F. Mathis-Ullrich), now extended and moved to FAU Erlangen-Nuremberg, the visceral surgery and radiation oncology departments at UHD (C. Michalski, J. Debus), and medical physics and surgical data sciences at DKFZ (O. Jäkel, L. Maier-Hein). In further collaborative projects, engineers, computer scientists, radiologists, surgeons, and radiation oncologists focus on automating local therapies towards clinical translation, for example within the joint Helmholtz Information & Data Science School for Health (HIDSS4Health, Section 4.1).

3.1. Research focus A: Novel beams, tailored compact accelerators & systems

The generation of temporally and spatially controlled beams at uHDR up to tens of grays per second in a single spill, train, or pulse, from compact, efficient devices, is a particular challenge in accelerator technology. In *AccelerateRT*, we strive to open new avenues for the research on, and application of, ultra-high dose rates stretching over several orders of magnitude, temporal and spatial patterns in micro-beams or application of novel internal radiation sources. Building on our expertise in energy research, we are in the unique position to also improve the important design parameters energy-efficiency and cost-efficiency next to maximizing the tumor-specificity of the application.

AccelerateRT has access to a unique portfolio of accelerator-based sources, covering a broad spectrum of ions, electron, X-ray and terahertz (THz) photon radiation from the start. HIT provides ion beams. The FLUTE facility [ASM8][1] delivers both ultra-short electron and high-field THz photon pulses. Short-pulsed X-ray modalities are available from KARA [ASM6]. Our research aims to greatly extend the range of intensities and temporal and spatial radiation patterns that are currently available by new approaches to beam instrumentation and AI-based precision control. Based on developments at KIT [ASM3, ASM4, EB5], non-equilibrium beam control will make short ion pulses available to *AccelerateRT* from HIT. Together, this enables systematic radiobiological research of a fundamentally new quality towards an improved therapeutic window (RF C) and beams with increased biological effectiveness. These studies will define an optimal set of design parameters for the tailored accelerator systems in *AccelerateRT*.

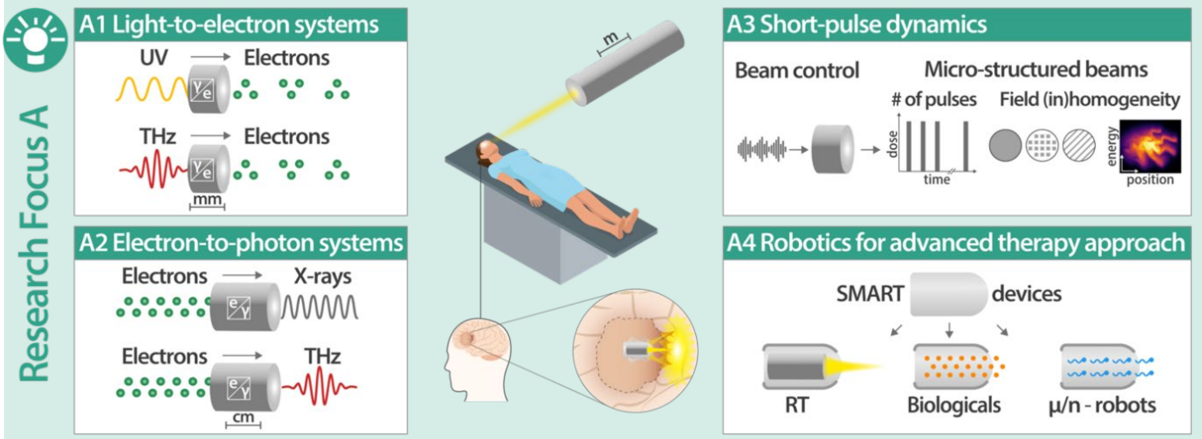


***Figure 1**: Overview of R&D modules of Research focus A: Novel beams, tailored compact accelerators & systems. Novel advanced accelerator technologies, i.e., light-to-electron (A1) and electron-to-photon (A2) systems, will provide a unique opportunity to decrease the size of current large-facility systems to compact (cm-mm scale) applicators which could operate with ultra-short pulse dynamics (A3), generating new treatment dimensions in terms of, e.g., dose rates or RT field structure. In parallel, robotics and miniaturization efforts (A4) to embed these compact size accelerators in "SMART" devices will not only advance RT but may have ramifications for AI and robotics-based tumor-specific delivery of biologicals and release of micro/nano robots that will be elaborated in collaboration with RF C.*

The research in modules A1–A4 is illustrated in Figure 1. Rethinking present-day strategies to miniaturize accelerators, we will investigate new technological approaches to pulsed light-to-electron systems, to develop the first prototype of a novel, miniaturized, pulsed electron source

[1] Previous work by PIs is cited by referring to the publications within the PI's CVs: Initials of the PI followed by the number of the respective publication number (Category A) are indicated in square brackets, e.g., [ASM8] means CV of Anke-Susanne Müller, publication number 8. Digital object identifiers of other publications are referenced directly in the text.

(A1). This comprises a major milestone on the way to a new high-precision intracorporeal radiotherapy, in particular, when combined with novel sensors and controls (RF B) for navigation and success monitoring. A compact accelerator-based source of short X-ray pulses and THz radiation with high electric fields will be devised up to application readiness (A2), employing different emerging technologies for the RT generation. The production of stable and reproducible ultra-short pulses with variable repetition rates for all probes/radiation modalities (ions, electrons, and THz photons) as basis for the radiobiological and biophysical studies will be investigated and implemented, supported by simulations and digital twins for various design aspects (A3). Having systematically characterized novel beams and their substructures for biological effects (C1 and C2), intracorporeal application of a particle or photon beam can best be realized by miniaturized accelerators for minimally invasive systems in conjunction with robotics (A4): We will explore the potential of implantable micro-robots as carriers for these sensor/source devices, including controlled intratumoral release of biological modulators. Ultimately, these developments will lead to minimally invasive in-body treatment systems with increasing efficiency, availability, and autonomy.

Module (A1) Light-to-electron systems. A drawback of electrons in RT is their limited range in tissue. Many groups study ultra-high energy electron (UHEE) accelerators with a larger penetration depth, seeking to spare healthy tissue by exploiting the FLASH effect for short pulses. While smaller than most ion accelerators, these systems still have a substantial spatial and energy footprint, which limits their widespread use and deployment. We will develop light-to-electron systems that overcome both, range limitation and footprint, by massive miniaturization of the accelerator system to the point where the electron pulses are generated directly inside the body. This requires mm-scaled devices that generate short pulses of particles to deliver ultra-high dose rates for exploitation of the FLASH regime (with dose rates above 40 Gy/s).

To date, commercially available miniature, intraoperative, in-body RT (IORT) systems provide continuous-wave X-rays. Significantly larger systems, such as the Mobetron devices used in *AccelerateRT* for comparative studies, also in (C1), can deliver medium-short (ms) electron pulses. Miniature sources of short-pulsed (ns down to ps) electron pulses of sufficient intensity for the envisaged uHDR treatment, however, do not yet exist. Dielectric laser accelerators, while small, cannot deliver the required pulse intensities due to the physical method employed. Recent work of *AccelerateRT* PIs on, for example, ultra-compact THz-based deflector systems indicate novel promising approaches, which exploit the expertise gained from the design of electron emitters for microwave power sources [JJ1]. Accordingly, the potential of different promising electron source technologies based on electron generation from short ultraviolet or infrared/THz light pulses in external or THz-induced accelerating fields will be evaluated with the goal of obtaining a system fully qualified for operation in the FLASH regime.

New systems biology models (RF C) that consider thermal aspects and heat propagation in a more holistic approach will address the challenge of tissue heating in minimally invasive systems. Precise short-pulse dosimetry (RF B) is crucial for reliability and reducibility in medical application. Model case III (Section 3.3) illustrates how this R&D module interacts with other research in *AccelerateRT* to implement novel SMART (**S**mart **M**iniaturized **A**ccelerators and Robotics for targeted tumor **R**adio **T**herapy) devices.

Module (A2) Electron-to-photon systems. Studies of the efficacy of new modalities for RT (RF C) require sources that allow for a combination of different types of radiation, from single- to multi-color schemes with short photon pulses ranging from THz to X-ray frequencies. For this purpose, we will develop compact electron-to-photon systems with the photon source close to the patient. The high temperature superconductor (HTS)-based beam guidance and transport systems will also be needed for the transport of He ions as outlined in the description of model case I. Beam optimization and control are enabled by methods of artificial intelligence [EB2, ASM5]. Advanced mathematical modeling and simulation [MH9] will provide the basis for the provision of appropriate beam qualities. Short electron pulses, as a first step from radio frequency-based accelerators (FLUTE), or from a laser-based accelerator (ATHENA) are sent through a novel short-period undulator and generate intense coherent X-ray photons. Both, novel HTS tape-stack systems and plasma systems emitting powerful betatron X-ray radiation will be investigated. New focusing methods and compact phase contrast high-resolution imaging complement studies with new MRI systems in RF B. Transition or edge radiation from the short electron pulses yields very high peak-field single-cycle radiation with up to GV/m electric field strength.

Module (A3) Short-pulse dynamics. A prerequisite for systematically investigating the biological effects of uHDR is a sound understanding and control of the challenging short-pulse dynamics for ions, electrons, and photons. Short pulses and variable repetition rates down to micro-beams and micro-structures in the GHz and THz range have to be delivered reliably and reproducibly. This module deals with the experimental and theoretical prerequisites (non-equilibrium beam physics, instrumentation, control). Here, we build on world-leading work by our cluster and associate PIs in the modeling, detection and control of short electron bunches [ASM2, EB2, EB4]. Both high-resolution and high-repetition rate devices have been developed previously and are ready to be adapted for application within *AccelerateRT*. The comparative work and experiment / model benchmarking will start on the currently operating accelerators, HIT, KARA, and FLUTE. These findings will then be transferred to the miniaturized systems under development in A1 and A2. Energy system-informed digital twins of all accelerator systems under investigation (including the miniaturized ones) are necessary to develop and to validate concepts for making accelerators energy-autonomous, independent from external energy sources (e.g., the power grid), and to improve the energy efficiency of the entire complex or setup [GDC4]. This is also of particular interest in view of the rapidly increasing energy costs that could severely hamper the dissemination of the systems and therapy approaches under development as well as threaten the operation of present hospital-based accelerators. The research on energy solutions for low-energy stable, and resilient research infrastructures, in particular, accelerators, is supported by the new, dedicated test center KITTEN at KIT [https://doi.org/10.1055/s-0042-1758608].

Module (A4) Robotics for advanced therapy approaches. For delivery of radiation in a minimally invasive setting we will employ robotics for advanced therapy approaches that may act as a carrier for compact accelerators and detectors as well as wireless implantable micro-robots that can be navigated through the body with high precision. Miniaturized batteries, biomedical (molecular) and biochemical (e.g., pH) sensors (together with C4), biocompatibility of materials and functional surfaces utilized, and “smart” and autonomous guidance of the robots will be investigated as required. This will be combined with controlled intratumoral release of biologicals and chemicals, intraoperative/minimally invasive image-guided implantation, and localization and tracking inside the body. Integration of miniaturized accelerators and detectors (B1), effective data transfer and analysis (B3), numerical simulations, as well as interpretation through machine learning methodologies will pave the way towards context-sensitive autonomous intracorporeal robotics.

The high level of accelerator control required to achieve the goals of (A1) and (A3) will be driven by a **cluster-funded W1 tenure-track (TT) professorship for autonomous accelerators**. The recently appointed **W3 professorship on laser-based accelerators at KIT** (M. Fuchs) will play an important role in developing new, compact sources of the THz and X-ray modalities for RFs A and C. A new **W3 professorship at KIT** for medical robotics will work closely with *AccelerateRT* and associate Pis on the technologies for (A4).

3.2. Research focus B: Novel approaches to radiation control and visualization

Today’s systems for radiation control, visualization of radiation effects, and data processing in RT come with limitations in size, dynamic range, readout speed, latency, response time, or radiation and magnetic-field compatibility. With *AccelerateRT*, we provide expertise in, and access to, technologies for all aspects of future radiation control and visualization devices which overcome these limitations, combined with a deep understanding of the medical requirements. The outcome will lay the groundwork for faster and/or higher-resolution treatment feedback, leading to more efficient and effective individualized cancer therapy. We will investigate novel fully integrated systems, including accelerator devices (RF A), sensors, online and offline data processing, and imaging, considering the compatibility of all applications to meet the clinical needs from day one. Fig. 2 gives an overview of the scope of RF B. The R&D modules focus on radiation control for a wide range of devices (B1), on the visualization of radiation effects with MRI and THz radiation (B2) and on data processing, Artificial Intelligence (AI), and further system aspects (B3).

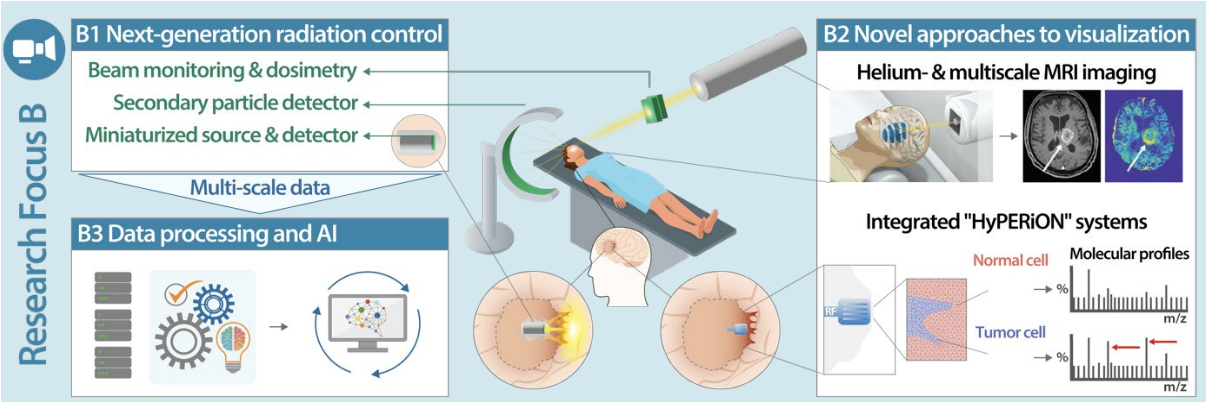


Figure 2*. Research focus B: Novel approaches to radiation control and visualization. Novel technologies are developed from a patient-need centric view. The broad spectrum of new beam modalities generated by large facilities up to miniaturized devices calls for development of novel detector technologies (green) towards next-generation radiation control and beam quality assurance (B1). Novel imaging modalities are developed using unique biophysical characteristics of, e.g., helium beams and advanced MR modalities (B2). Moreover, development and integration of next-generation High Performance Compact Magnetic Resonance (HyPERiON) systems will enable a spectrum of novel applications starting from identification of the tumor infiltrative zones via NMR microscopy to differential tumor NMR metabolomics. These are important prerequisites for tumor eradication towards high precision curative therapy. The extensive multiscale data generated in the framework of AccelerateRT will demand a powerful multidisciplinary data integration and processing module (B3).*

Module (B1) Next-generation radiation control. Novel devices to be developed in (B1) range from very small radiation detectors for intracorporeal systems generating uHDR (A1, A4) to systems for precision micro and nano dosimetry and for beam control and monitoring of secondary radiation, e.g., in He-CT (model case I). These developments will build on our previous work on particle detector systems [Uhu2, OJ2, OJ4, OJ5] as well as extensive experience in detector and readout system design, dosimetry, and detailed Monte Carlo simulations of particle interactions in tissue [AM1-10]. Current joint projects in this area include the development of a fast, radiation hard and magnetic-field compatible beam monitor based on HV-CMOS pixel detectors for HIT [https://doi.org/10.1016/j.nima.2007.07.115, UHu1] and a multilayer detector system for secondary ions.

