Laser-driven particle acceleration for radiobiology and radiotherapy: where we are and where we are going

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ABSTRACT

Radiation therapy of tumors progresses continuously and so do devices, sharing a global market of about $ 4 billions, growing at an annual rate exceeding 5%. Most of the progress involves tumor targeting, multi-beam irradiation, reduction of damage on healthy tissues and critical organs, dose fractioning. This fast-evolving scenario is the moving benchmark for the progress of the laser-based accelerators towards clinical uses. As for electrons, both energy and dose requested by radiotherapy are available with plasma accelerators driven by lasers in the power range of tens of TW but several issues have still to be faced before getting a prototype device for clinical tests. They include capability of varying electron energy, stability of the process, reliability for medical users. On the other side hadron therapy, presently applied to a small fraction of cases but within an exponential growth, is a primary option for the future. With such a strong motivation, research on laser-based proton/ion acceleration has been supported in the last decade in order to get performances suitable to clinical standards. None of these performances has been achieved so far with laser techniques. In the meantime a rich crop of data have been obtained in radiobiological experiments performed with beams of particles produced with laser techniques. It is quite significant however that most of the experiments have been performed moving bio samples to laser labs, rather moving laser equipment to bio labs or clinical contexts. This give us the measure that laser community cannot so far provide practical devices usable by non-laser people.

Keywords: Laser-driven particle accelerators, radiobiology, radiotherapy, dosimetry, radiation safety

1. INTRODUCTION

It is time to check state of the art and perspective of laser technologies addressed at implementing compact particle accelerators for biological researches and clinical uses. During a recent editorial work[1] I realized that the expectation level for this novel technology is quite high in a broad community of scientists, including laser, plasma and nuclear physicists, medical physicists, radiation biologists, radiologists and radiotherapists. Contributions from each one of these classes of expertise become highly desirable today to actually state where we are, where we should move and how. Physicists involved in the particle acceleration with laser techniques can provide not only the state of the art of laser-driven electron, proton and ion accelerators most suitable for biological studies and future clinical therapies, but also a deep insight into the most advanced experiments and novel ideas. It will come out that laser produced particles have been used in a variety of physical schemes to generate secondary sources of high-energy photons, another kind of ionizing radiation, the most used in radiation therapy of tumors. In turn, photons of tens of MeV have been used to produce, via photonuclear reactions, radionuclides of interest for the nuclear medicine. In addition, high-resolution ultrafast radiography has been performed with particles accelerated by laser[2]. On the other hand, radiotherapists can update our knowledge about the most advanced devices and protocols, very effective, they actually use in a hospital: the novel practice in radiotherapy of tumors is the benchmark (continuously moving forward) for the laser-driven technologies. While a number of biologists are systematically investigating the response of living matter to the particle bunches produced by lasers, some others are already speculating on how this new opportunity can extend and empower the most recent concepts of radiobiology. The action of such kind of radiation can be followed for the first time on femtosecond time scale and nanometric spatial scale. The novel acceleration technologies, based on the interaction of ultrashort intense laser pulses with matter, delivering sub-picosecond pulses of ionizing radiation, also demand a general renewing

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Medical Applications of Laser-Generated Beams of Particles IV: Review of Progress and Strategies
for the Future, edited by Kenneth W. D. Ledingham, Proc. of SPIE Vol. 10239, 1023904
© 2017 SPIE · CCC code: 0277-786X/17/$18 · doi: 10.1117/12.2270945

of dosimetry[3] and safety protocols. Both absolute and relative dosimetry are currently re-considered, in the framework of international standards[4]. While suitable existing devices are examined, including radiochromic foils, ionization chambers and Faraday cups, novel concepts for ad hoc detectors are introduced and need to be carefully investigated. Dosimetric simulations with Monte Carlo methods, in particular with the GEANT4 toolkit provide a precious support to this effort. Also radiological safety has to be reconsidered while thinking to transfer technologies based on high power lasers in a clinical context. It is not the same issue as with conventional accelerators delivering a well defined type of particle with an almost monoenergetic spectrum. We are dealing now with a mix of radiological products delivered by laser-matter interaction, at a given but changeable intensity, with a variety of materials acting as accelerating media. Of course this kind of problems have already been faced in high-power laser facilities devoted to studies on laser-matter interactions and in particular to particle acceleration, but for a medical facility the safety of patients and personnel is paramount, then also doses from any secondary radiation and any kind of other hazards have to be carefully minimized[5].

