LASER–PLASMA ACCELERATORS

# Ready for translational research

Laser accelerators promised to deliver high-energy particle beams for biomedical uses, but have struggled to meet constraints on dose control and stability. An experiment now enables translational research with proton beams at ultrahigh dose rate.

Leonida A. Gizzi and Maria Grazia Andreassi

When focused on a target, intense, ultrashort pulsed laser light can drive particle beams in a variety of accelerator configurations[1]. Laser–plasma accelerators are capable of accelerating particles at high energy over a very short distance, but are difficult to stabilize and control. Recently, laser–plasma acceleration of electrons has established itself as a reliable and powerful source of high-quality electron beams[2], paving the way to their exploitation in multidisciplinary science and biomedicine. For advanced radiotherapy approaches, efficient and compact sources of energetic particles, such as electrons and protons, are needed[3]. Now, writing in *Nature Physics*, Florian Kroll and colleagues report that they have used laser-accelerated proton beams to irradiate tumours in mice, demonstrating the readiness of laser-accelerated proton beams for translational research[4].

A major milestone for light ion and proton acceleration by lasers had been approaching for some time, with the potential for biomedical applications and hadron therapy being the key impetus[5]. The maximum particle energy, spectral distribution and stability have all kept improving, approaching the requirements for radiobiology. A growing number of in vitro studies demonstrated improved control of beam parameters, eventually meeting the high standards for radiobiology applications. As a reward for this effort, access in the laboratory to controlled, intense proton pulses — as short as a nanosecond or less — has now become available, enabling fundamental studies of radiobiological effects (Fig. 1) at larger scales. The challenge is to understand the role of the irradiation timescale in the many physical and chemical effects that lead to DNA damage. These damages, for example, include excitation and ionization of atoms and formation of free radicals from dissociation of molecules[6].

In the path towards clinical exploitation of laser–plasma accelerators, qualified in vivo studies are needed to validate therapeutic approaches and establish

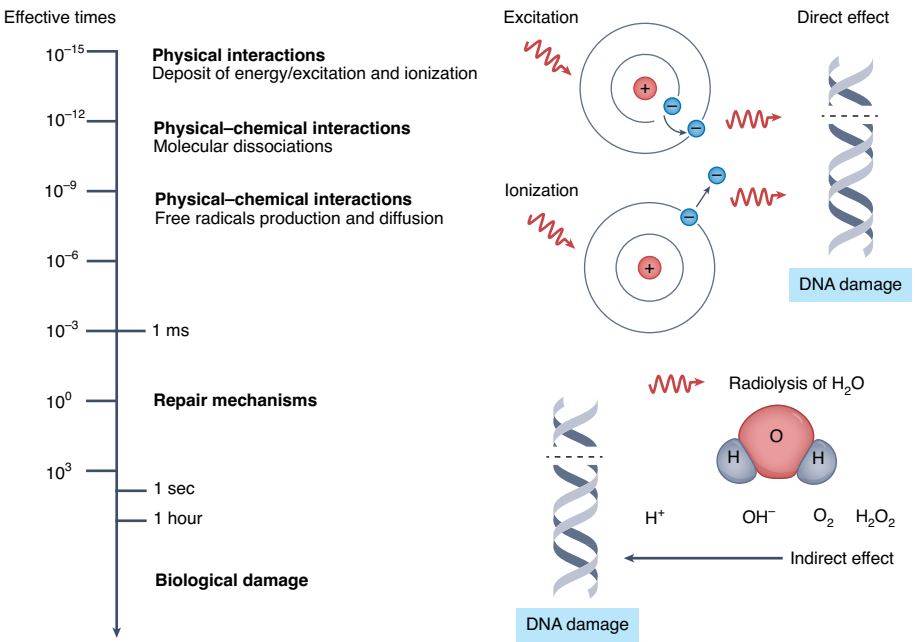


**Fig. 1 | Mechanisms behind radiobiological effects.** The timescales at which different physical and chemical reactions relevant to biological effects of ionizing radiation set in are illustrated. The intensity of processes occurring early during and after irradiation have a key role in the outcome of the biological effect and, eventually, in the control of therapeutic effects.

protocols. Until now, the possibility of systematic and reliable in vivo studies of tumour treatment with a laser–proton source was hindered by the low beam energy that was well suited for cell irradiation.

The platform demonstrated by Kroll and colleagues overcomes this limitation through the implementation of spectral phase control of the laser pulse that accelerates the protons as well as robust post-acceleration control and selection of the proton beam. They irradiated human tumours grown on mice ears, showing that a total dose exceeding 20 gray could be delivered homogeneously over a volume as deep as 40 mm. For comparison, early breast cancers are irradiated with total doses of around 50 gray delivered in several sessions. Along with the percent-level stability of the laser-accelerated proton beam, the achieved dose delivery is compliant with the features of the selected mouse ear tumour model for in vivo studies. This pilot irradiation study demonstrates the suitability of laser-driven proton sources for providing precise dose delivery and radiation-induced tumour growth delay compared with irradiations using conventional proton beams and X-rays.