AccelerateRT's research program to decipher the landscape of biophysical effects (RF C) and to develop and optimize new beam modalities for RT (A1–A3) requires consistent, fast, and precise dosimetry in a harsh radiation environment. We will investigate next-generation dosimetry techniques and devices that overcome the limitations of today's off-the-shelf devices in terms of dynamic range, speed, and response time and benchmark them against existing technology. In a first step we will evaluate the potential of segmented silicon-carbide diodes and organic scintillators for in-vivo photon/neutron flux measurements and of fast semiconductor detectors for dosimetry based on single-particle events and couple the novel dosimeters to real-time dose calculations. Subsequently, we will develop detector technology for tissue-equivalent dose meters which can be operated under uHDR conditions and validate them against micro- and nano-dosimetric simulations (C2).

AccelerateRT's goals towards minimally invasive miniaturized devices (RF A, model case III) require radiation sensors integrated in a device with ≤ 1 cm diameter. In the initial phase of the cluster, we will investigate if small-area pixelated semiconductor radiation sensors integrated with the radiation source are superior to extracorporeal radiation monitoring and subsequently design first prototypes based on existing sensor technology. Unmet challenges of these novel devices include ultra-low power consumption and heat dissipation, and possibly biocompatibility, all of which will be addressed with a systematic study of novel radiation sensor materials and a second round of prototypes.

The analysis of secondary radiation in proton and ion therapy allows real-time in-vivo monitoring, in addition to conventional dose monitoring, promising unprecedented ways to visualize radiation effects (B2). Previous studies, including our own work with wire chambers, scintillating fiber detectors, and TimePix silicon detectors [UHu1, OJ6, OJ7, http://dx.doi.org/10.5445/IR/1000096850], were based on small proof-of-concept setups for charged particle tracking, or prompt gamma-ray detection. In *AccelerateRT*, we will extend these setups towards viable multilayer detector systems based on state-of-the-art sensors (e.g., ALPIDE [https://doi.org/10.1016/j.nima.2016.05.016]) with large angular coverage. We will first optimize the detector system layout with simulations and work on modern particle tracking and reconstruction algorithms (B3) and conceptualize a fast custom readout system. Subsequently, this will be complemented by a system for prompt gamma-ray spectroscopy connected to the same readout system, that may be used to measure elemental concentrations. This will be followed by a first prototype system to be tested with phantoms at HIT.

Today's beam control devices, for example ionization chambers and radio-chromic films, exhibit severe shortcomings when operated with uHDR beam modalities [https://doi.org/10.1118/1.3244034]. To equip large facilities like HIT, fast (sub-µs) and radiation-hard (up to 10^{11} $cm^{-2}s^{-1}$) devices will be required. For a combination of RT with MRI (B2), operation in magnetic fields above 0.1 T will be necessary. In *AccelerateRT*, we will build on our ongoing HV-CMOS beam-monitor development to design an uHDR-capable successor. Another unmet challenge in *AccelerateRT* is the monitoring of uHDR electron beams and their microstructure, to be developed at FLUTE and later in miniaturized systems (A3, A1), with nanocoulomb charge pulses on a picosecond time scale. We will enable novel technologies for dose determination, e.g., charge-integrating pixelated silicon sensors. In parallel, detectors capable of resolving the microstructure of beams will be adapted to resolve THz radiation and uHDR pulses.

Module (B2) Novel approaches to the visualization of biochemical radiation effects. Research in this module will build on innovative MRI systems complemented with next-generation detector systems (B1). Based on existing THz radiation sources and diagnostic tools, *AccelerateRT* will explore the biomedical effects of THz radiation to inform the design of miniaturized minimally invasive diagnostic systems.

MRI-derived biomarkers promise to lead to better understanding and monitoring of tumor biology during radiation treatment and enable individual adaptation. Novel MR sequences and analysis techniques [JK8] may allow radiation-induced free radical imaging in-vivo using novel dynamic nuclear polarization MRI. Novel MRI systems for RT will be developed, fully integrated with the treatment machine, which allow individual monitoring and adaptation of treatment effects. Instrumented endoscopic systems exploiting micro- and nanotechnologies will use very compact HTS magnets for advanced correlated imaging. These novel MRI systems can be combined with the aforementioned systems for in-vivo monitoring (B1). We will employ advanced particle tracking and medical imaging software (B3) to reconstruct three-dimensional images with such systems to investigate which information beyond morphology derived from stopping power is available (C1, C2). The complexity of the underlying interactions, radiation transport, and detector systems require sophisticated Monte Carlo (MC) simulations to optimize beam delivery and detection.

To investigate the largely unexplored landscape of biomedical effects of THz radiation, both powerful THz radiation sources and extensive imaging and diagnostic tools are available for *AccelerateRT*. KIT accelerators provide various THz wavelengths, pulse lengths, intensities, and repetition rates, including high electromagnetic fields. Our diagnosis tools feature ultra-high time resolution, at least twelve orders of magnitude in frequency [ASM3], and ultra-fast recording of spatial dimensions with imaging techniques such as tomography and spectroscopy [EB4]. With these tools, *AccelerateRT* will systematically study the short- and long-term impulse reaction of living cells, bacteria, and tissue/skin, for the first time in the high-field regime (C1, C2). Based on the outcome, we will develop prototypes of novel minimally invasive diagnosis modalities of multi-dimensional spectroscopy and imaging in the most promising parameter range of the combined THz and optical regime. This work will draw on the available micro- and nanofabrication and nano 3D printing capabilities at KIT (KNMFi, KCOP, Section 5.2) to push miniaturization for intracorporeal use.

Module (B3) Data processing and AI. Exploiting the full potential of modern detection and diagnosis devices requires processing of large amounts of data with minimum latency and employing AI-based methods beyond what is possible with commercial systems and with a focus on explainable AI. Based on our broad experience in online and offline data processing and analysis both in large-scale physics experiments and in medicine, we will design and assemble a distributed real-time data processing system from a scalable toolbox of high-throughput data acquisition systems that will be able to efficiently adopt future advances in commercial components (FPGAs, CPUs, GPUs, telecommunication technologies). Data processing algorithms with novel AI-based methods will enable, e.g., on-the-fly data volume reduction, medical image processing, fast simulation of particle transport, charged particle tracking, and device control tasks. To make efficient use of imaging data (in-vivo monitoring, online MRI, spectroscopic imaging, treatment planning), a powerful and energy-efficient medical image processing pipeline will be implemented based on AI tools for image registration, segmentation, and feature analysis. The same set of tools will also be used in biophysical modeling (C2) and spatially resolved multi-parametric omics (C1). KIT's Steinbuch Centre for Computing (SCC) will provide valuable expertise for large-scale data processing and storage, strengthening the existing links through HiDSS4Health (Section 4.1).

Two W1 tenure-track professorships funded by *AccelerateRT*, on **novel detector and readout systems for medical applications at KIT** and on **AI for adaptive therapy at UHD** are planned to pave the way towards applicability and translation in RF B.

3.3. Research focus C. Biophysics and intelligent molecular systems for translation into next-generation precision medicine

Multi-scale radiobiological characterization and modeling of novel beam characteristics, devised by technological developments in RFs A and B, will be an important prerequisite for exploitation of the full potential of these innovations for life sciences. *AccelerateRT* builds on one of the world's most advanced and comprehensive life science research environments and a team with an excellent proven track record in translating basic research to disruptive biomedical diagnostics, e.g., molecular imaging with prostate-specific membrane antigen (PSMA) [UHa4] and fibroblast-activated protein 1 alpha inhibitor (FAPi) [UHa9] and therapies, e.g., intensity modulated radiotherapy (IMRT) and carbon ion beam therapy. Therefore, RF C will provide central cross-ExC support for rational design of therapy systems as well as to evaluate their potential to impact future clinical practice.

Deciphering the biophysical effect landscape of novel beams. Within the scope of *AccelerateRT*, an exceptionally broad range of beam qualities and parameters will be engineered. While RFs A and B will assure beam generation, reproducibility and accuracy, RF C will systematically decipher the biomedical effect space (C1 and C2) of the envisioned matrix of novel beam parameters and structures, i.e., variations of dose(-rates), LET, pulse (shape, frequency, intervals), energies, spatial (in)-homogeneity, etc., for a broad spectrum of beams, i.e., THz, photons, electrons, protons, helium, carbon and oxygen ions. In addition to the technological innovation required for beam generation, faithful biological model systems and multi-scale characterization of new beam parameter space at tissue-, cellular- and molecular level is envisioned.

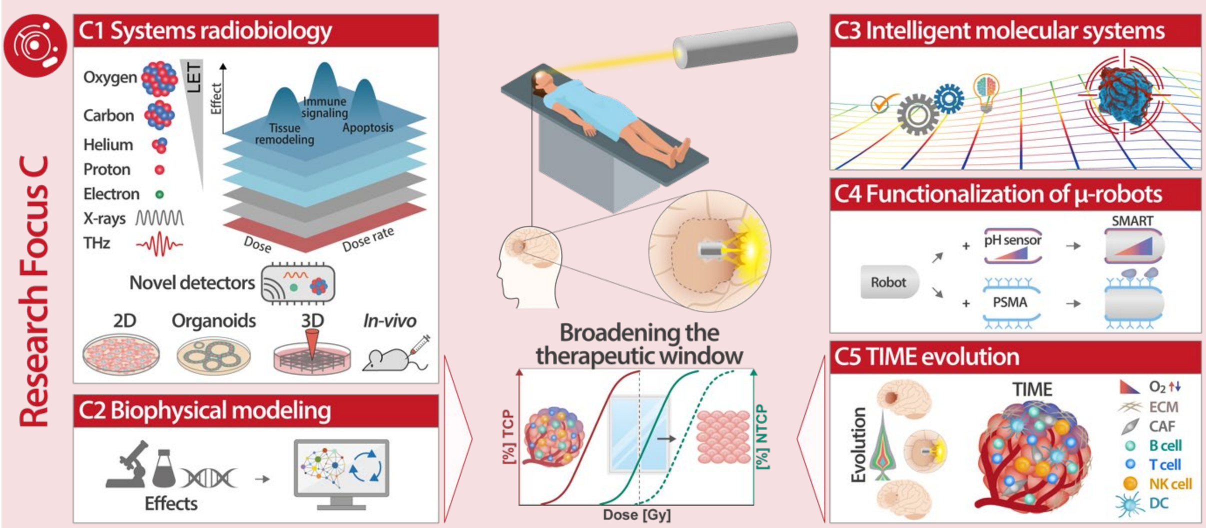


***Figure 3**: The aim of Research Focus C is to systematically decipher the biophysical effect landscape of novel beam qualities and characteristics studied in AccelerateRT by employing cutting-edge molecular and biomedical model systems (C1). Multi-scale effect space data are integrated into predictive biophysical models (C2) for simulations and development of optimal treatment planning scenarios. In C3 innovative materials are engineered eliciting their effects according to the beam specific bio-/chemo-/physical characteristics. Moreover, multifunctional molecular systems are engineered executing complex operations, from tumor cell/compartment specific uptake to targeted modulation of tumor biology. In C4, the information gained in different modules is utilized to biologically functionalize the robotic systems, i.e., adapt to RT field- and/or tumor characteristics, e.g., by navigating towards hypoxia/low pH gradients or enhanced adherence to tumor specific targets like PSMA. To exploit the full curative potential of the localized precision medicine, the effect of novel beam qualities and molecular systems engineered in AccelerateRT on the tumor-immune microenvironment (TIME) evolution (C5) is investigated. TIME-evolution parameters will instruct rational design of effective in-situ tumor vaccination strategies aiming to reconstitute the systemic tumor immune surveillance. Overall, our goal is to identify the most relevant constraints to substantially broaden the therapeutic window of multimodal cancer therapies.*

AccelerateRT will enormously benefit from the Innovation Campus “Health + Life Science Alliance Heidelberg Mannheim” and the new KIT Center Health Technologies (Section 5.1). The ExC will provide a seamless integration platform at the interface of biophysics with cutting-edge technologies like 3D cell printing and tissue engineering, human tumor and normal tissue organoid models and a plethora of chemical/biomolecular infrastructure and know-how that are developed in frame of UHD’s Flagship Initiative “Engineering Molecular Systems“ (FI EMS) and 3DMM2O. The ultimate goal of this RF will be to identify the optimal beam parameter space providing maximum efficacy for tumor eradication and simultaneously maximum sparing of the healthy tissue – to substantially broaden the **therapeutic window**. Identification of these biophysically optimal constraints could provide a blueprint for engineering compact or miniaturized accelerators for biomedical applications (Figs. 4 and 5).

Module (C1) Systems radiobiology. To investigate biological effects of novel beam modalities (A1–A4), we will employ a broad spectrum of radiobiological readouts from 4D DNA-damage repair (DDR) kinetic to well established high-throughput primary patient-derived multicellular tumor organoids, induced pluripotent stem cell derived normal-tissue organoids as well as paradigmatic preclinical *in-vivo* models of tumor and normal-tissue response. Phenomenological studies (phenomics) are complemented by advanced integrative -omics by integrating different analysis layers (proteomics, transcriptomics, epigenomics, functional genomics, etc.), implementing deep learning and advanced bio-statistical models to decipher the mechanism of action (MoA) at spatially resolved single-cell communication level. C1 will provide a wealth of instructive information and MoA of novel beam modalities and parameter variations of, e.g., linear energy transfer (LET), dose, dose-rate, pulse and pulse interval.

Module (C2) Integrative biophysical modeling. The library of information gained in (C1) will build the basis for hypothesis generation and modeling by R&D module C2 and, at the same time, provides a platform for C2 to validate and further evolve their models. C2 will in turn build on an outstanding arsenal of mathematical, biological, and chemical models and on pioneers of numerical methods for differential equations and MC simulation in a team from both participating institutions. Therefore, this module covers an exceptionally broad spectrum of analysis. Beyond high-end implementation of a multitude of biophysical models using in-house developed platforms such as FRoG (Fast dose Recalculation on GPU) [AM9, AM10], and MonteRay [AM2] simulation of radiation transport including biochemical reactions and micro-dosimetric dose quantities to study radiation effects on the single event level is envisioned (B1). Moreover, *AccelerateRT* will substantially expand on existing quantitative and mechanistic modeling and simulation platforms to decipher time-dependent DNA damage complexity, repair and oxygen tension for FLASH RT – the “UNIfied and vErsatile bio-Response Engine” (UNIVERSE) [AM4, AM5, AM7]. A recently introduced dynamic UNIVERSE is the first mechanistic model of radiation effect in biological systems that adopts oxygen depletion mechanisms into a time-dependent algorithm to specifically predict effects at uHDR. UNIVERSE could thus aid development, experimentation and interpretation surrounding dose-rate effects as well as the appraisal of clinical viability in the case of FLASH irradiation. Therefore, deep molecular, cellular and tissue analyses of the radiobiological effect-space combined with existing and envisioned utilities for biophysical modeling will be instructive to dissect the MoA of FLASH for high and low LET radiation and could serve as an integrative force for interpretation of data generated in this ExC.

