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Review

From ultrafast laser-generated radiation to clinical impact: a roadmap for radiobiology and cancer research at the extreme light infrastructure (ELI)

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Abstract The extreme light infrastructure (ELI) is emerging as a state-of-the-art facility providing international users with open access to ultrashort laser-driven particle bunches, ranging from a few femtoseconds to a few nanoseconds, for advanced radiobiology studies. ELI offers femtosecond-class laser pulses and ultrafast ionizing radiation characterized by extremely high instantaneous dose rates (10^7–10^{12} Gy/s). The versatility of ELI's cutting-edge technologies enables the generation of high repetition rate (1 Hz–1 kHz) secondary sources (protons, ions, electrons, and neutrons) with energies from a few MeV to several hundred MeV, achieved over sub-millimetre to millimetre-scale acceleration lengths, along with fundamental research in the field of ultrahigh intensity laser-matter interaction based on the use of the highest peak power laser pulses available worldwide. Harnessing these laser-driven particle sources for radiobiology and medical research demands a coordinated international effort, with a strong focus on advancing scientific instrumentation and refining experimental methodologies to support progress in ultrafast laser-driven radiation biology. This roadmap underscores the need for systematically designed experiments across ELI facilities, supported by preparatory research at users' home laboratories, alongside the ongoing development of instrumentation and infrastructure. These efforts are critical to rigorously assess and validate the therapeutic potential of these novel sources, paving the way for a transformative shift in radiation biology and medicine.

1 State of the art and rationale

After one century of development of radiofrequency-based particle accelerators, which have pushed the limits of beam selectivity and precision in dose delivery to enable clinical therapies, a novel approach has emerged in tandem with the advance of high-power lasers. These sources offer access to particle beams with unprecedented characteristics, such as ultrashort duration ion and electron

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bunches (from a few femtoseconds to several nanoseconds), high directionality, and unique dose delivery profiles. Laser-plasma acceleration, achieved over remarkably short distances (from a few micrometres to several millimetres), is opening new perspectives in the currently available radiation treatments by offering novel radiation modalities [1]. It enables the generation of particle beams with sub-nanosecond pulse durations, ultrahigh instantaneous dose rates ($>10^9$ Gy/s), Hz-level repetition rates, and extremely small beam sizes (sub-mm) thanks to the ultralow emittance and degree of laminarity of the source. These extraordinary features enable unprecedented radiobiological studies and, coupled with the potential for developing versatile and cost-effective systems, pave the way for future integration into clinical environments, including hospital-based infrastructures. Laser-accelerated particle beams, therefore, present a promising future complementary option to conventional acceleration technologies.

Recently, a major drive towards possible improvements in oncological patients' welfare undergoing radiotherapy has come from radiobiology, and is known as the "FLASH effect", whereby ultrahigh dose rate (UHDR) radiation, typically ≥ 40 Gy/s, significantly reduces normal-tissue radiotoxicity while preserving tumour control [2]. Based on the current interpretation of available data, the FLASH effect has been attributed to mechanisms such as transient oxygen depletion or altered reactive oxygen species (ROS) dynamics within tissues, making it a compelling strategy to enhance the therapeutic ratio in radiotherapy [3–6]. The unique temporal properties of laser-driven particle beam irradiation, characterized by multiple, temporally separated, ultrashort dose fractions (also known as "fast fractionation"), offers both opportunities and challenges for radiobiological research, including hitherto unexplored UHDR regimes. Unlike conventional accelerators, laser-driven sources can generate femtosecond to nanosecond duration, high-intensity UHDR pulses, which may further amplify FLASH-related effects, even if the latter is currently limited to single-shot dose delivery due to the repetition rate of available laser systems, which prevents from fully entering the FLASH regime in terms of mean dose rate. While the potential of such beams for FLASH radiotherapy is increasingly being recognized, the complex radiobiological mechanisms involved, particularly in the context of laser-driven beam delivery, is still not well understood, underscoring the need for dedicated experimental platforms to enable systematic radiobiological investigations, possibly exploiting wide-ranging assays [7].

In parallel, spatially fractionated approaches such as microbeam therapy (MBT) offer a distinct but potentially complementary approach for normal tissue sparing. MBT utilizes arrays of micrometre-wide, high-dose beams separated by regions of low-dose to produce steep spatial dose gradients. These steep dose gradients facilitate normal tissue sparing: the narrow, high-dose microbeams inflict less overall damage on healthy tissues, which are better able to repair sub-lethal injury in the low-dose valleys. Simultaneously, MBT offers enhanced tumour control, as tumour cells and neo-vasculature—typically characterized by impaired repair mechanisms—are more susceptible to damage from the high-dose peaks, potentially improving tumour ablation. Although MBT does not inherently require UHDR conditions, the ultrafast (ideally, single shot) delivery of the prescribed dose would allow "freezing" the motion of the patient (if their anatomy is accurately characterized), thus reducing "smearing" effects. Moreover, the prospect of combining spatial (MBT) and temporal (FLASH) effects (e.g. using laser-accelerated particle beams) represents an exciting frontier in radiotherapy research since MBT with UHDR could yield synergistic tissue-sparing effects by integrating spatial and temporal radiobiological advantages. To date, synchrotron-based studies in preclinical models have demonstrated MBT's promise in achieving tumour control with minimal toxicity [8], and ongoing efforts aim to adapt this technique to broader clinical application through optimization of beam parameters and integration with other therapeutic modalities [9, 10].