Laser-driven protons come in very short pulses leading to high rates at which the dose is delivered. This high dose rate makes it possible to use the platform developed by Kroll and colleagues for in vivo investigation of dose-rate effects to understand their role in the biological response to the irradiation by ionizing radiation[5].

In fact, recent studies show that when the therapeutic dose is delivered in a fraction of a second and at a rate in excess of around 40 gray per second, the so-called FLASH

effect[7] sets in. This effect is currently attracting major attention for radiotherapy because it is associated with sparing of healthy tissue while remaining effective on tumour tissue[8] and has proven effective in clinical trials[9]. To date, however, a full understanding of the FLASH effect is still lacking and the wider community is working on new experiments and models[6]. Extensive in vivo studies are required to clarify the mechanisms of radiation-induced delay of tumour growth for different doses and dose rates compared with conventional radiation sources. Future studies should also evaluate the effects of different modalities of dose delivery in fractions as well as the biological response, such as DNA damage-repair processes, and inflammatory and immune endpoints, to have a complete knowledge of the therapeutic potential of the fast dose deposition.

The intrinsic high dose rate of laser–plasma accelerators makes them potentially valuable for studies of the mechanisms underlying the FLASH effect, although the possibility of delivering the required multigray-level therapeutic dose in a 100 ms time frame is yet to be established. The 660 milligray per pulse delivered at millimetre-scale depth demonstrated by Kroll and colleagues is encouraging for FLASH research. A burst of a few of these pulses within a time window of 100 ms would be needed to enter the FLASH domain for laser-based proton sources. This in turn would require the drive laser to fire at a repetition rate of 100 Hz for that 100 ms — a performance that is within reach of current laser technology. However, further optimization of the dose per pulse is in order, with a number of proton acceleration enhancement solutions currently under investigation[10].

Biomedical research for next-generation clinical cancer radiotherapy needs sharp tools to access unprecedented parameter ranges. A challenge here is to employ radiation with the highest degree of control and trace biological effects of radiation back to the physical and chemical mechanisms occurring on ultrafast timescales. Laser accelerators are intrinsically ultrafast and are now ready to be fully utilized. ❐

Leonida A. Gizzi[1]✉ and Maria Grazia Andreassi[2]✉

[1]*Istituto Nazionale di Ottica, Consiglio Nazionale delle Ricerche, Pisa, Italy.* [2]*Istituto di Fisiologia Clinica, Consiglio Nazionale delle Ricerche, Pisa, Italy.*

✉*e-mail: la.gizzi@ino.cnr.it; andreassi@ifc.cnr.it*

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## Competing interests

The authors declare no competing interests.

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COMPLEX SYSTEMS

# One for all

Predicting collapses of a complex system is notoriously hard. Finding ways to pull a collapsed system back to normal is even harder. A theoretical study now shows how reviving a single unit of a failed network might restore its whole functionality.

Patrick Desrosiers and Xavier Roy-Pomerleau

Species extinctions, epileptic seizures and power grid blackouts are classical examples of dysfunctional states resulting from critical transitions in complex systems. Researchers have intensively worked over recent decades to find indicators that could help foresee tipping points[1–3], that is, thresholds beyond which the state of a system changes drastically, often irreversibly. How to intervene in systems that have already reached a dysfunctional state to restore their functionality is a much less explored problem. Writing in *Nature Physics*, Hillel Sanhedrai and colleagues[4] report that they have now demonstrated that a localized perturbation can drive a system back to a functional state, opening a new chapter in our understanding of the resilience of complex systems.

In the 1970s, combining experimental data and concepts from the qualitative theory of nonlinear differential equations, Crawford S. Holling[5] defined resilience as the ability of ecological systems to absorb changes and disturbances without collapsing. He argued that they have many stable states, each with a corresponding 'basin of attraction' — the set of initial conditions from which the system typically evolves into a given stable state. Resilience is closely related to the size of these basins. To illustrate his ideas, Holling proposed a basic — yet frequently used[3] — analogy: a mass subjected to the gravitational field on a landscape of peaks and valleys (Fig. 1a).

Later works[6] clarified the role of thresholds in ecological systems with multiple stable states, such as models describing the evolution of the population of a species. Plotting the equilibrium states of such systems as a function of a single model parameter can sometimes lead to diagrams similar to Fig. 1b, indicative of a dynamical catastrophe. Comparable diagrams were later obtained while investigating the global activity of neuronal networks[7] and the synchronization of oscillators[8,9]. Interestingly, Fig. 1b contains a hysteresis loop — the irreversible cycle ABCD — a hallmark of first-order phase transitions in statistical mechanics and explosive phenomena in network science[8].

The goal of Sanhedrai and collaborators was to design a realistic perturbation strategy that would force a system, in a dysfunctional state, to transition towards a functional state. For example, if the system is at point B in Fig. 1b, the aim would be to find a way up to the upper branch. Drastic solutions, such as applying a huge perturbation or dramatically increasing the relevant parameters to automatically propel the state to the higher branch, are