Module (C3) Intelligent molecular systems. In parallel to module C2, C3–C5 will focus on rational design of bench-to-bedside translation strategies for advanced technologies developed and knowledge gained within *AccelerateRT* as well as form a hub structure for reverse translation in this consortium. To this end, we will rely on our outstanding expertise in integrative data analysis, multiple high-throughput screening platforms (e.g., phage-/ribosomal displays), discovery of candidate molecules (targets) as well as a variety of scaffolds and versatile molecular engineering skills. The central aim of C3 is the **development of novel “multi-functional” drugs** that, like PSMA-ligands, could be utilized to treat as well as to detect tumors. This strategy will be tailored to the discovery of specific targets to be enriched in irradiated tissue that ideally could be specifically modulated, e.g., by uHDR/FLASH irradiation. Engineering molecular systems eliciting cooperative and synergistic operations on tissue/cellular and molecular levels at the interface with novel beam characteristics devised in this ExC will pave the way towards the development of next-generation intelligent medicine (iMed).

Module (C4) Biomedical functionalization of micro-robots. This module aims to transform the miniaturized robots into “smart” or even multifunctional “intelligent” robots by integrating the biological knowledge gained in the entire ExC into robot design and engineering. Biosensors and bio-robot communication interfaces will be developed for navigation of smart micro-robots released by minimally invasive flexible robotic devices into the tumor site, or even further advanced, to specific tumor niches, e.g., pH-sensor-driven identification of hypoxic regions for eradication of radio-resistant cells by compact accelerators (A4, Fig. 1). The ultimate goal will be the development of intelligent micro-robots that in addition to smart navigation could interact directly with specific beam characteristic (e.g., reactive oxygen species or molecular motion induced by the new beam), and/or elicit pharmacologic interventions, e.g., release of small molecule inhibitors or biologicals (e.g., immune cytokines) which will show to be a favorable combination with localized focal irradiation (C5).

Module (C5) Tumor-immune microenvironment (TIME)-evolution. System-level investigation of radiation interference with the TIME-evolution is the central subject of C5 that will instruct development of novel systemic and/or intratumorally administered therapeutics to elaborate the ExC's full synergistic potential towards a substantially improved and hopefully curative treatment of cancer. In analogy to the successful treatment strategy for infectious diseases, a highly personalized tumor-debulking RT step is followed by a localized molecular manipulation of the immune system aiming to reconstitute the tumor immune-surveillance [AA5, DJ3].

A **W3 professorship on biomedical functionalization of micro-robots at UHD**, funded by *AccelerateRT*, will boost RF C in its technological breadth, specifically in generating and exploiting new options for localized minimally invasive individual therapies.

3.4. How we interconnect our research: Model cases

Three **model cases** illustrate the power of *AccelerateRT*'s research approach to create innovative solutions in collaborative projects (Fig. 4). They build on contributions from, and give input to, the different R&D modules, considering the scientific, technological, and clinical view from day one. In model case I, a proof-of-concept idea for **CT with helium ions** will be developed towards a prototype of an integrated diagnosis system. Model case II combines our expertise in MRI-guided RT and HTS magnets towards a novel **MR "patient table"** for RT. In model case III, we will take the first steps for our vision of future **miniaturized RT devices for intracorporeal use** by combining accelerators, sensors, and robotics to become a reality.

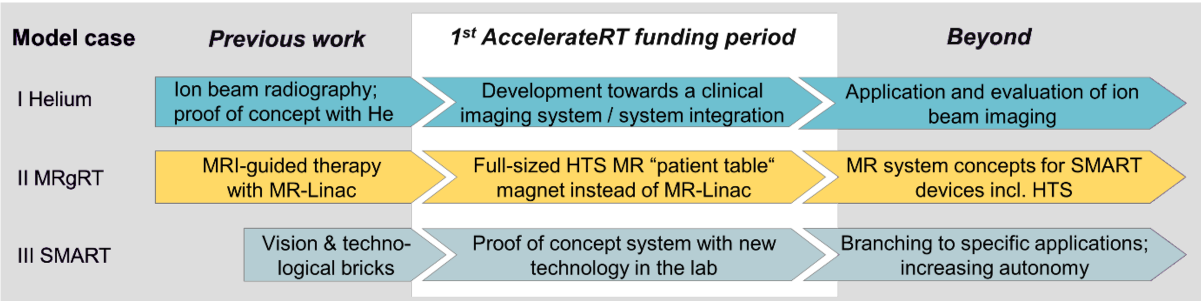


***Figure 4**: Schematic of the three model cases with different levels of technological readiness prior to the ExC (left). The developments during the first funding period (middle, white background) lead to perspectives for a potential second funding period and beyond (right).*

Model case I: Helium ion imaging and therapy. Development of helium (He) ion therapy illustrates well how cutting-edge medicine benefits from advanced technology combined with strong basic research in physics and biophysics. With the first patient treated with He beams at HIT in 2021 [AM2, JD10], the basis for a plethora of novel approaches in medicine is formed. We will address the challenge of accurately determining **particle beam ranges,** which is fundamental to precision ion therapy, with a novel tomographic method based on He ions. **Helium ion beam CT** (He-CT) has the advantage of i) extremely low dose imaging, with doses as low as during a transatlantic flight, ii) a novel diagnostic contrast, iii) unprecedented precision for range calculation, and iv) significantly reduced scatter as compared to X-rays. The technique will be explored first with He ion beams but will be extended to protons later to be available for a larger number of facilities. A prototype installation will use the HIT gantry, but a more compact and cost-efficient installation for patients in a seated position at a horizontal beamline will also be designed.

Over the last decade we have been investigating designs for ion beam CT based on various detectors [OJ7, OJ10, OJ8] and recently demonstrated that He ions offer the optimal properties for imaging [OJ3]. A proof of principle for He ion radiography serves as the basis for a He-CT system [OJ6]. Starting from a proof-of-concept development at DKFZ and HIT [OJ10], He-CT will be developed further and benefit from an upgrade of the HIT beam control system based on novel pixelated silicon sensors [UHu1], to control the low intensities needed for He-CT. *AccelerateRT* will design and build a large area multi-channel detector system based on state-of-the-art pixelated sensors (B1) for single particle tracking behind the patient. A data-acquisition system will be tailored to the detectors, and particle tracking and medical imaging algorithms adapted, towards first studies with phantoms and tissue (B3). The medical and biological information gained from studies with tissue will inform our radiobiology and biophysical modeling projects (C1, C2) and may lead to novel tissue contrasts for diagnosis. We will also develop a concept for a novel compact beam delivery system based on our expertise in HTS magnets (B2). At the end of the funding period, we expect an integrated He-CT system prototype operational at HIT and experience gained in all areas (accelerators, detectors, DAQ, imaging, biology), possibly leading to clinical studies beyond *AccelerateRT*.

Model case II: Magnetic resonance imaging-guided radiotherapy. The aim of this model case is to fuse MRI and RT technologies by rethinking the MR concept from the beam therapy perspective and integrating the needs of existing MR-guided RT approaches and devices. In *AccelerateRT*, we will also include functional imaging and tracing of radiation response on a molecular level (C3), already during therapy (B2). In the first step, we will evaluate novel biomarkers for predicting and detecting radiation response in MRI. Candidates are MR imaging of nuclei heavier than hydrogen (X-nuclei, e.g., sodium), and NMR spectroscopy techniques like chemical exchange saturation transfer. Both techniques will require high-field MR to have enough sensitivity. An interesting alternative to be investigated is hyperpolarized carbon-13, especially as a platform for studying FLASH and other beam mechanisms in *in-vivo* studies.

Besides functional imaging, MRI, even at low fields, is useful for guiding therapy and enabling compensation for breathing and other motion. It is a great opportunity to profit from synergies with the DFG Collaborative Research Center (CRC) 1527 HyPERiON at KIT. A first goal of *AccelerateRT* is the development of a dedicated single-sided MR that has its imaging field-of-view outside the magnet, providing much better access to the patient, as shown to work in some initial demonstrators [https://doi.org/10.1002/mrm.27861]. We will perform a design study for an MR table or MR wall based on HTS magnets. Within four years, a small-scale proof-of-concept HTS magnet will be built as a demonstrator for technology feasibility. In years 3–7, a full-sized HTS MR “patient table” magnet with low magnetic field imaging volume will be built. This system will allow imaging of organ motion during radiation similar to existing MR-Linacs. After year 7, a full-sized HTS MR “patient table” magnet with high magnetic field imaging volume may be built. Depending on the initial results, a high-field system for MR biomarker detection will be realized. In parallel, miniaturized MR detectors including radio frequency and gradient coils will be developed at KIT (B2). This will prepare for incorporation into SMART devices (A4, C4, model case III), likely based on an external field magnet. The work will be based on the prior work of the team at the MR-Linac at UHD and the BMBF-funded ARTEMIS project to integrate MRI into particle therapy as well as developments in MRI and MR spectroscopy technology at KIT.

Model case III: Miniaturized accelerator systems for SMART devices. The development and integration of miniaturized accelerator systems is a prime example of how synergies between the multiple disciplines and research foci within *AccelerateRT* may contribute to evolution of next generation precision medicine in a multi-step process. Indeed, all areas of expertise are required already for the first step: The compact accelerators able to provide uHDR electrons will be devised in (A1). Energy system design and solutions for novel components derived from observations on the system as well as pulsed beam modeling, benchmarked at the existing accelerator facilities, are derived from (A3) work packages, the beam and auxiliary control stem from (A2). The biophysical landscaping in RF C (C1–C3) provides the optimum parameter window for the miniature system. Finally, dose control and calibration are realized with the help of advanced dosimetry (B1). Once the first demonstrator systems of these miniature accelerators are ready, they can, with the help of robotics know-how (A4), be embedded in endoscopic, flexible robotic instrument-guided systems (**S**mart **M**iniaturized **A**ccelerators and Robotics for targeted Tumor **R**adio **T**herapy, SMART), ideally to treat tumors in preformed or physiologic cavities (Fig. 5, 1st generation). The next technological development will include biological functionalization of the robotic components to point to the right biological compartment (Fig. 5, 2nd generation). Also here, sensors and data processing (B1, B3) will come into play. With the new level of inter-institutional partnership and the commitment of the applicant universities to form a new focused strategic alliance, development of third generation "intelligent" SMART systems is foreseeable (Fig. 5, 3rd generation), albeit beyond the first funding period of *AccelerateRT*. Release of micro-/nano-robots [PF4-5, PF8], multifunctional molecular radiosensitizers, e.g., targeted DNA-damage repair inhibitors (DDRi) and/or release of immunocytokines to stimulate immune cell infiltration and activation may, together with RT, form an effective in-situ tumor vaccination strategy to systemically eradicate tumors, both at the treatment and abscopal sites. It is conceivable that, given the challenges in developing SMART systems, their successful design, development, and application would mark a novel era in precision medicine well beyond cancer treatment.

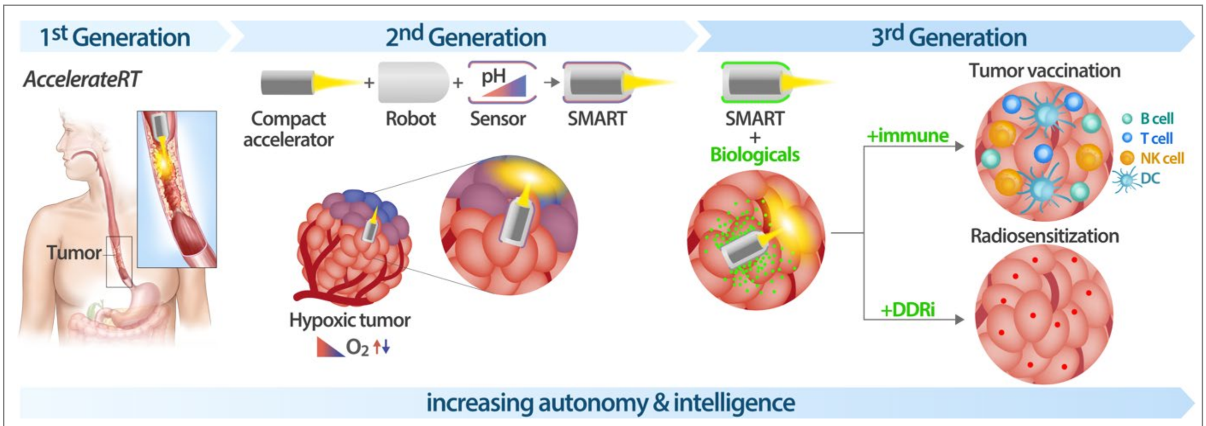


***Figure 5**: Three generations of precision cancer medicine with increasing miniaturization and autonomy, the last one being a vision extending beyond AccelerateRT.*

3.5. Outcome and vision

AccelerateRT aims to shape the future of radiation medicine towards more effective and more efficient therapies matching the individual needs of patients of any age, gender, and medical condition. We will bring radiation medicine to an entirely new level by rethinking existing concepts, by bringing in novel concepts based on the latest technology and by applying these technologies towards the discovery of novel biological radiation effects. For example, we will reinvent brachytherapy with miniaturized accelerators, to be further augmented by micro-robotics and intelligent biomedicine (Fig. 5). We will also design MR devices from the patient's and treatment perspective using HTS magnets for improved MRI-guided RT. Our work on He-beam imaging and therapy is targeted towards a completely new field of “helium medicine”. We will improve the energy efficiency of existing RT infrastructures and design novel devices to be smaller and faster, and to provide higher resolution and efficiency. Results from *AccelerateRT* will drive basic research in all research fields involved. Examples include: the systematic comparative survey of the biological effect landscape of novel beam modalities over an exceptionally large parameter range, next-generation sensing, dosimetry, data processing, and imaging, and novel beam source technologies. Results from *AccelerateRT* will generate significant benefits for future cancer patients, where we envision RT to be fast, precise and highly personalized, ubiquitous, and affordable.

Our long-term structural goal is to establish UHD and KIT as internationally leading center for oncotechnological innovations and advanced radiation sciences, embedded in an excellent environment (Section 5). *AccelerateRT* will bring together unique breadth, outstanding expertise, and critical mass in medicine, biology, mathematics, physics, and engineering to make this vision a reality. We envision *AccelerateRT* as a world-leading hub for creativity, innovation, and professional training – a nucleus of a new “Health Technology Valley” in the state of Baden-Württemberg, contributing significantly to the field of health, one of the grand challenges facing humankind.

4. Structures and strategies in the Cluster of Excellence

4.1. Support of early career researchers

AccelerateRT pursues a multidisciplinary approach that will attract and involve early career researchers (ECRs) on all levels; optimally supporting them will be key to cluster success. Our vision is that researchers leaving the ExC will not only be technology or healthcare specialists, but also generalists in adjacent fields with a broad multidisciplinary perspective who are used to working in international teams. This will make them highly attractive both for academia and a large variety of employers, ranging from health, IT, and high-tech industry to consulting or societal and government bodies.

AccelerateRT will fund ECR positions for doctoral and postdoctoral researchers, tenure-track positions towards professorships and senior scientist positions (Section 6). We will establish the ***AccelerateCareers* program** to empower our ECRs for high-quality multidisciplinary and collaborative research within the cluster, to promote early independence and international visibility, and to assist ECRs with reliable paths towards their next career levels in science or industry. *AccelerateCareers* is complemented by qualification and career development measures through UHD’s *Graduate Academy*, the *heiSKILLS Competencies & Language Centre*, *hei_INNOVATION* and KIT’s *Karlsruhe House of Young Scientists* (KHYS), that offer highly relevant courses in, e.g., entrepreneurial or didactic skills. These will be open to all cluster ECRs, including offers tailored to *AccelerateRT*’s requirements (Appendix 5).