Pioneering work by Yogo et al. [11, 12] conducted at KPSI-QST (Japan) first demonstrated that laser-accelerated protons can induce DNA double-strand breaks in human cancer cells, confirming their biological relevance. Follow-up studies, such as those by Doria et al. [13] at TARANIS-QUB (UK), showed that proton beams delivered at instantaneous dose rates in excess of 10^9 Gy/s caused significant DNA damage in vitro. Research by Manti et al. [14] and Hanton et al. [15] extended these findings by exploring sub-lethal effects, oxidative stress responses, and DNA repair mechanisms, further supporting the efficacy of UHDR exposures at potentially mitigating radiation-induced damage to healthy cells. Experiments conducted by Zeil et al. [16] at HZDR (Germany) confirmed the biological equivalence between laser-accelerated proton pulses and conventional beams, strengthening the case for clinical translation. Furthermore, Bayart et al. [17] demonstrated enhanced tumour cell lethality under ultrafast dose fractionation, while Raschke et al. [18] reported non-target effects associated with reduced nitroxidative stress, providing early evidence for the therapeutic promise of laser-driven beams in FLASH radiotherapy paradigms. Recently, Flacco et al. reported on a single-pulse, laser-driven proton beam delivering up to 20 Gy in <10 ns at dose-rates $>10^9$ Gy/s, which retained full anti-tumour efficacy while reducing oxidative-stress-linked DNA damage in healthy cells and mitigating developmental injury in vivo, in a zebrafish embryo model [19]. These first proof-of-principle results, achieved with a large kJ-class laser system operating at low repetition rate, support the feasibility of laser-driven particle FLASH approaches, although with less than 5-MeV proton energies, and the need to develop experimental platforms for future radiobiological and translational studies at clinically relevant particle energies and repetition rates. Simultaneously, the transformative FLASH radiotherapy concept [6] is gaining momentum, with laser-accelerated protons shown to be compatible with ultrahigh dose-rate protocols [20].

To support the current biological findings, Chaudhary et al. developed comprehensive experimental protocols for radiobiological studies using laser-driven protons, addressing critical aspects such as dosimetry and reproducibility, and presented the first experimental proof of cellular irradiations with ultrahigh dose rate laser-driven carbon ions [21, 22]. From a technical perspective, Schell et al. [23] and Masood et al. [24] have proposed advanced treatment planning and gantry-based beam delivery solutions, potentially enabling precise control even with relatively broad energy spreads which are typical features of laser-plasma accelerators. The in vivo applicability of laser-accelerated beams was convincingly demonstrated by Kroll et al. [25], who achieved conformal tumour

irradiation in mice with outcomes comparable to conventional proton therapy. Complementary work by Oppelt et al. [26] showed no significant differences between laser-driven and LINAC-based electron beams in animal models. The Dresden Platform, part of the HZDR/OncoRay network, integrates clinical and research LINACs, a proton cyclotron, and a laser-driven proton accelerator to deliver variable dose-rate regimes, ranging from femtoseconds to minutes. This platform has proven its capabilities through coordinated FLASH-effect studies in zebrafish embryos [27].

A promising frontier lies in the development of very high energy electrons (VHEE), in the energy range of 50–300 MeV, with laser-accelerated beams showing significant potential for deep tissue targeting. Investigations by Glinec [28], Fuchs [29], Panaino [30], Subiel [31], Labate [32], Polanek [33], Swenson [34], and more recently by Guo [35] have laid the groundwork for VHEE implementation in laser-based systems. VHEEs offer deep penetration and precise dose conformity, making them suitable for treating large and/or deep-seated tumours. Their focussed beam profiles help minimize exposure to healthy tissue while potentially capitalizing on high-dose-rate biological effects, including those associated with FLASH effects [36]. In addition, laser-driven VHEE bunches show ultrashort duration down to 1 fs [37] (or even attosecond level [38]) and can deposit their dose in tissues in sub-picosecond timescale [39]. This technology could transform radiotherapy for radio-resistant and inoperable tumours in challenging anatomical locations.

In parallel, fast neutron therapy through laser-based sources marks a potentially interesting development in oncology. Historically, fast neutrons have shown high relative biological effectiveness (RBE), particularly for treating radio-resistant tumours [40]. However, their clinical usage has been limited due to infrastructure demands and the challenge associated with spatial dose control. Additionally, the damage inflicted to healthy tissue was too high for a clinically viable therapeutic ratio. Recent technological advances, such as proton-neutron combination therapies and improved selectivity [41], aim to reduce normal tissue complications and revisit the potential for their clinical application. Laser-driven neutron production now offers compact, high-flux neutron sources with tailored energy spectra [42]. Furthermore, the possibility of using ultrashort neutron bunches opens new avenues for UHDR neutron therapy, potentially enhancing tumour control while further reducing normal tissue damage.

2 Pilot experimental achievements in ultrafast radiation biology at ELI

The Extreme Light Infrastructure (ELI) is the world's largest and most advanced multi-site high-power laser research facility. ELI features cutting-edge laser systems that are largely used to drive secondary radiation sources offered to international users through open access. ELI has a legal status of European Research Infrastructure Consortium (ELI ERIC) that enables the operation of research infrastructures of pan-European interest. ELI ERIC was established to jointly manage the operations of the ELI facilities for the benefit of international academic and industrial researchers [43, 44]. The scientific breakthroughs underpinning these facilities have been recognized with the award of two Nobel Prizes in Physics, in 2018 for ultrashort laser pulse generation, and in 2023 for attosecond science.

Building upon its interdisciplinary strengths in physics, laser engineering, and biology, ELI has the unique opportunity to advance biomedical applications of UHDR radiation, VHEE, and MBT therapy to potentially transform cancer treatments in the future. With its three state-of-the-art user facilities—Attosecond Light Pulse Source (ALPS) in Hungary, Beamlines in the Czech Republic, and Nuclear Physics (NP) in Romania (the latter not being a full ELI ERIC member yet)—ELI provides an unprecedented diverse range of lasers and secondary sources, equipped with flexible experimental platforms/endstations for users to systematically investigate biological effects of laser-accelerated protons, ions, electrons, and neutrons.