The challenge of working together across scientific disciplines and bridging the differences between their epistemic cultures is addressed by our **collaboration support strategy**. Measures include training on interdisciplinary communication skills for ECRs, as well as monitoring and further developing the quality of interdisciplinary interactions as part of the cluster governance (Section 4.3). Our training program will include aspects of **research ethics** and is targeted to all cluster researchers, supported by the KIT *Academy for Responsible Research, Teaching, and Innovation* (ARRTI) and the UHD *Graduate Academy*. We will foster **innovation**, **new research directions**, and **scientific independence** of ECRs through a biannual call for **“Trailblazing Proposals”**. Successful proposals will receive seed money with maximum flexibility.

AccelerateRT will fund **24 doctoral researcher (DR) positions**. Doctorates in the cluster will be particularly attractive for graduates of the **new joint medical engineering study program** of UHD and KIT, which has started in 2022/23 with the bachelor study program, followed by the master study program in 2024/25. The research-oriented master curriculum will focus on topics closely related to this cluster. Also, physics, engineering, and medicine graduates will find a stimulating environment for their doctorate. We will enhance the study programs at UHD and KIT in these subjects with dedicated courses as well as research projects at our unique infrastructures and undergraduate theses on cluster topics, with **annual best-thesis awards**.

For the **structured training of DRs**, *AccelerateRT* will enhance existing structures with cluster-specific measures. Initially, the DRs will become members of existing graduate schools like KSETA (Karlsruhe School of Particle and Astroparticle Physics: Science and Technology), HGSFP (Heidelberg Graduate School for Physics), HBIGS (Heidelberg Biosciences International Graduate School), and HIDSS4Health (Helmholtz Information & Data Science School for Health) as appropriate and profit from their established topical and key-skill training. We will enhance their portfolios by offering joint training courses and seminars, e.g., in medical imaging, advanced detectors, biomedicine, and technology transfer to medical diagnostics, supplemented by peer instruction formats and communication training for multidisciplinary teams. Each DR will be **supervised by a *Thesis Advisory Committee* (TAC)** of at least two senior cluster scientists from different fields, to strengthen the collaboration between the cluster disciplines. Annual meetings of DR and TAC, each involving a written report and presentation, will ensure close supervision and scientific quality control. After the research and transfer portfolio of the cluster has been further sharpened, we aim at strengthening the doctoral training by founding an *AccelerateRT Graduate School* in which DRs will develop mutual understanding of the requirements and challenges in medicine and technology.

AccelerateRT will also offer **24 postdoctoral qualification positions** for three-year *Cluster Fellowships* with excellent individual research conditions and perspectives for a further career in academia and as sought-after specialists in the health-care industry. The Cluster Fellows are central to driving the research in *AccelerateRT*; they will be recruited internationally. They will gain **leadership and supervision experience** at an early career stage, e.g., as coordinators of R&D modules or as members of a TAC. To ensure the quality of their work, the Cluster Fellows will deliver midterm and final project reports. We will support four outstanding Cluster Fellows towards a junior research group with a DR and seed funding. This is complemented by the *Young Investigator Group Preparation Program* at KIT, which offers a position and support for applications for a third-party funded junior research group from applicants not yet at KIT or only recently employed.

The **international visibility and competitiveness** of DRs and Cluster Fellows will be enhanced by **awards for outstanding doctoral theses and for key contributions** of Cluster Fellows to our research. **Travel grants** will enable research stays at partner institutions and summer schools, as well as presentations at topical workshops and conferences. In our **guest program**, we will host high-profile visiting scientists who work on joint projects with DRs and Cluster Fellows.

On the level of junior group leaders, *AccelerateRT* plans to establish three tenure-track (W1 towards W3) **junior professor groups** at the interface of medicine, physics, engineering, and computer science. We will also offer **six permanent senior scientist positions** for researchers with key expertise indispensable for the continuity of the cluster projects, with sustained funding through the participating institutes. Outstanding national and international postdoctoral researchers will be attracted to these positions. Successful junior researchers will profit from the *heiTRACKS* program at UHD, which includes, e.g., “+3 Financing” for up to three-year bridge financing for Emmy Noether group leaders and holders of ERC starting grants, and benefit from the management program “Towards a Professorship” on their path to a professorship. The Young Investigator Network (YIN) at KIT will help increase the young researchers’ visibility.

All ECRs will be offered **personal and professional development** measures, including individual mentoring by two experienced cluster scientists, with annual feedback meetings and coaching towards careers in and outside academia. PIs and senior scientists will be offered training courses to improve their mentorship and feedback communication skills. Annual *Industry Talk* events will attract local industry partners and enable **early contact between ECRs and prospective employers**, building on, e.g., the KIT Business Club.

4.2. Support of equity and diversity

Inspired by our research, which is targeted towards highly personalized medical treatment and therefore considers diversity by design, *AccelerateRT* will establish the ***AccelerateDiversity* program:** We will raise **awareness of equity, diversity, and fairness** among all cluster members by regular training and provide **diversity-aware procedures** and **individual support**, tailored to cluster requirements. These measures will be coordinated by an **Equity and Diversity Manager**, supported by the Cluster Office (Section 4.4). The program is embedded in two universities that maintain and enhance **highest equity and diversity standards** with equity plans, annual equity monitoring reports, equity awareness policies, and central measures to foster equal opportunities and diversity. *AccelerateRT* will be supported by UNIFY (Unit for Family Diversity & Equality) at UHD and CDM (Gender and Diversity Management) at KIT.

In all scientific disciplines of *AccelerateRT*, **women are still underrepresented** in leading positions (e.g., 16% female professors at the KIT Physics Department, 15% at the Medical Faculty Heidelberg), compared to the respective student gender ratios (e.g., 25% female physics graduates at KIT, 55% in medicine at UHD in 2021). To improve this situation, *AccelerateRT* will **actively increase the number of female researchers at the professorial and postdoctoral level**: The cluster will fund two W3 professorships with the goal to recruit outstanding women (Section 5.2). We aim for at least ten *Cluster Fellowship* positions (Section 4.1) filled by women (at least 40% women, aligned with KIT's and UHD's gender-equity goals). Two support positions will be allocated for female researchers who take high-level leadership positions in the cluster or bodies of the applicant universities. We will actively encourage and support participation in career programs for female researchers like the *Olympia Morata* program at UHD as well as mentoring programs such as KIT's *x-Ment*. We will also put forward role models: Boards and committees as well as invited speakers at conferences and workshops will be gender-balanced as much as possible (at least 40% women on average). *AccelerateRT* scientists will support networks to strengthen the community and increase the visibility of top female scientists, such as the KIT Women Professors Forum, of which ExC scientists are founding members.

Further gender-equity measures are **tailored to individual disciplines**: In medicine, we will provide incentives and encouragement for female clinicians to pursue a career in research, e.g., through supporting personnel. For science, technology, engineering, and mathematics (STEM) subjects, we will contribute to the universities' activities to attract female students as part of our science communication program (Section 4.5). Female student ambassadors will present our research at high schools, highlighting, e.g., interdisciplinarity, clear career paths, and international networking.

Through its Cluster Office, *AccelerateRT* will promote an inclusive and welcoming work environment for **researchers from any background and nationality**. We will assist cluster researchers in finding suitable support for their individual situation, e.g., through the applicant universities' International Offices, or through UNIFY, and will offer counseling on career planning. The dual-career service at both universities will be involved in recruiting outstanding international scientists by supporting their partners in continuing their professional careers at the new location. Special care will be taken for the onboarding of underrepresented groups. Naturally, all cluster-wide events and communications will be in German and in English, with language courses available to facilitate integration. To attract the best talents worldwide (Section 4.1), we will have a strong focus on fair and transparent selection processes for ECRs by defining and communicating objective selection criteria.

It is our strong belief that a **healthy work-life balance** is key to productive collaboration. We will schedule all cluster events during regular working hours, offer hybrid options as appropriate, and provide solutions for young parents to participate in workshops and conferences. These measures will build on **UHD's and KIT's extensive support for families** – both are certified by *audit family-friendly university*, e.g., with sufficient childcare spots for children under three years, care in emergency situations, schoolchild care, and support for nursing care of relatives.

4.3. Strategies for research data and research software management and provisions for research infrastructures and instrumentation

Due to its multidisciplinary nature, *AccelerateRT* will produce research data varying widely in size and format as well as in legal and ethical requirements, from laboratory measurement data to sensitive personal health data. While we already employ state-of-the-art research data management (RDM) solutions for individual research fields, a central innovation to be developed in *AccelerateRT* will be a **common data space** for the entire cluster. As a first step, we will develop common data hubs for each RF. We will install a **Cluster RDM Team**, headed by a **Research Data Manager** financed by the cluster and supported by PIs with a data-science profile (e.g., L. Maier-Hein). Prior to submitting a full proposal, we will create a **comprehensive RDM plan**, with tools like the Research Data Management Organizer (RDMO), supported by the *Competence Centre for Research Data* (UHD), *RDM@KIT*, and the new KIT Center Health Technologies. The plan will address data and metadata descriptions and workflows, data storage and archiving, exchange and accessibility, as well as legal frameworks, responsibilities and resources. We will follow Open Science principles, generate FAIR (Findable, Accessible, Interoperable, Reusable) data, and provide interfaces to RDM solutions developed in related German National Research Data Infrastructure (NFDI) consortia. To enhance RDM skills across *AccelerateRT*, we will offer **RDM training** tailored to the needs of cluster scientists and install **RDM contact persons** for each RF. The RDM plan will be continuously adapted to the cluster requirements.

The RDM team will draw from our experience in various research fields: The HIRO research database in Heidelberg integrates clinical routine data and research data in radiation oncology and provides regulated access. In *AccelerateRT*, we will build on this concept of **systematic data provisioning**, promising significantly faster development cycles. Computer codes are routinely made available in the applicant universities' GitLab repositories, and high-level data are regularly provided as supplementary material to journal publications. For central storage and processing of large data volumes and for collaborative software development, *AccelerateRT* will draw from experience with related international large-scale projects, such as the computing center *GridKa*, and the solutions being developed in the **NFDI consortia** *NFDI4Ing*, *PUNCH4NFDI,* and *NFDI4Health*. UHD and KIT will support *AccelerateRT* with jointly operated services for long-term storage of research data. Collaborative platforms for data sharing, project planning and co-authoring (e.g., heiBOX and bwSync&Share) will be expanded and made mutually accessible. The ExC will collaborate with expert teams at the *Scientific Software Center at the Interdisciplinary Center for Scientific Computing* (UHD) and *Software Sustainability and Performance Engineering* (KIT) on **reproducible science and software sustainability** and optimal use of computing resources.

Provisions for sustained and safe operation of major infrastructures and laboratories (e.g., HIT, FLUTE, KARA, Section 5.2) will be adopted by KIT and UHD. *AccelerateRT* will provide funds for their extension and the integration of new instruments to be developed or purchased.

4.4. Management, governance, quality assurance

The **governance** of *AccelerateRT* (Fig. 6) is modeled on successful large international collaborations in basic research and designed to steer a diverse team towards a common goal. Efficient procedures will ensure results of highest quality and scientific exchange on all levels.

***Figure 6**: Governance of the Cluster of Excellence AccelerateRT*

Two **spokespersons**, one from each applicant university, represent *AccelerateRT* in relation to the university leadership and outside parties, oversee all procedures and take responsibility for all administrative acts. These activities are supported by the **Cluster Office**, headed by the **managing director**. The Cluster Office also implements and coordinates cluster-wide activities, such as the workshop program, equity and diversity (Section 4.2), sustainability, **science communication and transfer** (Section 4.5), and quality management for the cluster. The Cluster Office also interacts closely with the research data experts (Section 4.3) and the **sustainability manager**, who ensures sustainability aspects are considered in all cluster activities. The central governing body is the **Executive Board** (EB), headed by the spokespersons. The six elected EB members include representatives from the cluster scientists (4) and ECRs (2). Ex-officio members include the head of the Finance Committee (see below), the scientific coordinators of the three Research foci, the research data manager, the equity and diversity manager (Section 4.2), the sustainability manager, and the managing director. The EB is responsible for the election of the spokespersons, the overall coherence and evolution of the research program and the planning of cluster-wide activities. It oversees the implementation of equity, diversity and sustainability measures and best practices for the management of research data and software. As part of our collaboration support strategy (Section 4.1), the EB will monitor and further develop the quality of interdisciplinary interactions in the cluster. The EB will meet quarterly. The spokespersons call together an annual meeting of all scientific and administrative cluster members. The cluster scientists elect the EB representatives and the three members of the **Finance Committee** (FC) for two-year terms. The FC provides advice on the cluster budget to the spokespersons and the EB. An **International Advisory Board** (IAB) with ten representatives from science, industry, patients, and media is appointed by the universities to review the cluster activities and provide scientific and strategic recommendations to the EB and the university leadership.

The multidisciplinary research in *AccelerateRT*'s three **Research foci** is organized bottom-up: Each R&D module is coordinated by two lead PIs together with an experienced postdoctoral researcher. They foster regular dialog among all experts to optimize scientific output, to leverage synergies and to enable frequent adjustment of technological options and clinical requirements as well as "scouting" of emerging technologies. The lead PIs of the R&D modules will appoint **Scientific Coordinators** of their RF, to be endorsed by all PIs. The coordinators represent the RF in the EB and are responsible for overarching aspects such as coherence of the research program, strategic and resource planning, and scientific exchange among the R&D modules. They are supported by contact persons for sustainability and research data and software management within each RF. To foster interdisciplinary research, innovation, and technology transfer, the EB will install two **cross-sectional boards**: The **Translation Board** will evaluate the potential of *AccelerateRT* results for medical practice, to be realized outside the ExC. The **Innovation Board** will identify results that may lead to innovative new products, supported by the technology transfer units of UHD and KIT. For *AccelerateRT* to react to new developments swiftly, the EB can install a small number of **Topical Boards** to explore "hot topics" identified by cluster scientists, further cross-sectional boards, or close obsolete boards.

In the above management structure, **scientific quality is assured at various levels**. All cluster researchers will follow regulations **on good academic practice** as well as guidelines and principles for responsible action of the applicant universities and undergo regular internal reviews. In addition, the cluster will benefit from the UHD quality management program heiQUALITY. In the case of conflicts, an ombudsperson will be assigned to mediate. The overall scientific quality and strategic positioning of the cluster shall be improved through interaction with the IAB. Regular evaluations of all measures mentioned above will be presented to the EB.

4.5. Science communication and knowledge transfer, research-oriented teaching

Health belongs to the **grand challenges** of society and is of great interest to the public. However, the corresponding basic research remains largely unnoticed. Cluster scientists are already strongly engaged in **science communication** to increase the visibility of their research and to facilitate dialog with the public in outreach events and social media. These efforts build on successful outreach formats, e.g., public events at TRIANGEL Open Space, Karlsruhe. We would like to convey that **radiotherapy will be made safer and more energy efficient, sustainable, and affordable** through our research. More generally, we aim to increase **acceptance for novel technologies** and large infrastructure and the need for academic research. We are also eager to learn about citizens' concerns and needs, also regarding **ethical aspects of technological progress.** Ethical literacy is a common goal of both universities, and cluster members will have access to seminars at ARRTI (Section 4.1).

Successful science communication and knowledge transfer requires close interplay with **public relations professionals**. *AccelerateRT* will open a novel science communication avenue that combines natural science, engineering, and medicine with art and architectural history in a **science visualization project** with Prof. Inge Hinterwaldner (KIT). *AccelerateRT* will follow a cross-media communication strategy with content tailored to different audiences, e.g., with short videos showcasing role models for young women, and study and career opportunities. The efforts will be organized by our Science Communication & Transfer Coordinator (Section 4.4) and in close collaboration with the Corporate Communications department at KIT and the Communications and Marketing department of UHD. To optimally support these efforts, one of the IAB members should have a background in communication and/or media. An important goal is **to reach out to young people**. We will address high school students by providing teacher training and by developing and offering particle therapy Master Classes. Student ambassadors will inspire high school students with our research, and with STEM and medical subjects in general. We will **address industry partners internationally** by presenting our research and potential cluster products at international trade fairs.