Recent pilot radiobiology experiments using various particle beams available at different instruments operating at the ELI facilities (see Fig. 1) have confirmed the feasibility and potential of laser-accelerated particles for biomedical research, as outlined as follows:

- *Laser-Accelerated Protons (LAP)*

The L3-HAPLS PW-class laser at ELI Beamlines was employed at the ELIMAIA-ELIMED beamline [45–48] to accelerate short duration proton bunches. Currently, 10-J, sub-30 fs laser pulses are focussed onto thin solid targets to achieve peak laser intensities exceeding 10^{21} W/cm^2, enabling the generation of proton beams with broad energy spectra and cut-off energies around 40 MeV. The ELIMED section consists of a system of permanent magnet quadrupoles for ion beam collection and injection into a dipole-based magnetic chicane, which selects the desired energy based on user requirements. This is followed by an in-air section for sample irradiation. In addition to standard laser and laser–plasma diagnostics, the beamline is equipped with online ion beam diagnostics (including real-time data analysis tools), as well as absolute and relative dosimetry systems. During the first pilot experiments, a proton beam with an energy of approximately 25 MeV was selected, characterized, and controlled using dedicated dosimetric systems. It was subsequently delivered to normal and cancer cell cultures, as well as to zebrafish embryos. Among these, normal human fibroblasts (AG01522) were exposed in a multi-shot irradiation regime, and DNA double-strand breaks were assessed demonstrating comparable DNA damage responses to previous single-shot experiments [49]. In addition, depth-targeted irradiation, simulating clinical proton therapy, was successfully demonstrated. Apoptosis and DNA double-strand breaks (DSBs) were quantified through immunostaining in the zebrafish model. The ability to harness ultrashort, high-intensity proton pulses holds strategic therapeutic value, as it could enable novel treatment paradigms that maximize tumour control while minimizing damage to healthy tissue.

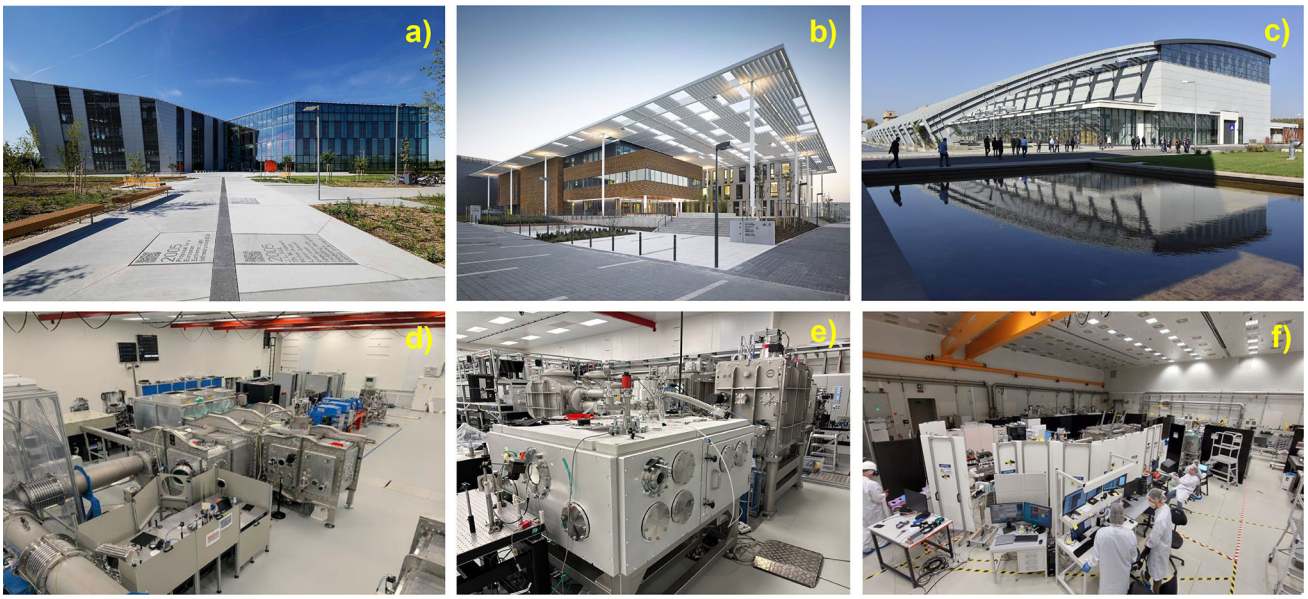

Fig. 1 ELI ALPS (**a**), ELI Beamlines (**b**), and ELI NP (**c**) facilities of the Extreme Light Infrastructure (ELI ERIC). Pilot experiments in ultrafast radiation biology have recently been undertaken at the ELIMAIA-ELIMED (**d**), ALFA (**e**), and LEIA-n (**f**) beamlines

- *Laser-Driven Neutrons (LDN)*

The LEIA-n beamline was commissioned at ELI ALPS with the SEA laser at 10-Hz repetition rate [50]. With the utilization of the SYLOS 1-kHz, 9-fs laser operating at ELI ALPS, the neutron yield was recently increased by a factor of three [51]. The n-LEIA beamline has demonstrated ion acceleration up to cut-off energies of 2 MeV and the generation of fast neutrons (2–3.5 MeV) via DD fusion. The primary target system currently available is a high-repetition-rate (ultrathin) liquid sheet target, enabling 1 kHz operation. The beamline is equipped with various diagnostics, including Thomson parabola ion spectrometers, time-of-flight neutron detectors, and a bubble detector neutron spectrometer. The short neutron bunches produced measurable biological effects in cells, opening promising avenues for the exploration of neutron therapy through investigation of biological effects by novel neutron capture compounds and development of innovative fields (e.g. radiodynamic therapy). Post-irradiation fluorescent staining revealed significant DNA DSBs formation and apoptosis induction, even at sub-100 mGy levels. A rigorous comparison with cyclotron-based (D+D) neutron irradiation at identical dose levels demonstrated strong dose-dependent correlations in biological effects, confirming the reproducibility of laser-driven neutron sources for radiobiological applications. Further research is required to determine whether such ultrashort neutron pulses can replicate the normal tissue-sparing benefits observed in other FLASH radiotherapy modalities, when delivered at FLASH-relevant dose rates.

- *Laser-Accelerated Electrons (LAE)*

The L1-ALLEGRA kHz laser at ELI Beamlines, currently delivering 50 mJ of energy on target, is used at the ALFA beamline to reach intensities exceeding 5×10^{18} W/cm^2 and to accelerate record-energy electron beams (up to 50 MeV) with ultrashort (few fs) bunch width at 1 kHz repetition rate, along with the capability to deliver and measure relevant doses on user samples [52–54]. A stable electron beam is available to users for in-air irradiation, with average dose rates up to 6 Gy/min. In addition to laser and laser–plasma diagnostics, the accelerated electron beams are characterized using an electron spectrometer under vacuum. In-air diagnostics (Lanex screens and radiochromic films) are also available to monitor the electron beam direction and to measure its current and dose rate. Recently, pioneering irradiations of zebrafish embryos were carried out with mean dose rates up to 1 Gy/s.

The SYLOS kHz laser at ELI ALPS was also used at the eSYLOS beamline [55] to accelerate 15–35 MeV ultrashort-duration electron bunches for the irradiation of cells and zebrafish embryos [56]. The electron beam parameters (energy, current, divergence angle) at eSYLOS are tunable by adjusting the laser–plasma interaction conditions. Laser and laser–plasma diagnostics (including interferometry and shadowgraphy), as well as electron beam diagnostics (energy spectrometer, beam profile monitors, charge and divergence angle detectors), are available. The first pilot experiments demonstrated dose-dependent increases in DNA double-strand breaks (DSBs) and apoptotic cell density, along with reductions in survival rates. Morphological abnormalities, such as reduced embryo length, smaller eye diameter, and pericardial and yolk sac oedema, also followed dose-dependent trends. Notably, improved survival of healthy embryos and reduced damage were observed when compared to conventional LINAC electron beams of equivalent energy, suggesting potential therapeutic advantages of laser-driven electron beams in cancer treatment. However, these findings require confirmation through further studies.

- *Laser-Accelerated Ions (LAI)*

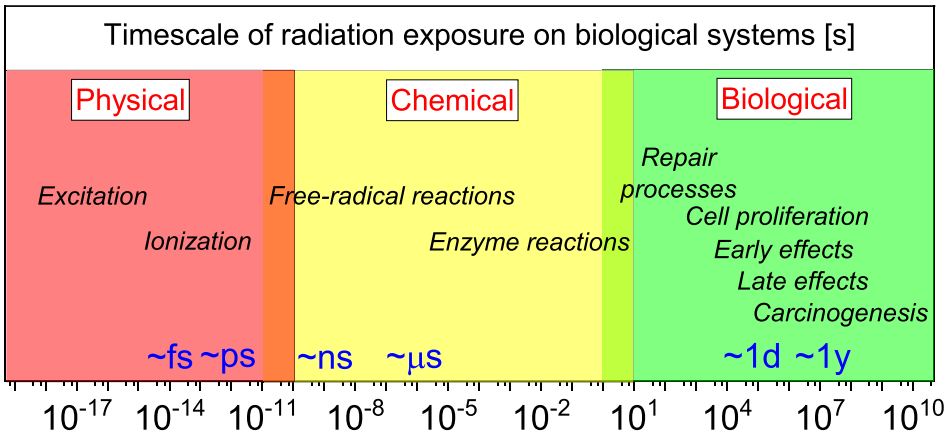

Fig. 2 Different time windows of effects causing biological damage (or repair) after interaction of ionizing radiation with biological tissues. Physical effects mainly occur in < 1 ps, chemical ones up to 1 s, while biological effects require > 1 s

The 10 PW arm of the high-power laser system of ELI NP and the corresponding target area enabled the acceleration of carbon ions with record energy of about 110 MeV per nucleon. Such beams can be used to investigate cellular radiobiological response to heavy ions both *in vitro* and *in vivo* for pre-clinical research. This will be further explored at ELI-NP within a recently awarded project on medical applications of high-power lasers (project name: "Dr. LASER"), which is included in the Romanian Health Program and co-funded by the European Union and the Romanian Government [57]. The overall objectives of the project are to research, innovate, develop, and pilot test novel treatment and diagnostic methods based on high-power lasers. A substantial part of the project is devoted to the experimental demonstration of UHDR carbon-ion generation by ultrahigh-intensity laser pulses, and the study of radiobiological effects of UHDR irradiation with such ion beams towards future hadrontherapy. The project also includes the construction of a beamline for ion beam extraction, energy selection, and transport, as well as an irradiation endstation for assays on *in vitro* and *in vivo* samples.

3 Methodology and strategic approach

The ELI facilities provide a unique, open-access platform for investigating laser-driven ionizing radiation sources across diverse fields, including medical physics, dosimetry, and radiobiology for biomedical applications. By leveraging state-of-the-art beamlines capable of delivering laser-accelerated particle bunches, ELI supports multidisciplinary research in both fundamental science and translational applications.

The particle beam ultrashort duration (femtoseconds for electrons to nanoseconds for ions), ultrahigh instantaneous dose rate (10^7–10^{12} Gy/s), and tuneable energy (10–100 MeV/n for protons and ions at 0.01–1 Hz, and 10–300 MeV for electrons at 0.01–1 kHz) not only make them ideally suited for preclinical radiobiology studies, but also for radiobiology fundamental research aimed at revealing the interplay between the physical, chemical, and biological effects of radiation exposure of living systems, each of which occurs on different timescales, as illustrated in Fig. 2.

Laser-accelerated UHDR particle bunches can be delivered to biological samples in less than 1 ns for protons, or even less than 1 ps for electrons, corresponding to the lifetime of reactive chemical species in biological media [58]. If the spatial separation between individual proton tracks is sufficiently small, reactive chemical species from adjacent tracks may diffuse, interact, and recombine. This interaction could reduce their availability to cause DNA damage, resulting in physicochemical effects that are not observed at conventional or even FLASH dose rates, ultimately impacting cell survival outcomes [59].