AccelerateRT may generate numerous results of high commercial interest for companies in the healthcare sector, especially (i) advanced algorithms and software solutions for treatment planning, modeling and visualization, in particular in real time; (ii) techniques, software and dedicated hardware for ultra-fast, real-time processing of large amounts of multi-source data; (iii) new technologies and compact devices for unconventional imaging and application of radiation; (iv) biomarkers, targets and drugs for visualizing treatment effects or for manipulating tissue sensitivity, e.g., against radiation. Securing intellectual property (IP) and accelerating **technology and knowledge transfer** are key steps for translating new technologies and products. The Innovation Board (Section 4.4) will create awareness and provide support in accordance with the innovation and technology transfer offices at UHD, KIT, and DKFZ. Based on the long-standing and trustful cooperation between the transfer offices of the participating institutions, an individual agreement will be implemented that defines the responsibilities and obligations as well as the rights of each institution for IP generated by the institutions in the implementation of their respective work programs in the cluster. This agreement will be in place before the full cluster proposal is submitted and will be based on the existing EU consortium agreement or the German Federal Ministry for Economic Affairs and Climate Action (BMWK) model agreements for R&D cooperation from a regulatory point of view.

AccelerateRT will **enhance research-oriented teaching** at UHD and KIT, both in the new joint medical engineering study program (Section 4.1) and in our established study programs. Students will profit from innovative teaching formats based on our R&D projects as well as access to our unique infrastructures and larger networks, such as the new KIT Center Health Technologies. The teaching program will be linked to our DR training (Section 4.1) and continuously adapted to new developments to realize strong synergies between research and education.

5. Environment of the Cluster of Excellence

5.1. Strategic development planning at the universities

The research proposed in *AccelerateRT* can only be pursued by bringing together a wide range of expertise and infrastructures: Heidelberg University (UHD) and Heidelberg University Hospital (UKHD) are a center of life science and medical research; KIT – the Research University in the Helmholtz Association – has a broad technology portfolio relevant to RT.

AccelerateRT originates from the established cooperation of the two applicant universities. Within the **Heidelberg-Karlsruhe Strategic Partnership** (HEiKA, Appendix 5), in which both universities jointly and strategically develop their complementary competencies. Joint activities include research projects, support of ECRs, innovation, and teaching. Within six HEiKA Research Bridges interdisciplinary research is coordinated and funded. In one of them ("Medical Technology for Health"), *AccelerateRT* PIs and associated PIs (specified in Section 5.2) have been working together in joint projects. The close partnership is also underlined by a new **joint medical engineering bachelor/master study program** (Section 4.1). Building on HEiKA, the partners have further developed their portfolios: UHD aims at expanding the range of research subjects and bundling technological and engineering expertise with the newly founded **Faculty of Engineering Sciences**. The faculty focuses on innovative engineering approaches such as molecular biotechnology, engineering of molecular systems and medical technology and is therefore mostly complementary to engineering at KIT. KIT has recently bundled its health technology expertise in the **new KIT Center Health Technologies**.

AccelerateRT will further solidify and expand this cooperation by bringing together virtually all expertise within HEiKA under the aspect of exploring novel beams and technologies for improving radiation medicine. New professorships will be created in and around the cluster (Sections 3 and 5.2). Within the **structure and development planning** of UHD and KIT, our research activities and the strategic goals of both universities will be further aligned. To intensify the interaction with existing coordinated research programs and centers, we have the support of KIT and UHD for funding a small number of additional (tenure track) professorships in strategically important fields like NMR/MRI or molecular systems engineering from sources other than *AccelerateRT*.

AccelerateRT also builds on the **long-standing cooperation of UHD / UKHD with DKFZ**, e.g., in medical physics education and clinical cooperation units. DKFZ and UKHD are partners within national initiatives against cancer, like the German Consortium for Translational Tumor Research Therapy (DKTK), the National Centers for Tumor Diseases (NCT). Within the Helmholtz Association, KIT is also strategically linked with DKFZ, with common activities like the joint KIT-DKFZ-UHD graduate school HIDSS4Health (Section 4.1).

AccelerateRT's goals are very well aligned with those of the **Health + Life Science Alliance**, which bridges seven life science and medical institutions in Heidelberg and Mannheim: Heidelberg University, DKFZ, EMBL, Max Planck Institute for Medical Research, University Hospital Heidelberg, University Hospital Mannheim and the Central Institute of Mental Health. The Health + Life Science Alliance is funded by the State of Baden-Württemberg as part of its Innovation Campus strategy and provides ample collaboration opportunities between the Alliance institutions and fosters the development of joint technology platforms.

In the long term, our goal is to establish UHD and KIT as an international center of translational accelerator-based sciences by founding a **HEiKA Center for Innovative Biomedical and Radiation Technology**, supported by both partner universities. The HEiKA Center will be instrumental in connecting the Rhine-Neckar Metropolitan Region with the Technology Region Karlsruhe towards establishing a new **"Health Technology Valley"** in the southwest of Germany. The organizational form of the center will be further specified within the first funding period.

5.2. Resources provided by the institutions

AccelerateRT benefits from **strong commitments of the applicant universities**, established networks (Section 5.1), and UHD's and KIT's University of Excellence frameworks and projects, with funding available to strategically strengthen new research directions opened up by the cluster (Appendix 5). The applicant universities guarantee sustained funding for the professorships to be created in *AccelerateRT* (Section 3), will operate infrastructures relevant to the cluster (Section 4.3 and below) with highly trained personnel, and provide laboratory and office space to host cluster researchers and their projects.

AccelerateRT offers unique scientific and technological breadth and "critical mass" in its relevant scientific disciplines. **We envision the scientific network of *AccelerateRT* to be substantially larger than the 25 cluster PIs** and their research groups, with additional researchers ("associate PIs") and their groups contributing. One cluster PI (F. Mathis-Ullrich) has moved to a full professorship at the Friedrich-Alexander University of Erlangen-Nuremberg recently, while preparing this draft proposal. The move opens new cooperation opportunities for *AccelerateRT* with further clinics and research fields, as well as connection to relevant industry partners in Erlangen (e.g., Siemens Healthineers). At the same time, joint publications and supervision of doctoral researchers with PIs at KIT and UHD will be continued. In addition to the cluster professorships, the applicant universities have appointed several **new professorships** which add to the research environment, e.g., in biomedical engineering (M.F. Spadea, KIT), in laser-driven accelerators (M. Fuchs, KIT), in experimental biophotonics in the life sciences (M. Kreysing, KIT), in visceral surgery and robotic surgery (C. Michalski, UHD) and in neurosurgery (S. Krieg, UHD).

In Heidelberg, the cluster will benefit from internal structures such as the Fields of Focus (FoF, Appendix 5) that bring together research and teaching on a topic-related basis, create connections to the excellent institutional non-university research environment (the "Heidelberg Research Campus", with UHD, UKHD, DKFZ, EMBL and MPIMR as cooperating institutions), and are strategic instruments for the further development of UHD. Cluster spokespersons automatically become members of the Research Council(s) of the applicable Fields of Focus to promote the inclusion of newly recruited cluster researchers in the local specialist community. Networks specific to *AccelerateRT* include the Heidelberg Institute for Radiation Oncology (HIRO), a well-established structure for cooperation and sharing infrastructure for radiooncological research joining UHD, DKFZ, and HIT. HIRO, together with OncoRay, Dresden, are appointed National Center for Radiation Research in Oncology (NCRO) with a proven track record of joint activities. Moreover, *AccelerateRT* will synergize with networks such as DKTK and NCT. *AccelerateRT* will be also backed by a long-standing collaboration with additional partners at DKFZ, especially in the area of medical physics, radiology, machine learning, and AI (M. Kachelrieß, K. Maier-Hein, H.-P. Schlemmer, J. Seco, T. Gehrke, K. Giske), cell and molecular biology, functional genomics, and clinical radiobiology (S. Fröhling, M. Boutros, P. Lichter, A. Ernst, M. Baumann, P. Huber, S.A. Trump, S. Pfister, C. Ball, G. Ungerechts, S. Eichmüller). At UHD, associate PIs cover the areas of pathobiology and pathophysiology (P. Schirrmacher, A.v. Deimling), molecular systems engineering and advanced materials (C. Selhuber-Unkel), medical physics (J. Bauer), tumor microenvironment at the European Center for Angiosciences (J. Sleeman), and medicine and immune oncology (W. Wick, M. Platten). Collaborators at EMBL provide, e.g., next-generation sequencing, advanced microscopy, cryogenic electron microscopy, and large-scale data analysis (W. Bennes, S. Mattei, R. Pepperkok, J. Korbel).

At KIT, existing strong internal research and collaboration networks connected to *AccelerateRT* include the Accelerator Technology Platform (ATP), which combines KIT expertise and infrastructures for accelerator research, the KIT Centers Health Technologies and Elementary Particle and Astroparticle Physics (KCETA), which bundles research and enabling technologies for large-scale international experiments (Appendix 5). They will ensure strong and flexible links to the existing research portfolios at KIT, stimulating a continuous evolution of cluster research topics. *AccelerateRT* will be supported in its accelerator research by an expert on AI-based accelerator control (A.S. García). The ExC's research on radiation control and visualization is supported by experts on silicon sensors and radiation hardness (I. Perić, A. Dierlamm), on superconducting quantum sensors (S. Kempf), on ultrafast readout systems and electronic packaging (M. Caselle, A. Kopmann), on dosimetry, neutron detection and simulation of particle transport (R. Stieglitz, R. Engel, A. Ferrari), on X-ray spectroscopy, phase-contrast imaging, and nano-characterization (T. Vitova, T. Baumbach), and on 3D ultrasound computed tomography (N. Ruiter). The ExC will also profit from expertise on mathematical models for dose calculations and RT treatment planning and simulation of oxygenation in tumor tissue (M. Frank) and computer science research in sensor data collection and interchange (M. Beigl). Further engineering support is provided in optical technologies in medicine (W. Nahm), microwave and radio wave technologies (T. Zwick), cryogenics (S. Grohmann), energy applications of superconductivity (M. Noe), and integration of energy systems (V. Hagenmeyer). The ExC's research in radiobiology and molecular systems is supported by expertise in biomaterials and biological chemistry (S. Bräse, U. Schepers) and in vitro and in-vivo tumor biology (V. Orian-Rousseau). Additional expertise in arts and humanities includes research on collaborative science (S. Götze) and on image theory and scientific imagery (I. Hinterwaldner).

A unique set of existing **complementary top-notch infrastructure** (Tab. 2) covers all fields relevant to the cluster: Accelerator-based facilities; synthesis, characterization, and fabrication centers; imaging platforms; simulation and robotics laboratories; and data facilities (Section 4.3). In addition, we will employ existing clinical treatment systems (MR-Linac, Cyberknife, Helical Tomotherapy, Mobetron) and scanners (CT, MRI with dynamic nuclear polarization, positron emission tomography, and combinations thereof). This is complemented by a wide range of state-of-the-art enabling technologies, including the CellNetworks Core Technology Platform, one of UHD's core facilities, high-performance and high-throughput computing at KIT's SCC, dosimetry laboratories, and software platforms for Monte Carlo simulation, medical imaging, and therapy planning.

***Table 2**: Infrastructures relevant for AccelerateRT in * Heidelberg and ** Karlsruhe*

Infrastructure	Description/Application within *AccelerateRT*	R&D modules/ model cases
HIT*	Synchrotron-based beams of protons, helium, carbon and oxygen ions (clinical and research platform)	A3, B1, B2, C1-5, MC1
FLUTE**	High-intensity THz radiation, short-bunch electron beams	A1, B1, C1-5
KARA**	Benchmark facility for microstructured beams, high-throughput synchrotron-based characterization, short X-ray pulses	A3, B1, C1-5
ATHENA**/ cSTART**	Short-pulse photon facilities with associated THz and laser laboratories	A2, C1-5
KNMFi**/ KCOP**	Nano and micro fabrication and characterization	A1, A2, A4, B1, C4
Advanced Detector Lab (ADL)**	ASIC design, irradiation center (protons, neutrons, X-rays), ultra-fine pitch flip-chip bonding	B1, C1, C4
KNMR**	Hyperion facilities for high sensitivity MR, HTS magnet prototyping	A2, A3, B2, C1, C3, C4, MC2
Imaging Lab*	High field experimental, (pre)-clinical MRI as well as hybrid MRI-PET/CT systems. Multiscale, optical, microCT/PET, HR-US, IGRT (SmART)	C1, C3, C5
Artificial Intelligence and Cognitive Robotics (AICOR)*	Imaging and AI based cognitive guided localized interventional therapies. Operations with collaborative robotic manipulators and multimodal sensors	A4, C4, MC3
Advanced Microscopy Facilities*	Structural biochemistry, HD-CRYONET – the cryo-electron microscopy network of UHD, advanced light microscopy facilities incl. "superresolution" microscopy	C1, C3, C4, C5
IOmics – platforms*	Integrative multiscale Omics, spatially resolved radiomics, single cell multiomics (transcriptome, genome, epigenome, proteome), clinical data integration, a.o. the largest next generation sequencing (NGS) facilities and comprehensive immunemonitoring units	C1, C3, C4, C5, MC3
Medico-legal unit*	CE certification of medical instruments, research with patient-derived data, compliance with EU Medical Device Regulations	C3-5 M1, M2, M3

5.3. Cooperation with other institutions

AccelerateRT's PIs **cooperate with academic partners worldwide**. Examples in the applicant universities' international and national networks include UHD's Center Latin America (HCLA) in Santiago de Chile, which offers postgraduate and continuing education in cooperation with local partner universities, and the German-Japanese network of universities HeKKSaGOn (UHD, Kyoto, KIT, Tohoku Sendai, Göttingen, Osaka). CERN (Switzerland) pursues R&D on accelerator magnets and particle detectors and will therefore be a key partner for the fast transfer of technologies from basic research to RT. Collaboration with Paul Scherrer Institute (PSI, Switzerland), will be instrumental for the further development of FLUTE, ultra-fast beam diagnostics, and particle biophysics. *AccelerateRT* will also benefit from well-established national networks, such as the Helmholtz Program "Matter and Technologies" and the accelerator technology platform ATHENA, as well as connections with international partners, e.g., in the EU-funded EuPRAXIA network and with Imperial College London.

Important partners for ion beams, radiation oncology, biophysical modeling and radiobiology will include a well-established network of national (GSI, HZDR, OncoRay, Helmholtz Center Munich) and international (UCSF, LBL, Harvard University, and Albert Einstein College of Medicine in the US, CNAO in Italy, and CRUK RadNet in the UK) institutions.

Cluster activities will also benefit from established **cooperation with industrial partners**. Examples of fields in which industrial cooperation is envisaged to be of particular value include accelerator technologies (Varian/Siemens Healthineers, Elekta, IBA-Proton Therapy, Bilfinger Noell), medical technologies and software (Zeiss, Viewray, Accuray, Raysearch, BrainLab IntraOp), robotics technologies and programming (OttoBock, Storz, ArtiMinds), pharmacological DDR and immune modulators (Merck KGa, Bayer, BioNtech), energy technologies (ABB, TransnetBW), and detector technologies (Hamamatsu, PTW).