Furthermore, coherent stopping power losses, potentially driven by collective molecular excitations, are predicted when UHDR particle bunches interact with matter [60]. These processes, which occur on sub-picosecond timescales—prior to any chemical interaction—are highly dependent on the charge density of the incoming particle bunch and may trigger nonlinear dose deposition and beam self-focussing. This, in turn, can enhance the energy delivered to biological tissues. Thus, laser-driven UHDR, ultrashort particle bunches at ELI offer a powerful tool for separating in time and investigating radiobiological processes on different timescales (< 1 ps, 0.1-1ns, > 1 ns), requiring high temporal resolution probes that are not available using conventional accelerator technologies.

The ELI infrastructure serves as a globally unique radiobiology platform, offering an unprecedented combination of ultrashort secondary sources in open-access User Calls published twice a year. ELI invites international teams to propose and execute experiments based on the scientific merit of the proposals and beam time availability. This fully user-driven approach fosters innovation by providing access to a broad spectrum of ultrashort radiation pulses. Such a unique and versatile offering provided by the ELI infrastructure enables radiobiologists to fully exploit complementary secondary sources using the same biological model system (e.g. zebrafish embryos or established cancer cell lines), thereby ensuring consistency across different experimental conditions.

In addition to the available beamlines, ELI offers on-site dosimetry laboratories and a range of support infrastructures to conduct biomedical research through the preparation of radiobiology experiments and post-irradiation data analysis. The biomedical research laboratories at ELI ALPS comprise two fully equipped rooms housing a diverse array of instruments with the aim of supporting techniques such as cell culture, molecular analysis, histology, zebrafish studies (breeding, fishing, and postprocessing), microscopy, and injection procedures. The radiobiology laboratories at ELI Beamlines can provide support for in vitro activities, e.g. cell culture and post-irradiation evaluation (clonogenic survival, immunocytochemical staining, etc.). Furthermore, a specifically designed Biosafety-Level-2 (BSL-2) laboratory to work with blood and patient-derived samples is under construction along with a room for temporary hosting rodents and zebrafish samples.

The exploitation of laser-driven UHDR beams for biomedical research still requires coordinated advances across three interlocking fronts:

- *Beam delivery and dosimetry*

Laser-driven sources must be engineered for sub-millimetre spatial precision, shot-to-shot energy and intensity consistency, and accurate quality-controlled dose delivery in both preclinical platforms and future therapy prototypes. To this end, bespoke dosimetry systems that are capable of reliably measure and monitor extreme, sub-nanosecond dose rates in offline, online, and real-time modes, should be developed in tandem with applying computational engines such as Monte Carlo transport models (including nano-level codes like Geant4-DNA) specifically tailored to laser-driven particle spectra. Absolute dosimetry methods and reference dosimetry protocols must be established, along with multi-centre comparisons promoted to enable standardization and reduce dose uncertainties. Those combined tools can then benchmark experimental results achieved at ELI against literature data from clinical and research conventional accelerators to quantify their unique strengths and limitations.

- *Integrated biological research approach*

A broad suite of models—from 2D and 3D cell cultures to zebrafish and rodent studies—should be employed to probe critical questions at macroscopic, microscopic, and molecular scales. These include measuring dose–depth distributions and 3D dose maps; determining radiobiological effectiveness (RBE) and modifying factors; defining normal tissue toxicity thresholds; and elucidating molecular pathomechanisms such as radical chemistry dynamics, DNA damage patterns, mitochondrial signalling, immune modulation, ferroptosis, and lipid metabolic pathways. In addition, the use of different laser-accelerated particle species, doses, and dose rates for tumour cell irradiation can improve our understanding of tumour responses and the modulation of immune profiles. This approach could open up new possibilities for radiation-induced conditioning of the tumour microenvironment, thereby supporting the development of innovative combinations with modern immunotherapeutic and anticancer biological strategies.

- *Translation through partnership*

Ongoing close collaboration among laser–plasma physicists, medical and nuclear physicists, and radiobiologists, in addition to active involvement of industrial and clinical stakeholders, will bridge the gap between experimental demonstration and next-generation radiotherapy, to ensure that each technological and biological insight drives the field towards safe and effective patient treatments. With its on-site biological laboratories, ultrashort duration and ultrahigh (temporal and spatial) resolution particle beams, and a truly international collaborative model, the ELI infrastructure provides a unique experimental ecosystem for advancing radiobiology research. By addressing current limitations through a coordinated scientific strategy, ELI aims to lay the foundation for next-generation radiotherapy techniques based on laser-accelerated particle sources.

While the radiation-biology studies carried out so far by the high-power-laser community have provided unprecedented insights, several limitations remain from a clinical-translation perspective. Current constraints include beam reproducibility; stability of particle energy and intensity; accurate dosimetry under extreme pulse conditions; and variability in biological responses. These challenges are the focus of ongoing technical and biological optimization. Nonetheless, the ability to deliver ultrashort, high-dose-rate exposures already enables direct investigation of mechanisms relevant to emerging modalities such as FLASH and spatially fractionated therapy, thereby addressing key unanswered questions in clinical radiotherapy. Beyond these scientific and technical challenges, a major obstacle to clinical adoption is the stringent engineering, safety, and regulatory framework that medical-grade systems must satisfy. Consequently, the clinical implementation of laser-driven radiotherapy will likely follow a longer-term development path, requiring coordinated efforts among engineers, medical physicists, radiation oncologists, and regulatory bodies. As the field matures, however, these hurdles can be systematically overcome, paving the way for medically compliant solutions that capitalize on the unique advantages of laser-accelerated particles.

4 Tailoring and developing the research instrumentation suit

The scientific instrumentation, tools, methods, and technical solutions currently available at the three ELI facilities require continuous upgrades and enhancements to advance the state-of-the-art in laser-driven ultrafast radiation biology. These improvements are essential for providing unique capabilities to the specialized international user community and for enabling the achievement of its ambitious scientific goals.

Table 1 Summary of technical specifications of laser-driven particle beams achievable at ELI in the range of interest for biomedical research

Particle species	Particle energy	Particles/Shot	Bunch duration	Dose/shot	Instantaneous dose rate	Repetition rate
Protons/Ions	5–100 MeV/n	10^8–10^{10}	0.1–10 ns	0.1–10 Gy	10^7–10^9 Gy/s	0.01–10 Hz
Electrons	5–300 MeV	10^8–10^{10}	1–100 fs	1–100 mGy	10^{10}–10^{12} Gy/s	10 Hz–1 kHz
Neutrons	1–10 MeV	10^5–10^7	0.1–10 ns	1–100 μGy	10^2–10^4 Gy/s	1 kHz

Dose and dose-rate values are estimated for a particle beam spot size of 1 cm^2.The upper limit of each estimated range indicates the projected value which is expected based on planned source optimization (or enhancement)

A key priority is to increase particle flux in both single-shot and multi-shot ("fast fractionation" at high repetition rate) regimes with the mission of achieving FLASH-relevant dose levels (mean dose rate) with unprecedented features (instantaneous dose rate) on biological samples. This will require optimisation of the performance of laser-plasma accelerators and the development of new secondary sources, such as ultrafast beams of heavier ion species (e.g. He, C, and N), neutron beams with ultrahigh instantaneous dose-rate, and VHEEs, which are of significant interest to the user community.

Simultaneously, the development of dedicated, compact particle beam transport solutions is critical, along with advanced sample/animal irradiation endstations. The design and development of compact neutron moderation systems is also planned with the goal to deliver high-flux thermal or epithermal neutron energies ($\sim 10^9$ neutrons in a single shot are expected to be generated using 10-PW laser pulses, i.e. $\sim 10^{14}$ n/sr/s). In addition, the development of micro and mini particle beams delivered onto biological samples is considered.

These systems must enable precise control over key beam parameters such as spot size, directionality, energy, pulse duration, intensity, and dose. Additionally, the ability to provide users with controlled environmental conditions for biological samples during irradiation, such as temperature, gas supply, humidity, pH, and normoxic or hypoxic environments, and access to animal facilities, tailored to specific experimental requirements should be considered.

Finally, the deployment of robust absolute and relative dosimetric systems, both online and offline, is essential for reliable operation of laser particle beams and precise real-time control of the dose delivered onto biological samples. This must be complemented by rigorous, standardized quality control protocols applicable to all available types of particle beams, along with potential treatment planning to fulfil irradiation plans. Achieving such standards remains a significant challenge, particularly due to the ultrashort duration and extreme intensity of laser-driven particle beams.

Table 1 provides an overview of the achievable technical specifications for laser-driven particle beams at the ELI facilities in the range of interest for biomedical research. Table 2 provides a breakdown of key particle beam parameters available for biomedical research at major conventional accelerator facilities worldwide, along with the technical specifications of laser systems at leading laser facilities where radiation biology and biomedical research are conducted through in-house, collaborative, or open-access research.

Figure 3 schematically outlines the critical path and objectives of the proposed roadmap for radiobiology and cancer research using laser-driven, ultrashort particle bunches available at ELI. The roadmap requires coordinated efforts between the ELI ERIC research infrastructure, the broader multidisciplinary community of ELI users, and national laboratories conducting relevant research in the field. The objectives are grouped into three main categories: (i) laser–plasma accelerators, (ii) dosimetry and control, and (iii) radiobiology and medical research. While some of the required technological developments can be pursued in parallel, others can only begin once key technologies have reached an advanced level of maturity and reliability. As a result, the roadmap is divided into two implementation phases: short-term (1–2 years) and mid-term (3–5 years), as indicated in Fig. 3.

5 Conclusions and perspectives

The ELI facilities are uniquely positioned to drive a new era of laser-driven ultrafast radiation biology with potential future applications in cancer therapy. By combining cutting-edge laser and laser–plasma technologies with the expertise of biological and clinical users, ELI—under the umbrella of the ELI ERIC infrastructure—offers a research platform that is both distinct from and complementary to conventional accelerator-based systems. This is further supported by an open-access model that prioritizes scientific excellence, enabling international experts to submit high-quality proposals for peer-reviewed selection.

Addressing current technical challenges, such as beam stability, energy scaling, and high-repetition-rate operation of secondary sources, will be essential to unlocking transformative advances in radiation medicine. As the world's largest laser-based research infrastructure, ELI holds a singular position in the global scientific landscape. Unlike conventional accelerator facilities, ELI is optimized to deliver ultrashort, ultrahigh-intensity radiation pulses and multi-species particle beams generated via laser–plasma interactions (see Tables 1 and 2). This specialization allows ELI to access novel regimes of beam temporal structure, dose rate, and energy deposition that are beyond the reach of traditional sources. Crucially, ELI combines these physical innovations with a multi-

Table 2 Summary of key particle beam parameters available for biomedical research at major conventional accelerator facilities worldwide, and laser beam specifications at leading laser facilities conducting radiation biology experiments

Conventional facility	Particle type	Particle energy	Particle dose rate	Particle bunch width	User access mode	Biological endpoints
PSI [63] (Switzerland)	Protons	70–230 MeV	10^3–10^4 Gy/s	3 ns	Open Access	DNA damage; cell survival; dosimetry
GSI [64] (Germany)	Protons/Ions	Up to 300 MeV/u	0.3–120 Gy/s	150 ms	Open Access	DNA damage; cell survival
GANIL [65] (France)	Protons/Ions Neutrons	Up to 300 MeV/u 1–40 MeV	0.5 Gy/min ~ 10^7 n/s (flux)	~ 1 ns ~ 1 ns	Open Access	DNA damage; cell survival
CLEAR [66] (CERN)	Electrons	60–220 MeV	Up to 10^{11} Gy/s	1–4 ps	Open Access	FLASH radiotherapy, dosimetry
ELBE [27] (Germany)	Electrons Neutrons	Up to 40 MeV 0.1–15 MeV	Up to 10^9 Gy/s 10^4–10^5 n/s (flux)	150 fs ~ 1 ns	Open Access	DNA damage; cell survival
PITZ [67] (Germany)	Electrons	Up to 22 MeV	Up to 10^4 Gy/s	~ 1ps	Collaborative Research	FLASH radiotherapy; tissue response