6. Anticipated budget

Table 3: *Anticipated budget of AccelerateRT (in kEUR, without program and university allowance)*

	2026	2027	2028	2029	2030	2031	2032	Total
Funding for staff	4,177	4,260	5,596	6,716	6,850	6,987	7,127	41,713
Direct project costs	832	867	922	787	842	787	837	5,874
Instrumentation	1,240	2,740	1,490	690	440	390	220	7,210
Total	6,249	7,867	8,008	8,193	8,132	8,164	8,184	54,797

The proposed staffing of *AccelerateRT* includes three tenure-track (W1) professorships and one full professorship (W3); these are required to strategically boost important research areas of the ExC. Two well-endowed grants leading to W3 professorships will be used to recruit outstanding female researchers within a relevant field of *AccelerateRT* (Section 4.2). In addition, *AccelerateRT* will fund six tenure-track positions towards permanent senior staff positions upon evaluation. Limited-duration qualification positions will be provided for doctoral researchers (24) and postdoctoral researchers (24). The cluster office, headed by the managing director, will be staffed with three full-time equivalents for general administration, finances, and outreach. *AccelerateRT* will also fund a research data manager. In total, twelve positions in “other categories” (technical and administrative) have been included.

AccelerateRT will provide annual budgets for personnel (about three positions for each W1 and five positions for each W3) and small (<200 kEUR) investments for the four professorships funded by the cluster. The grants to recruit outstanding women include budgets comparable to those for W3 professorships. Each R&D module will receive funding for personnel (3–6 positions) and small investments, adjusted for contributions already covered by the professorships. We reserve funds for about two large (>1 MEUR) investments in instrumentation projects, e.g., for novel beam modalities, where the detailed cost planning depends on the results of our research. Our spending profile assumes that the larger part of the investments will be required early in the funding period and that positions will be filled with a small delay. An annual rise of 3% in personnel costs has been included.

Appendix

1. The 25 most important publications, Category A

The 25 most relevant publications are listed in thematic order. The publications reflect the key competencies of the cluster PIs regarding the research proposed in *AccelerateRT*.

1. **Müller A-S**. *Accelerator-Based Sources of Infrared and Terahertz Radiation.* **Reviews of Accelerator Science and Technology** (2010) 03(01): 165-183. https://doi.org/10.1142/S1793626810000427
2. Funkner S, Niehues G, Schmidt DA and **Bründermann E**. *Terahertz Absorption of Chemicals in Water: Ideal and Real Solutions and Mixtures.* **Journal of Infrared, Millimeter, and Terahertz Waves** (2014) 35(1): 38-52. https://doi.org/10.1007/s10762-013-0017-0
3. Marek A, Avramidis K, Ginzburg N, Illy S, **Jelonnek J**, Jin J and Thumm M. *Extended Feedback System for Coupled Sub-THz Gyro-Devices to Provide New Regimes of Operation.* **IEEE Transactions on Electron Devices** (2020) 67(12): 5729-5735. https://doi.org/10.1109/TED.2020.3028531
4. Tuckmantel T, Pukhov A, Liljo J and **Hochbruck M**. *Three-Dimensional Relativistic Particle-in-Cell Hybrid Code Based on an Exponential Integrator.* **IEEE Transactions on Plasma Science** (2010) 38(9): 2383-2389. https://doi.org/10.1109/TPS.2010.2056706
5. Wächter M, Ovchinnikova E, Wittenbeck V, Kaiser P, Szedmak S, Mustafa W, Kraft D, Krüger N, Piater J and **Asfour T**. *Integrating multi-purpose natural language understanding, robot's memory, and symbolic planning for task execution in humanoid robots* **Robotics and Autonomous Systems** (2018) 99: 148-165. https://doi.org/10.1016/j.robot.2017.10.012
6. **Ullrich F**, Lussi J, Chatzopoulos V, Michels S, Petruska AJ and Nelson BJ. *A Robotic Diathermy System for Automated Capsulotomy.* **Journal of Medical Robotics Research** (2017) 3. https://doi.org/10.1142/s2424905x18500010
7. **Arndt T**, **Holzapfel B**, Noe M, Nast R, Hornung F, Kläser M and Kudymow A. *New coil configurations with 2G-HTS and benefits for applications.* **Superconductor Science and Technology** (2021) 34(9). https://doi.org/10.1088/1361-6668/ac19f4
8. **Simon F**. *Silicon photomultipliers in particle and nuclear physics.* **Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment** (2019) 926: 85-100. https://doi.org/10.1016/j.nima.2018.11.042
9. Dierlamm A, Balzer M, Ehrler F, **Husemann U**, Koppenhöfer R, Perić I, Pittermann M, Topko B, Weber A, Brons S, **Debus J**, Grau N, Hansmann T, **Jäkel O**, Klüter S and Naumann J. *A Beam Monitor for Ion Beam Therapy Based on HV-CMOS Pixel Detectors.* **Instruments** (2023) 7(1). https://doi.org/10.3390/instruments7010009
10. Nassar O, Mager D and **Korvink JG**. *Wireless Double Micro-Resonator for Orientation Free Tracking of MR-Catheter During Interventional MRI.* **IEEE Journal of Electromagnetics, RF and Microwaves in Medicine and Biology** (2021) 5(1): 78-83. https://doi.org/10.1109/JERM.2020.3010093

11. Friedrich F, Horner-Rieber J, Renkamp CK, Kluter S, Bachert P, **Ladd ME** and Knowles BR. *Stability of conventional and machine learning-based tumor auto-segmentation techniques using undersampled dynamic radial bSSFP acquisitions on a 0.35 T hybrid MR-linac system.* **Med Phys** (2021) 48(2): 587-596. https://doi.org/10.1002/mp.14659
12. Birk M, Dapp R, Ruiter NV **and Becker J**. *GPU-based iterative transmission reconstruction in 3D ultrasound computer tomography.* **Journal of Parallel and Distributed Computing** (2014) 74(1): 1730-1743. https://doi.org/https://doi.org/10.1016/j.jpdc.2013.09.007
13. **Maier-Hein L**, Vedula SS, Speidel S, Navab N, Kikinis R, Park A, Eisenmann M, Feussner H, Forestier G, Giannarou S, Hashizume M, Katic D, Kenngott H, Kranzfelder M, Malpani A, Marz K, Neumuth T, Padoy N, Pugh C, Schoch N, Stoyanov D, Taylor R, Wagner M, Hager GD and Jannin P. *Surgical data science for next-generation interventions.* **Nature biomedical engineering** (2017) 1(9): 691-696. https://doi.org/10.1038/s41551-017-0132-7
14. Niklas M, Schlegel J, Liew H, Zimmermann F, Rein K, Walsh DWM, Dzyubachyk O, Holland-Letz T, Rahmanian S, Greilich S, Runz A, **Jäkel O**, **Debus J** and **Abdollahi A**. *Biosensor for deconvolution of individual cell fate in response to ion beam irradiation.* **Cell Rep Methods** (2022) 2(2): 100169. https://doi.org/10.1016/j.crmeth.2022.100169
15. Tessonnier T, Mein S, Walsh DWM, Schuhmacher N, Liew H, Cee R, Galonska M, Scheloske S, Schömers C, Weber U, Brons S, **Debus J**, Haberer T, **Abdollahi A**, **Mairani A** and **Dokic I**. *FLASH Dose Rate Helium Ion Beams: First In Vitro Investigations.* **Int J Radiat Oncol Biol Phys** (2021) 111(4): 1011-1022. https://doi.org/10.1016/j.ijrobp.2021.07.1703
16. **Dokic I**, Meister S, Bojcevski J, Tessonnier T, Walsh D, Knoll M, Mein S, Tang Z, Vogelbacher L, Rittmueller C, Moustafa M, Krunic D, Brons S, Haberer T, **Debus J**, **Mairani A** and **Abdollahi A**. *Neuroprotective Effects of Ultra-High Dose Rate FLASH Bragg Peak Proton Irradiation.* **Int J Radiat Oncol Biol Phys** (2022) 113(3): 614-623. https://doi.org/10.1016/j.ijrobp.2022.02.020
17. Liew H, Mein S, **Dokic I**, Haberer T, **Debus J**, **Abdollahi A** and **Mairani A**. *Deciphering Time-Dependent DNA Damage Complexity, Repair, and Oxygen Tension: A Mechanistic Model for FLASH-Dose-Rate Radiation Therapy.* **Int J Radiat Oncol Biol Phys** (2021) 110(2): 574-586. https://doi.org/10.1016/j.ijrobp.2020.12.048
18. Tessonnier T, Ecker S, Besuglow J, Naumann J, Mein S, Longarino FK, Ellerbrock M, Ackermann B, Winter M, Brons S, Qubala A, Haberer T, **Debus J**, **Jäkel O** and **Mairani A**. *Commissioning of helium ion therapy and the first patient treatment with active beam delivery.* **Int J Radiat Oncol Biol Phys** (2023). https://doi.org/10.1016/j.ijrobp.2023.01.015
19. Afshar-Oromieh A, **Haberkorn U**, Schlemmer HP, Fenchel M, Eder M, Eisenhut M, Hadaschik BA, Kopp-Schneider A and Röthke M. *Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience.* **Eur J Nucl Med Mol Imaging** (2014) 41(5): 887-97. https://doi.org/10.1007/s00259-013-2660-z
20. Lindner T, Loktev A, Altmann A, Giesel F, Kratochwil C, **Debus J**, **Jager D**, Mier W and **Haberkorn U**. *Development of Quinoline-Based Theranostic Ligands for the Targeting of Fibroblast Activation Protein.* **J Nucl Med** (2018) 59(9): 1415-1422. https://doi.org/10.2967/jnumed.118.210443

21. Tawk B, Rein K, Schwager C, Knoll M, Wirkner U, Horner-Rieber J, Liermann J, Kurth I, Balermpas P, Roedel C, Linge A, Loeck S, Lohaus F, Tinhofer I, Krause M, Stuschke M, Grosu AL, Zips D, Combs SE, Belka C, Stenzinger A, **Herold-Mende C**, Baumann M, Schirmacher P, **Debus J** and **Abdollahi A**. *DNA-Methylome based Tumor Hypoxia Classifier Identifies HPV-negative Head & Neck Cancer Patients at Risk for Locoregional Recurrence After Primary Radiochemotherapy.* **Clin Cancer Res** (2023). https://doi.org/10.1158/1078-0432.CCR-22-3790

22. Lan Y, Moustafa M, Knoll M, Xu C, Furkel J, Lazorchak A, Yeung TL, Hasheminasab SM, Jenkins MH, Meister S, Yu H, Schlegel J, Marelli B, Tang Z, Qin G, Klein C, Qi J, Zhou C, Locke G, Krunic D, Derner MG, Schwager C, Fontana RE, Kriegsmann K, Jiang F, Rein K, Kriegsmann M, **Debus J**, Lo KM and **Abdollahi A**. *Simultaneous targeting of TGF-β/PD-L1 synergizes with radiotherapy by reprogramming the tumor microenvironment to overcome immune evasion.* **Cancer Cell** (2021) 39(10): 1388-1403.e10. https://doi.org/10.1016/j.ccell.2021.08.008

23. Rapp C, Dettling S, Liu F, Ull AT, Warta R, Jungk C, Roesch S, Mock A, Sahm F, Schmidt M, Jungwirth G, Zweckberger K, Lamszus K, Gousias K, Kessler AF, Grabe N, Loehr M, Ketter R, Urbschat S, Senft C, Westphal M, **Abdollahi A**, **Debus J**, von Deimling A, Unterberg A, Simon M and **Herold-Mende CC.** *Cytotoxic T Cells and their Activation Status are Independent Prognostic Markers in Meningiomas.* **Clin Cancer Res** (2019) 25(17): 5260-5270. https://doi.org/10.1158/1078-0432.Ccr-19-0389

24. **Paulino C**, Kalienkova V, Lam AKM, Neldner Y and Dutzler R. *Activation mechanism of the calcium-activated chloride channel TMEM16A revealed by cryo-EM.* **Nature** (2017) 552(7685): 421-425. https://doi.org/10.1038/nature24652

25. Palagi S, Mark AG, Reigh SY, Melde K, Qiu T, Zeng H, Parmeggiani C, Martella D, Sanchez-Castillo A, Kapernaum N, Giesselmann F, Wiersma DS, Lauga E and **Fischer P**. *Structured light enables biomimetic swimming and versatile locomotion of photoresponsive soft microrobots.* **Nat Mater** (2016) 15(6): 647-53. https://doi.org/10.1038/nmat4569

2. The 25 most important publications, Category B

Books and book chapters

1. **Bründermann E**, Hübers H-W, Kimmitt M F. **Terahertz Techniques**, in *Springer Series in Optical Sciences*, Springer-Verlag (2012) 151:1-386. *Book*. https://doi.org/10.1007/978-3-642-02592-1
The book is primarily aimed at graduate students and researchers who are new to the field. Active THz researchers may find helpful information and the book can serve both as a useful introduction as well as a reference for all involved in THz research. Online accesses, English, Springer-Verlag: ~19´000. Translation in Chinese: Space Microwave Technology Academic Works Book (2016).

2. **A.-S. Müller** and M. Schwarz. **Accelerator-Based THz Radiation Sources,** in Synchrotron Light Sources and Free-Electron Lasers: Accelerator Physics, Instrumentation and Science Applications, edited by E. J. Jaeschke, S. Khan, J. R. Schneider and J. B. Hastings, Springer International Publishing, Cham, 2016, pp. 83. *Book chapter.* https://doi.org/10.1007/978-3-319-14394-1_6

3. Schlegel W, Karger CP, **Jäkel O** (Eds). **Lehrbuch - Medizinische Physik [Textbook –Medical Physics]**,Springer,2018,Heidelberg. https://link.springer.com/book/10.1007/978-3-662-54801-1
Given our longstanding experience in medical physics education, we published a textbook for medical physics following the curriculum of the DGMP, which has over 570´000 chapter downloads by early 2023.

4. **Ladd ME**, Quick HH, Bock M, Berger M, Breithaupt M, Nagel AM, Bitz AK, Komljenovic D, Laun FB, Kuder TA, Bachert P, Lanzman RS, Wittsack HJ. **Magnetresonanztomographie und –spektroskopie [Magnetic resonance imaging and spectroscopy],** Chapter 9 in Medizinische Physik [Medical Physics], Springer, 2018, ISBN: 978-3-662-54800-4, https://link.springer.com/chapter/10.1007/978-3-662-54801-1_9
This textbook was published with the aim of providing the German-speaking community with a textbook on medical physics, the focus of which is on the acquisition of the specialist knowledge required to obtain a certification in medical physics approved by the German Society for Medical Physics (DGMP). The textbook has been downloaded more 570´000 times by early 2023.

5. Wannenmacher M, Wenz F, **Debus J** (Eds). **Strahlentherapie [Radiotherapy],** Springer; 2., überarb. Aufl. 2013 Edition (2. Januar 2013) ISBN-10: 9783540883043 ISBN-13 : 978-3540883043

6. Sefkow F and **Simon F**. **Calorimeters**, in Handbook of Particle Detection and Imaging, 2nd ed., Springer (2021).

Patents

7. **Arndt T**. **Magnet device based on the Bitter principle and use of a magnet device based on the Bitter principle,** WO002022063425A1, 2020

8. Li N, Link G, **Jelonnek J**. **Process for the additive manufacture of a mould using microwave radiation, microwave printing device and additive printing device for 3d printing of a filament comprising a fibre composite material,** WO2020188075A1, 2014

9. Almog N and **Abdollahi A**. **Compositions and methods for treating neoplasia,** WO2012027462A2, US2011/048951, 2011
   The invention features compositions comprising microRNAs that are differentially regulated in dormant versus fast growing neoplasias, and related methods of using the microRNAs for inducing or prolonging dormancy in a neoplastic cell or otherwise inhibiting the growth of a neoplastic cell.