Laser facility	Particle type	Laser power	Laser repetition rate	Laser pulse width	User access mode	Biological endpoints
DRACO [25] (Germany)	Protons Electrons	1 PW	1 Hz	30 fs	Collaborative Research	Cell survival; Zebrafish; Rodents
CLF [68] (UK)	Protons Electrons	0.5 PW	0.05 Hz	30 fs	Open Access	DNA damage; cell survival
LULI [19] (France)	Protons	0.1 PW	1 shot/90 min	1 ps	Open Access	DNA damage; cell survival; Zebrafish
BELLA [20] (USA)	Protons	1 PW	1 Hz	40 fs	Open Access	DNA damage; cell survival
LION [69] (Germany)	Protons	2.5 PW	1 Hz	27 fs	Collaborative Research	DNA damage; cell survival; Zebrafish
ELI (ALPS, Beamlines, NP)	Electrons Protons/Ions Neutrons	7–15 TW 1 PW 10 PW	1 kHz 1–10 Hz 1/60 Hz	8–15 fs 23–30 fs 23–150 fs	Open Access	DNA damage; cell survival; Zebrafish; FLASH radiotherapy

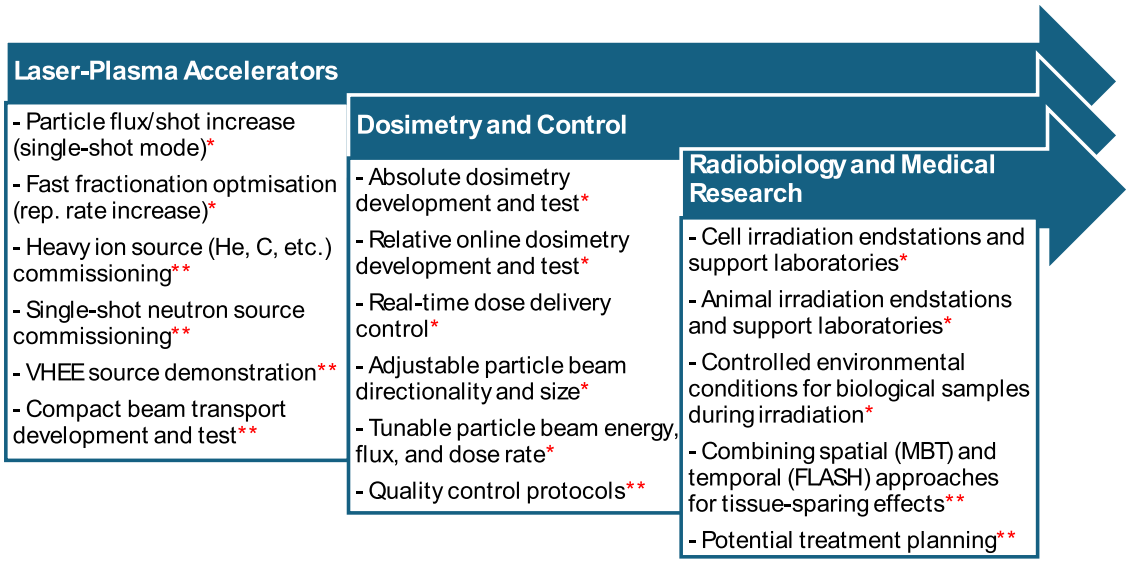

Fig. 3 Objectives of the proposed roadmap for ultrafast radiation biology and cancer research to be pursued by the ELI ERIC research infrastructure, the broader multidisciplinary community of ELI users, and individual national laboratories (* indicates the "short-term" and ** the "mid-term" phases)

disciplinary framework that integrates physics, biology, and medicine. Its open-access structure fosters international collaboration and promotes the clinical translation of research breakthroughs.

At this stage, a coordinated, interdisciplinary, and collaborative research agenda at the international level is essential to fully realize the scientific and biomedical potential of UHDR laser-plasma sources. This should prioritize the enhancement of available scientific instrumentation (and performance specifications), tools, methods, and technical solutions that will advance the global state-of-the-art in laser-driven ultrafast radiation biology. Specific and unique features of laser-driven particle beams available at ELI can be explored to reveal and understand new biological effects. In addition, the unprecedented opportunity to conduct statistically robust radiobiology experiments studying the same biological endpoints (e.g. using the zebrafish model) across a broad range of particle beams available at the ELI, multi-site infrastructure within a very short temporal window (1–2 weeks) can be effectively explored.

Close collaboration and shared objectives among laser-plasma physicists, medical physicists, and biologists are key to ensure the generation of scientifically strong and reproducible results. The integration of laser-driven particle beams into possible future radiotherapy schemes represents a paradigm shift, combining the physical and biological advantages of ultrashort particle bunches with novel dose delivery mechanisms. These innovations offer exciting prospects for the next generation of cancer treatments, helping to bridge the gap between theoretical progress and future clinical applications.

Ultimately, ultrashort laser-based radiation sources and related technologies could be implemented within a versatile irradiation facility, where a central laser system serves as the core driver. Such a facility would generate multi-species particle beams with a wide range of characteristics (energy, dose rate, etc.) for both clinical and research applications. Available beams could be delivered sequentially or simultaneously, enabling multi-species particle beam treatment approaches that optimize dose distribution, enhance biological effectiveness (e.g. through UHDR and FLASH effects), and investigate the synergistic effects of combined radiation modalities (e.g. integration with an MBT approach).

In addition, the concomitant availability of medical imaging techniques based on laser-driven ultrafast X-ray sources—such as high-resolution phase contrast imaging, which is particularly valuable for visualizing soft tissues like those found in breast tumours—using broadband Betatron radiation generated via laser wakefield acceleration [61, 62], would further enhance the modular character of such an irradiation facility.

Such a multi-functional research infrastructure for ultrafast radiation biology has the potential to lead to discoveries of new mechanisms to be tested in pre-clinical settings prior to their clinical translation of adaptable, individualized treatment regimens, and leveraging the unique advantages of ultrashort, laser-driven radiation sources.

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References

1. S.V. Bulanov, V.S. Khoroshkov, Plasma Phys. Rep. **28**, 453 (2002)
2. M.C. Vozenin, J. Bourhis, M. Durante, Nat. Rev. Clin. Oncol. Clin. Oncol. **19**, 791 (2022)
3. A. Borghini et al., Int. J. Mol. Sci. **25**, 2546 (2024)
4. N. Giannini et al., Front. Oncol. **14**, 1373453 (2024)
5. G. Tsakanova et al., Int. J. Mol. Sci. **22**, 11525 (2021)
6. Y. Wang et al., Nanoscale Adv. **7**, 711 (2024)
7. M. Durante et al., British J. Rad. **91**, 20170628 (2018)
8. F.A. Dilmanian, J.G. Eley, S. Krishnan, Int. J. Radiat. Oncol. Biol. Phys. **92**, 469 (2015)
9. R. Ortiz, J. Ramos-Méndez, Sci. Rep. **14**, 26585 (2024)
10. A. Reynolds, L. Marignol, Int. J. Radiat. Biol. (2025). https://doi.org/10.1080/09553002.2025.2473981
11. A. Yogo et al., Appl. Phys. Lett. **94**, 181502 (2009)
12. A. Yogo et al., Appl. Phys. Lett. **98**, 053701 (2011)
13. D. Doria et al., AIP Adv. **2**, 011209 (2012)
14. L. Manti et al., JINST **12**, 03084 (2017)
15. F. Hanton et al., Sci. Rep. **9**, 1 (2019)
16. K. Zeil et al., Appl. Phys. B **110**, 437 (2013)
17. E. Bayart et al., Sci. Rep. **9**, 10132 (2019)
18. S. Raschke et al., Sci. Rep. **6**, 1 (2016)
19. A. Flacco et al., Sci. Rep. **15**, 16511 (2025)
20. J. Bin et al., Sci. Rep. **12**, 1484 (2022)
21. P. Chaudhary et al., Frontiers in Physics **9**, 624963 (2021)
22. P. Chaudhary et al., Phys. Med. Biol. **68**, 025015 (2023)
23. S. Schell, J.J. Wilkens, Med. Phys. **37**, 5330 (2010)
24. U. Masood et al., Appl. Phys. B **117**, 41 (2014)
25. F. Kroll et al., Nat. Phys. **18**, 316 (2022)
26. M. Oppelt et al., Rad. Env. Biophys. **54**, 155 (2015)
27. J. Metzkes-Ng et al., Sci. Rep. **13**, 20611 (2023)
28. Y. Glinec et al., Med. Phys. **33**, 155–162 (2006)
29. T. Fuchs et al., Phys. Med. Biol. **54**, 3315 (2009)
30. C.M.V. Panaino et al., Cancers **17**, 181 (2015)
31. A. Subiel et al., Phys. Med. **42**, 327 (2017)
32. L. Labate et al., Sci. Rep. **10**, 17307 (2020)
33. R. Polanek et al., Nucl. Instrum. Methods Phys. Res. A **987**, 164841 (2021)
34. K. Swendson et al., Sci. Rep. **11**, 5844 (2021)
35. Z. Guo et al., Nature Comm. **16**, 1895 (2025)
36. K. Kokurewicz et al., Sci. Rep. **9**, 10837 (2019)
37. O. Lund et al., Nat. Phys. **7**, 219 (2011)
38. M.J.H. Luttikhof et al., Phys. Rev. Lett. **105**, 124801 (2010)
39. D. Horvath et al., Phys. Med. Biol. **68**, 22NT01 (2023)
40. L.T. Santanam et al., Int. J Rad. Oncol. Biol. Phys. **68**, 1546 (2007)
41. S. Aljabab et al., Cureus **13**, e14844 (2021)
42. K. Osvay et al., Eur. Phys. J. Plus **139**, 574 (2024)
43. https://www.eli-laser.eu/
44. A. Harrison et al., Europhys. News **54**, 5 (2023)
45. https://up.eli-laser.eu/equipment/elimaia-elimed-1415545205
46. D. Margarone et al., Quant. Beam Sci. **2**, 8 (2018)
47. F. Schillaci et al., Quant. Beam Sci. **6**, 30 (2022)
48. G.A.P. Cirrone et al., Front. Phys. **8**, 564907 (2020)
49. P. Blaha et al., Front. Phys. **13**, 1567622 (2025)
50. L. Stuhl et al., Phys. Rev. Res. **7**, 023137 (2025)
51. https://up.eli-laser.eu/equipment/leia-n-1415610562
52. https://up.eli-laser.eu/equipment/alfa-1415577923
53. C.M. Lazzarini et al., Phys. Plasmas **31**, 030703 (2024)
54. I. Zymak et al., Photonics **11**, 1208 (2024)
55. https://up.eli-laser.eu/equipment/sylos-electron-1415578144
56. E.R. Szabó et al., Int. J. Rad. Bio. **94**, 985 (2018)
57. https://www.eli-np.ro/projects/drlaser/
58. R. Roots, S. Okada, Rad. Res. **64**, 306 (1975)
59. S.J. Thompson, K. Prise, S.J. McMahon, Phys. Med. Biol. **68**, 05500 (2023)
60. A. Curcio et al., Phys. Rev. Res. **6**, 033334 (2024)

61. S. Fourmaux et al., Optics Lett. **36**, 2426 (2011)
62. J. Wenz et al., Nat. Comm. **6**, 7568 (2015)
63. K.P. Nesteruk et al., Med. Phys. **48**, 417 (2021)
64. F. Luoni et al., Front. Phys. **8**, 568145 (2020)
65. X. Ledoux et al., Eur. Phys. J. A **57**, 257 (2021)
66. D. Gamba et al., Nucl. Inst. Meth. Phys. Res. A **909**, 480 (2018)
67. F. Stefan et al., Phys. Med. **104**, 174 (2022)
68. C.J. Hooker et al., Laser Soc. Jpn. **37**, 443 (2009)
69. J. Hartmann et al., Proceedings of SPIE. **11779** (2021)