10. Javaherian K, **Debus J** and **Abdollahi A**. **Means and methods for the treatment of angiogenesis-, fibrosis- and cancer-related diseases with protein oligomers comprising nc-1-fc,** WO2019201892A1, 2019

11. Giesel F, Zechmann C, Von Tengg-Kobligk H, Muenter M, **Debus J**, Neumann R. **Method to derive anatomical and/or pathological structures from data of imaging technologies,** US8369925B2, granted, 2013

12. Eder M, Kopka K, Schäfer M, Bauder-Wüst U, **Haberkorn U**. **Labeled inhibitors of prostate specific membrane antigen (psma), their use as imaging agents and pharmaceutical agents for the treatment of prostate cancer,** WO2015055318A1, 2014

13. **Haberkorn U**, Loltev A, Lindner T, Mier W, Giesel F, Kratochwil C. **FAP Inhibitor,** WO2019154886A1, 2019.
    The invention relates to a compound of formula (I), a pharmaceutical composition comprising or consisting of said compound, a kit comprising or consisting of said compound or pharmaceutical composition and use of the compound or pharmaceutical composition in the diagnosis or treatment of a disease characterized by overexpression of fibroblast activation protein (FAP).

14. Rommelaere J, Lacroix J, Schlehofer J, Witt O, Deubzer EH, Kern S, **Herold-Mende C**, Geletneky K, Leuchs B. **Use of parvovirus for eliminating cancer stem cells (CSCs),** US9700588B2, 2010

15. Martin-Villalba A, Kleber S, Wiestler B, Krammer P, **Herold-Mende C**, Sancho-Martinez I. **Neutralization of CD95 activity blocks invasion of glioblastoma cells in vivo,** US9309320B2, 2007
    The present invention relates to methods for treating an individual with high grade glioblastoma multiforme by preventing or disrupting the binding of CD95 to its ligand, CD95L, in vivo, whereupon that neutralization of CD95 activity reduces undesirable glial cell migration and invasion into body tissue.

16. Rothenstein D, Bill J, **Fischer P**. **A conjugate complex facilitating the transport of a cargo through a medium,** (Patent pending), US20200215202A1. 2018

17. Wu Z, Qiu T, **Fischer P**. **Slippery micropropellers penetrate the vitreous humor,** (Patent granted JP, EU, US pending), JP7160921B2, 2018

18. Jeong HH, Lee TC, and **Fischer P**. **Method for encapsulating a nanostructure, coated nanostructure and use of a coated nanostructure,** (Patent granted, EU, US, JP) EP3274083B1, US10464037B2, 2016

19. **Fischer P** and Ghosh A**. Magnetic Nanostructured Propellers,** (Patent granted US), US8768501B2, granted 2014

Software/ Databases

20. **Asfour T. The KIT whole-body human motion database,**
URL: https://motion-database.humanoids.kit.edu
https://doi.org/10.1109/TRO.2016.2572685

21. **Maier-Hein L. Initiation of the open source toolkit for Simulation and Image Processing for Photonics and Acoustics (SIMPA),**
URL: https://github.com/IMSY-DKFZ/simpa

22. **Matthis-Ullrich F** et al. **An Open Source Framework for Reinforcement Learning in Robot-Assisted Laparoscopic Surgery "LapGym"**,
URL: https://github.com/ScheiklP/lap_gym
A framework for building RL environments for robot-assisted laparoscopic surgery that models the challenges posed by surgical tasks, and sofa_env, a diverse suite of 12 environments. Motivated by surgical training, these environments are organized into 4 tracks: Spatial Reasoning, Deformable Object Manipulation & Grasping, Dissection, and Thread Manipulation. Each environment is highly parametrizable for increasing difficulty, resulting in a high-performance ceiling for new algorithms. Establishment of a baseline for model-free RL algorithms (PPO), investigating the effect of several environment parameters on task difficulty

Technical/ Methodical publications and pre-prints

23. **Husemann U** within the CMS Collaboration. **The Phase-2 Upgrade of the CMS Tracker**, CERN-LHCC-2017-009 (2017), http://dx.doi.org/10.17181/CERN.QZ28.FLHW
Technical Design Report for the upgrade of the tracking detectors of the CMS experiment at the CERN LHC. Dr. Husemann's group contributed to the silicon sensor design and to assembly and metrology procedures for a novel type of double-layer detector module.

24. Scheikl PM, Gyenes B, Younis R, Haas C, Neumann G, Wagner M, **Mathis-Ullrich F**. **LapGym - An OpenSource Framework for Reinforcement Learning in Robot-Assisted Laparoscopic Surgery,** arXiv preprint arXiv:2302.09606 (2023).

Spin-offs

25. **Korvink J**- Co-founder of **Voxalytic GmbH**
Voxalytic offers customizable capabilities for liquid state NMR spectroscopy, and are especially applicable when screening medium to large chemical libraries, when sample volumes are small, or unusual environmental conditions apply.

3. The 25 most important additional qualification indicators

	Indicator (cumulative)	Number(s) and description
1	**National Academy Members**	**2 *AccelerateRT* PIs** are elected members of the German National Academy of Sciences – “**Leopoldina**”
2	**Presidents of Academic Societies**	**6 *AccelerateRT* PIs** act(ed) as presidents of scientific societies: German Society for Radiation Oncology (DEGRO), European Society for Applied Superconductivity, German Society for Medical Physics (DGMP), German Society for Computer- and Robot-assisted Surgery (CURAC)
3	**DFG Collaborative Funds**	***AccelerateRT* PIs** participated as PIs and/or coordinators in **24 DFG collaborative projects**, such as High Priority Programs (SPP), Collaborative Research Centers (SFB/TRR), Clinical Research Units (KFO), Research Units (FO) within the last 5 years
4	**EU Collaborative Funds**	***AccelerateRT* PIs** act(ed) as PIs and/or coordinators of **22 EU-funded collaborative research projects** within the last 5 years
5	**ERC Grants**	***AccelerateRT* PIs** have received **4 ERC Advanced or Consolidator Grants** within the last 5 years
6	**Young Investigator Group awards**	**5 Young Investigator Groups** were established by ***AccelerateRT* PIs** in framework of competitive national /international programs, i.e., European Research Council (ERC-Starting Grant), German Cancer Aid (Deutsche Krebshilfe, Max-Eder), Helmholtz
7	**BMBF National Networks**	***AccelerateRT* PIs** act(ed) as PIs and/or coordinators of **31 BMBF funded national network projects**
8	**Scientific Review Committees**	***AccelerateRT* PIs** are chairs/members of **41 academic review boards,** such as DFG and BMBF, DKH or similar
9	**Coordinator positions in coordinated programs**	***AccelerateRT*** PIs act(ted) **as coordinator/speaker of** **8 coordinated programs** such as training networks (RTG), graduate schools, or similar
10	**Patents**	**170** applied or granted **patents** by ***AccelerateRT* PIs** in the entire area of research proposed

The 25 most important additional qualification indicators – continued

	Indicator (individual)	Name / topic	year	Name(s) of *accelerateRT* PIs
11	**Presidency**	**Vice President of the DFG**	2014 - 2021	**Marlis Hochbruck**
12	**Award**	**Merck** KGaA **350th Anniversary Award**, in the category, development of **innovative therapeutics**	2018	**Amir Abdollahi and Ivana Dokic**
13	**Award**	**Erwin Schrödinger Award** by Donors' association for the promotion of humanities and sciences in Germany (**Stifterverband für die deutsche Wissenschaft**) for “outstanding contributions in preparation, development and clinical implementation of cancer therapy with ion beams”	1999	**Jürgen Debus** together with Wolfgang Enghardt
14	**Award**	**Erwin Schrödinger Award** by Donors' association for the promotion of humanities and sciences in Germany (**Stifterverband für die deutsche Wissenschaft**) for “development of a method to diagnose prostate cancer more reliably and even treat it in a targeted manner”	2018	**Uwe Haberkorn** together with Michael Eisenhut, Matthias Eder and Klaus Kopka
15	**Award**	**Research Award** by Donors' association for the promotion of humanities and sciences in Germany (**Stifterverband für die deutsche Wissenschaft**) for the realization of high temperature superconductors	2006	**Bernhard Holzapfel** together with Ludwig Schultz
16	**Award**	**World Technology Award 2016** in the category **„Information Technology – Hardware“**	2016	**Peer Fischer**
17	**Award**	**Baden-Württemberg State Research Award**	2022	**Anke-Susanne Müller**
18	**Awarded fellowship**	Senior Fellow of the **International Society for Magnetic Resonance in Medicine**	2021	**Mark Ladd**
19	**Awarded fellowship**	Fellow of the **Royal Society of Chemistry**	2014	**Jan Korvink**
20	**Award**	**Walther und Christine Richtzenhain-Award** for transfer of cancer research results into clinical translation	2005	**Amir Abdollahi**

The 25 most important additional qualification indicators – continued

	Indicator (individual)	Name / topic	year	Name(s) of *accelerateRT* PIs
21	**Award** for young scientists	**Heinz Maier-Leibnitz Prize**, awarded by the German Research Foundation (DFG) for outstanding achievement	2013	**Lena Maier-Hein**
22	**Award** for young scientists	**Christoph-Schmelzer-Award** by the Society for the Promotion of Tumor Therapy with Heavy Ions for outstanding PhD thesis	2009	**Andrea Mairani**
23	**Award**	Winner of NEO2019 – **Innovation award** of technology-region Karlsruhe	2019	**Franziska Mathis-Ullrich**
24	**Grant** for Excellent Women Scientists	**Helmholtz W2/W3 Grant for excellent women scientists**	2012	**Tabea Arndt**
25	**Grant** for Excellent Women Scientists	**Helmholtz W2/W3 Grant for excellent women scientists**	2018	**Anke-Susanne Müller**

4. Third-party funding

	Name	Funding body	from-to	Description	Institu-tion
1	**ARTEMIS**	BMBF	2019 - 2023	Adaptive Radiotherapy with MR controlled ion beams	UHD DKFZ
2	**PREDICT**	EU Horizon 2020	2017-2022	Marie Curie innovative training network (ITN): Radiomics as decision support tool for diagnos-tics and theragnostic in oncology	UHD HIT DKFZ
3	**Ion Radio-graphy**	DFG	2019-2022	Ion-radiography with adaptive energies for precision radiotherapy	UHD DKFZ HIT
4	**FLASH Particle Therapy**	NIH/NCI	2022-2027	Program Grant P01 for development of Particle FLASH together with UPenn, Duke and Oxford University	UHD
5	**HOLOMAN**	ERC	2018 - 2024	Holographic acoustic assembly and manipulation (Holoman), Advanced Grant to Peer Fischer	UHD

Third-party funding - continued

	Name	Funding body	from-to	Description	Institu-tion
6	**NEURAL SPICING**	ERC	2021	Neural Spectral Image Decoding, Consolidator Grant Lena Maier-Hein	DKFZ
7	**CRC 1527: HyPERiON**	DFG	2022-2026	Compact high-performance magnetic resonance systems	KIT
8	**Hybrid Networks**	Helmholtz	2021-2026	Helmholtz Young Investigator Group	KIT
9	**CRC 1173: Wave Phenomena**	DFG	2019-2023	Wave phenomena: Analysis and numerics	KIT
10	**KC^4**	CERN	2021-2026	KIT-CERN Collaboration on Coated Conductor Development & Production	KIT
11	**CMS outer tracker upgrade**	BMBF	2021-2024	Upgrade of the silicon tracker of the CMS experiment for the high-luminosity LHC	KIT
12	**HiSCORE**	ERC	2021-2027	ERC Synergy Grant	KIT
13	**KIRuRC**	MWA	2021	AI-based registration and robot-assisted surgery	KIT
14	**ATHENA**	Helmholtz	2018-2022	Demonstration of Injection and Storage of a Laser-Wakefield-accelerated Electron Beam in a Compact Storage Ring	KIT
15	**ULTRA-SYNC**	ANR-DFG	2019-2022	ULTRAfast exploration and control of electron bunch dynamics in SYNChrotron light sources	KIT

5. Information about the applicant universities

5.1. Heidelberg University

Established in 1386, Heidelberg University is the oldest university in today's Germany and one of Europe's strong research institutions. Its successes in all rounds and funding lines of the Excellence Initiative and the Excellence Strategy, as well as its positions in internationally recognized rankings, substantiate Heidelberg University's leading role in the scientific and research landscape. In educating students and advancing outstanding early-career researchers, Heidelberg University emphasizes research-based teaching and excellent, well-structured support for doctoral candidates and postdocs. With its aspiration of connecting traditional values with future-oriented scientific concepts in research and teaching, the University is building bridges to the future – according to its motto: Zukunft. Seit 1386.

Research University

Heidelberg University is a comprehensive research university. Its broad subject spectrum in thirteen faculties includes the humanities and the social sciences, law, the natural and engineering sciences, and the life sciences, as well as medicine. Four interdisciplinary Fields of Focus shape the profile of Heidelberg's research strategy: "Molecular Foundations of Life, Health, and Disease" (FoF 1), "Patterns and Structures in Mathematics, Data, and the Material World" (FoF 2), "Cultural Dynamics in Globalised Worlds" (FoF 3), and "Self-Regulation and Regulation: Individuals and Societies" (FoF 4). Core facilities with state-of-the-art infrastructure, highly qualified staff and open access for all scientists provide excellent preconditions to perform cutting-edge research. Core facilities are a key feature of the strong research campus that Heidelberg University forms together with its extra-university partners.

FoF 1 promotes cooperation between the life sciences, engineering sciences on a molecular level and medicine, with the participation of strong local partners (DKFZ, EMBL, MPI for Medical Research, ZI). Its research activities are closely intertwined with the Health+Life Science Alliance Heidelberg Mannheim. The life sciences and new interdisciplinary research in molecular systems engineering offer the potential to build the basis for highly innovative technologies. FoF 2 primarily coordinates research activities between the Faculties of Physics and Astronomy, Mathematics and Computer Science, and Chemistry and Earth Sciences. FoF 3 promotes cooperation between the Faculties of Philosophy, Modern Languages and Theology. FoF 4 coordinates activities at the Faculties of Behavioural and Cultural Sciences, Economics and Social Sciences, and Law. At the institutional level, Heidelberg University also relies on the Heidelberg Karlsruhe Strategic Partnership (HEiKA) with the Karlsruhe Institute for Technology.

Support of early-career researchers

Integrating students into the research process from the very beginning of their studies and supporting young researchers at all stages of their career are essential strategic fields of action for Heidelberg University. With more than 8,800 doctoral candidates, Heidelberg has the largest number of young researchers working towards a doctorate at a German university. As an integrated quality program for doctoral training, the heiDOCS program ensures the continuous optimization of the overall conditions for doctoral candidates at the University. In this context, all counselling and support, advanced training and funding offers have been brought together under the umbrella of the Graduate Academy. After the doctorate, Heidelberg University offers its postdoctoral researchers clearly structured career paths aimed at attracting and retaining young talent from all over the world. heiTRACKS is the framework for a wide range of support measures aimed at young researchers who have completed their doctorate.

Transfer

With an integrated concept for application, consulting and science communication, Heidelberg University has placed the transfer of knowledge and technology at the center of its Excellence Strategy. The key objective is to make scientific results usable for all segments of society. hei_INNOVATION, the University's Transfer Agency, supports the translation of research findings into applications. Besides supporting spin-offs, the agency also facilitates out-licensing and patent applications. The Rectorate's Communications and Marketing (KuM) department develops and implements a scientific communication strategy to inform the public at large, as well as specific target groups, about expertise, research projects and scientific findings. In the field of knowledge and technology transfer, 50 invention disclosures were filed in 2022; the granted and pending patent families amount to 244 at the end of the reporting period. 28 contracts for the utilization of intellectual property were concluded with industry at the time of submission, and the revenue generated from these contracts amounts to €23 million (2022).

Interdisciplinarity

The University is committed to fostering its strong disciplinary basis, but also to promoting dialogue beyond traditional disciplinary boundaries, and turning research findings to good use for society and the economy. Within the Excellence Strategy, Heidelberg University continues to advance its goal of fully realizing its potential as a comprehensive research university. Its four Fields of Focus are being further linked by two Flagship Initiatives (FI Engineering Molecular Systems and FI Transforming Cultural Heritage), which each deepen cooperation and networking between two neighboring FoFs. Three central, interdisciplinary institutions – the Heidelberg Center for the Environment, the Interdisciplinary Center for Scientific Computing and the Marsilius Kolleg – further connect all FoFs and act as incubators for new research initiatives throughout the University.

Internationality

Heidelberg University owes its high international visibility to its high-quality branding and its long-term research partnerships with institutions from all over the world. In particular, Heidelberg University has established four centers abroad, which – together with their related research hubs in Heidelberg – are the institutional bridges connecting the University to its strategic focus regions: Heidelberg Center Latin America (HCLA) in Santiago de Chile, Heidelberg University Association in New York City, Heidelberg Centre South Asia (HCSA) in New Delhi and Heidelberg University Office Kyoto (HUOK). 27 institutional partnerships with universities all over the world, exchange arrangements with about 480 international universities, and the University's membership in networks such as the German-Japanese University Consortium HeKKSaGOn, the 4EU+ European University Alliance, the League of European Research Universities (LERU) and the Coimbra Group underscore the strength of Ruperto Carola's international ties. One important outcome: Almost 30 percent of the University's doctoral candidates and postdoctoral researchers come from abroad.

Diversity

SEMPER APERTUS is the basic principle of Heidelberg University. This commitment to diversity in all forms is rooted in the fundamental belief that engaging with new ideas, perspectives, cultures, and people creates the essential conditions for innovation and knowledge. All diversity-related measures are coordinated by UNIFY – the Unit for Family, Diversity & Equality. In response to the specific requirements of cultural diversity, a "Mobility in International Research Cooperation" program has been extended to include junior researchers. The Dual Career Service for postdocs provides extensive counselling to support the partners and families of newly-hired professors at Heidelberg University. Measures for female postdocs and the active recruitment of female researchers are being pursued and have led to a significant increase in the number of women among newly appointed professors. Over the course of the Excellence Initiative and the Excellence Strategy, the ratio of newly appointed female professors has risen from 12.5 percent in 2007 to 31 percent in 2022.

Sustainability

Heidelberg University feels bound to actively contribute to the scientific investigation, assessment and discussion of global change, and to the development of tools, methods and technologies for a more sustainable use of the earth's resources. The Heidelberg Center for the Environment makes Heidelberg the first university within the State of Baden-Württemberg to bring together environmental science activities in research, teaching and transfer across disciplines in one institution. Research projects related to sustainable development exist, in particular, in the Earth Sciences, in Geography, Environmental Physics, Environmental Economics, Environmental Law and in the Biodiversity Research Unit, among others.

Research Data and Software Management

The University pursues an open science strategy that not only includes open access to scientific publications, but also aims to ensure open availability of research data and research software according to the FAIR principles. Wherever possible, research data is published as open access. Data-curation support is provided by the Competence Centre for Research Data, a joint service facility of the University's Library and Computing Centre. It offers expertise in data management and data publication. The University's Scientific Software Centre (SSC) provides support for the sustainable development and availability of research software.

Existing cooperation

The Cluster of Excellence *AccelerateRT* builds on the complementary strengths of Heidelberg University and KIT in the life sciences and engineering. The HEiKA Strategic Partnership provides the basis for the cooperation between Heidelberg University and KIT. Within HEiKA, the two universities jointly and strategically advance their competencies, focusing on activities in research, innovation and teaching, as well as the support of early-career researchers. Examples include the HEiKA Research Bridge "Medical Technology for Health" and the new joint bachelor/master program in medical engineering that has recently started.

Facts and Figures

Study and Teaching Total number of students 29,897 Degree programs 186 **Professorships and Young Researchers** Total number of professorships 557 Total number of doctoral candidates 8,872	**Faculties** Biosciences • Chemistry and Earth Sciences • Engineering Sciences • Mathematics and Computer Science • Physics and Astronomy • Philosophy • Modern Languages • Theology • Law • Behavioural and Cultural Studies • Economics and Social Sciences • Medical Faculty Heidelberg • Medical Faculty Mannheim
Research 28 DFG-funded Collaborative Research Centers (CRCs) 12 DFG-funded CRCs under Heidelberg leadership 15 DFG-funded Research Training Groups 9 Long-term projects in cooperation with the Heidelberg Academy of Sciences and Humanities 84 ERC Grants total 36 ERC Grants running (5 Advanced, 11 Consolidator, 14 Starting and 6 Synergy Grants) 11 Nobel Laureates (57 Nobel Laureates share a connection with Heidelberg University or the city) 20 Leibniz Prize Laureates 3 Alexander von Humboldt Professorships	**Excellence Strategy** **University of Excellence** The Comprehensive Research University – Heidelberg: The Future since 1386 **Clusters of Excellence** STRUCTURES: A Unifying Approach to Emergent Phenomena in the Physical World, Mathematics, and Complex Data 3D Matter Made to Order together with Karlsruhe Institute of Technology (KIT) To date of submission

5.2. Karlsruhe Institute of Technology (KIT)

KIT – The Research University in the Helmholtz Association. As one of the biggest science institutions in Europe and the only German University being also a national research lab, we combine a long-standing university tradition with mission-based research. Our research environment is characterized by scientific excellence, connecting fundamental and application-oriented research in a unique manner. Our mission is to create and disseminate knowledge for the society and the environment by conducting top-level research, providing excellent academic education, and creating innovations. From fundamental research to application, we excel in a broad range of disciplines, i.e. in natural sciences, engineering sciences, economics, and the humanities and social sciences. Our *three core tasks* of research, teaching, and innovation are carried out by 5,700 scientists including around 400 professors, more than 2,000 postdoctoral researchers and staff scientists, and more than 3,200 doctoral researchers; all based in 118 institutes. Teaching is organized by 11 KIT Departments, and mission-based research by 11 Helmholtz Programs, all being assigned to the five Divisions defining the governance structure as well as our disciplinary profile (I: Biology, Chemistry and Process Engineering; II: Informatics, Economics and Society; III: Mechanical and Electrical Engineering; IV: Natural and Built Environment; V: Physics and Mathematics).

With our *KIT 2025 Strategy*, we target to deliver world-class science and design the future viability of our society and environment, particularly in the fields of energy, mobility, and information. KIT is one of eleven *Universities of Excellence* in Germany. The leitmotif *Living the Change* of our successful excellence university proposal reflects our commitment to societal change that we wish to shape by outstanding achievements in research, education, and innovation in close dialogue with society. *Living the Change* also addresses cultural change at KIT to respond more dynamically to internal and external changes and to foster the institutional capacity for renewal. In order to address cultural change and to boost scientific excellence, we are establishing 100 new professorships, among these 40 to 50 tenure track professorships. We recently appointed our first Vice-President for Digitalization and Sustainability to further advance these two interdisciplinary research and technology fields across the entire institution. With the 2nd *KIT Further Development Act* (adopted in 2021) the legal foundation for further integration of university and large-scale research center was consolidated in the spirit of the KIT 2025 Strategy.

Research: Knowledge creation at KIT is based on a broad disciplinary foundation with a focus on natural sciences and engineering, including economics, humanities, and social sciences, with fundamental and applied research represented alike. The research conducted at KIT encompasses both fundamental and applied research reflecting autonomous, knowledge-driven development of disciplines and research topics as well as our commitment to the Helmholtz Programs aimed at long-term research goals. As of 2023, we are conducting nine DFG Collaborative Research Centers and two Clusters of Excellence, the latter together with Heidelberg University and Ulm University, respectively.

We foster collaborative research within our interdisciplinary KIT Centers, which facilitate cooperation in topic-oriented manner by stimulating new research directions and bundling competencies from different institutes to tackle complex research challenges associated with technological and societal changes. Eight KIT Centers that represent the major interdisciplinary topics of KIT (Energy, Elementary Particle and Astroparticle Physics, Information – Systems – Technologies, Climate and Environment, Materials, Humans and Technology, Mobility Systems, and Mathematics in Sciences, Engineering, and Economics) connect scientists, consolidate cross-divisional research activities, and represent the strategic research fields externally. A ninth KIT Center Health Technologies has been started by March 1, 2023. Together with the KIT Center Elementary Particle and Astroparticle Physics (KCETA) with its strong technology backbone, this new center provides a vibrant and fertile science environment for *AccelerateRT*.

In fulfillment of our mission as a national research center, KIT's research adds pivotal contributions to addressing critical and pressing challenges facing society, science, and industry. These research and development activities are part of the overarching program structure of the *Helmholtz Association*. In the fourth phase of program-oriented funding, which runs from 2021 to 2027, KIT is significantly involved in eleven research programs in four research fields: Energy, Earth and Environment, Information, and Matter. With our holistic approach in energy research, we take up a leading role within the Helmholtz Association, thereby shaping the energy system transformation for a more resilient and sustainable tomorrow. This also provides a valuable knowledge base for the AccelerateRT research program.

KIT's research infrastructure is unparalleled among German universities in terms of size, scope, and complexity. It includes cutting-edge laboratory equipment, modern information systems, and large-scale experimental facilities. This leads to new horizons in research, drives technical innovation, and offers experimental chances to users at all stages of their academic career. Consequently, this unique feature is integrated in our one-of-a-kind research-oriented teaching environment. Especially with the concept "Research Infrastructures in Research-Oriented Teaching (RIRO)", we enhance the attractiveness for young scientists, promote the integration of KIT's large-scale research infrastructures in teaching, and establish early connections between the next generation of scientists and experienced researchers working at these infrastructures.

Among the best examples of our cooperation strategy is the existing longstanding strategic partnerships with Heidelberg University (HEiKA). In HEiKA, we combine the expertise of two Universities of Excellence with complementary profiles. *AccelerateRT* will profit from this unique life-science and engineering research environment and from KIT's national lab infrastructures. Further assets include the HEiKA Research Bridge "Medical Technology for Health" and the new joint medical engineering study program.

In 2022, KIT members received 11 ERC Grants, two Gottfried Wilhelm Leibniz Prizes, a Humboldt Professorship, and a Baden-Württemberg State Research Award (for *AccelerateRT* co-spokesperson Anke-Susanne Müller). In national and international rankings, we hold top positions, especially in the natural sciences and engineering.

Teaching: In 2022, around 22,300 students studied at KIT, among them 29% female and 20% from foreign countries. Our education and training opportunities for students and young scientists are unique: Nowhere else can they participate in using infrastructure of a large-scale research institution while collaborating across disciplinary boundaries. The spirit of KIT entails the commitment that all researchers are involved in teaching and that all our students have the opportunity to participate in fascinating research projects at an early stage of their studies. Our 11 KIT Departments offer 44 Bachelor and 59 consecutive as well as 6 additional Master programs. Studies at KIT provide optimal preparation for careers in and outside academia. We aim not only at educating next generation excellent researchers, innovators and policymakers, but also create students with reflective, ethical and sustainable mindsets: Our *KIT Academy for Responsible Research, Teaching, and Innovation (ARRTI)* supports researchers, innovators, and lecturers in applied ethics in research, teaching, and innovation, while emphasizing cross-disciplinary communication. ARRTI also advocates a transdisciplinary perspective to engage citizens in the discourse on techno-ethical issues.

Innovation and Transfer: Innovation, i.e., transforming scientific findings, is one of the three core tasks of KIT besides research and teaching. To address the global pressing challenges facing humanity, KIT's trend-setting research activities in the areas of energy, mobility, and information are to give rise to concrete developments and products that contribute to general prosperity, social and economic benefit and concurrent sustainability (e.g. in 2022: 91 invention disclosures, 43 patent applications). The *KIT-Gründerschmiede* supports KIT students and employees in starting a business and entrepreneurship, from student start-ups to high-tech enterprises based on most recent scientific discoveries. Various teaching and training formats and a comprehensive range of consulting services prepare for a career as an entrepreneur (163 spinoffs and startups from 2019 to 2022). Moreover, we recognize the importance of engaging with the public and promoting knowledge transfer through participatory research formats such as real-world labs, and citizens' dialogs.

Promoting Young Talent: KIT aims to provide young scientists with an excellent framework to support their career development. Our *Karlsruhe House of Young Scientists* (KHYS) advises, qualifies, and supports young scientists, maintains the quality of the doctoral research phase, and supports our many internally and externally funded coordinated research programs for the promotion of young scientists. In addition, tailor-made funding programs support postdoctoral researchers in their scientific careers and the full development of their potential. With our *Young Investigator Group Preparation Program*, we are continually increasing the number of junior research groups and junior professorships. Since 2008, the *Young Investigator Network* (YIN) as a self-governed network of junior research group leaders and junior professors, has been very successful in increasing the visibility of its members, e.g. through a variety of events, peer-to-peer mentoring and interdisciplinary cooperation. Offering reliable career paths is essential to us when recruiting and retaining excellent young scientists. By introducing *tenure-track professorships*, KIT has ensured transparency and predictability in the hiring process: After a successful probationary phase and evaluation, a tenure-track professorship provides for immediate transition to a lifetime professorship. For our top young scientists, the tenure-track professorship is an essential pillar in the KIT career system. In order to advance this cultural change, we will establish further tenure-track professorships in the next few years: Since 2017, 20 tenure track professorships (W1) have already been filled, 15 have current searches, and by 2025 we endeavor to have reached our goal of 40 to 50 tenure track professorships. In the medium term, we will fill about half of the full professorships (W3) at KIT by way of the tenure track system that we have established in the recent years, thus providing reliable and attractive career pathways, and diversifying our professorial staff.

Equal Opportunity and Diversity: In all our fields of action maintaining and enhancing equal opportunities of women and men is an essential objective and a consistent guiding principle. Due to its engineering and natural science line-up, KIT has significantly lower proportions of women among students and scientists compared to other universities. Within our Excellence Strategy, we tackle the challenge of substantially increasing the numbers of female senior scientists and leading staff. As of 2017, we only had 13% female professors. Yet, we have reached a seminal 30–40% of female professors in new appointments annually since then, which we will further improve in order to lastingly alter our culture towards a distinguished research environment in which female role models and success stories thrive. By adopting a Diversity Statement in 2022, we have enhanced the esteem of diversity further. Besides equal opportunities, our diversity strategy places a strategic focus on internationalization. The added values of its cultural diversity – individuals from more than 120 countries do research, teach, work, and study at KIT – are highlighted in its internationalization strategy adopted in 2018.

Facts and Figures

Academics		**Research** (2023)		**Budget**	
Students (WT 2022/23)	22,373	Clusters of Excellence	2	*(MEUR, 2022)*	1,122.9
Doctoral graduations (2022)	533	CRCs (speaker KIT)	6	Federal funds	331.7
		CRCs (co-applicant)	3	State funds	319.6
Employees (2022)	9,905	DFG Res. Training Groups	8	Third-party funds	471.6
Teaching and research	5,704	ERC Grants (since 2009 / 2023)	36/18		
Professors	402	G.W. Leibniz Prizes (total)	10		
Infrastructure and services	4,201	Humboldt Professorships	3		
Trainees	368	H.-M.-Leibnitz-Prizes (total)	7		