Though the rate of survivals increases regularly year by year, cancer is still the first cause of death everywhere. The number of *new* cases of cancer in the world is estimated to have been about 14 millions in the year 2012, with an expectation of more than 20 millions in 2020[6]. About 50% of cases are treated with radiation therapies, possibly in combination with surgery and/or chemotherapy, with an emerging problem for the access of low- and middle-income countries (LMIC) to radiation therapy[7], particularly to the more expensive hadron therapy. Among these treatments, more than 90% use RF-driven linear accelerators of electrons (RF-Linac). Other techniques include internal radiation (brachytherapy) and proton-ion beams (hadron therapy). In most cases electrons delivered by a RF-linac are not used directly on the tumor but converted into photons (hard X-rays) by bremsstrahlung through a suitable target. In some case electrons are used directly, either to cure superficial tumors or in the Intra-Operative Radiation Therapy (IORT) which can be applied during surgical operation of a tumor[8,9]. Radiation therapy techniques evolve and progress continuously and so do accelerators and dose delivering devices, which share a global market of about $ 4 billions, growing at an annual rate exceeding 5%[10]. Most of the progress involves precision in tumor targeting, multi-beam irradiation, reduction of damage on healthy tissues and critical organs, fractionation of dose delivering for a more effective cure[11]. Among these novel techniques and protocols of treatment, particularly effective appears the so-called Cyberknife. This technique uses a multitude of small beams which creates a large dose gradient resulting in the delivery of high dose to the tumor while minimizing the dose to adjacent healthy tissues[12].

Basically, requested electron kinetic energy ranges from 4 to 25 MeV, but rarely energy above 15 MeV is used. Required dose/rate usually ranges from 1 to 10 Gy/min. These two ranges of performances are presently well fulfilled by plasma accelerators driven by ultrashort laser pulses of "moderate" peak power, i.e. tens of TW, operating within high efficiency laser-plasma interaction regimes at a pulse repetition rate of the order of tens of Hz[13]. However further work has to be done on laser acceleration in order to reach the clinical standard in terms of the electron output stability and reproducibility. Several tasks have to be afforded before proceeding to a technical design of a laser-driven linac prototype for clinical tests. A first task is the optimization of both laser and gas-jet (or other possible targets) as well as their coupling (involving mechanical stability and optical design). Another task is the energy control of the electron bunch to provide different electron energies on clinical demand. These goals would require a complex scientific and technological investigation addressed to both the laser system, in order to make it as stable, simple and easy to use as possible, and the physics of the acceleration process, in order to get the highest possible efficiency, stability and output control. We may nevertheless try and list some of the expected advantages of future Laser-linac's for clinical uses. Laser technology strongly reduces size and complexity of the acceleration section (Mini-linac) of the device; it also totally decouples the "driver" from the acceleration section: we can imagine in a hospital a single high power laser plant in a dedicated laser-room (with no need for radioprotection) which delivers pulses to a number of accelerators located in several treatment or operating rooms, suitably radioprotected. Laser managing and maintenance can proceed independently from the managing and maintenance of the Mini-linac's. Each Mini-linac could be easily translated and rotated according to the given radiotherapy plan. Current studies could prove that the extreme dose-rate per pulse delivered by the Laser-linac would reduce the total dose for a therapeutic effect. This latter of course would be a major advantage of laser-driven radiotherapy.

The original idea of Laser Wake-Field Acceleration[14] and the advent of the decisive CPA laser technology[15] originated one of the most appealing scientific case of the last decades. Since then, a number of schemes for laser driven acceleration of electrons in plasmas have been proposed and studied, some of which have been successfully tested till very recently[16,17]. New experimental records have been reported in the recent literature, in terms of the maximum electron energy achieved, the minimum energy spread, as well as maximum collimation, stability, and so on. These records are in general obtained with lasers of outstanding performances and/or with very sophisticated methods hardly applicable for practical uses. On the other hand, several labs are intensively working on scientific and technological innovations aimed at demonstrating that reliable laser-based devices can be built which are able to produce electron beams fulfilling requirements of specific applications. A major task is addressed to the possible clinical use of electron laser-linac's and their potential advantages with respect to the existing RF-linacs operating today for millions of daily hospital treatments in the world.

This is the context in which the exciting progress of laser-driven electron acceleration try to make this technique competitive with existing RF-based devices involved in 90% of tumor treatments with radiation therapy. It has to be said however that hadron therapy, presently limited to a few percent of global treatments, is by far the most desirable way for the future to treat many tumors with ionizing radiation. This is due to the peculiar character of energy deposition of hadrons in a medium: treating a tumor at a given depth, monoenergetic protons or ions of suitable kinetic energy deliver most of the dose in a thin layer (Bragg peak) around the tumor site, while either electrons or gamma rays leave lot of their energy inside healthy tissues, before and after the tumor, with possible damages on these latter tissues. It has to be said, this drawback for electron-based clinical devices has been strongly reduced with modern configurations allowing multi-beam irradiations at different angles[11,12]. Nevertheless, hadron therapy still remains a primary option for the future of radiotherapy, 70 years after its first conceptual proposition[18] followed by pioneering experimental tests[19]. Since then, hadron therapy was occasionally performed inside accelerator facilities devoted to high energy physics, until the opening (1990) of a first clinical center equipped with a proton accelerator facility at Loma Linda Hospital in California (USA). In the last decades both the number of centers and the number of treated patients grew almost exponentially worldwide as shown in Figure 1[20]. More than 137,000 patients were treated with this therapy worldwide from beginning up to 2014, including 15,000 in 2014, 86% of which were treated with protons and 14% with carbon ions or with other particles.

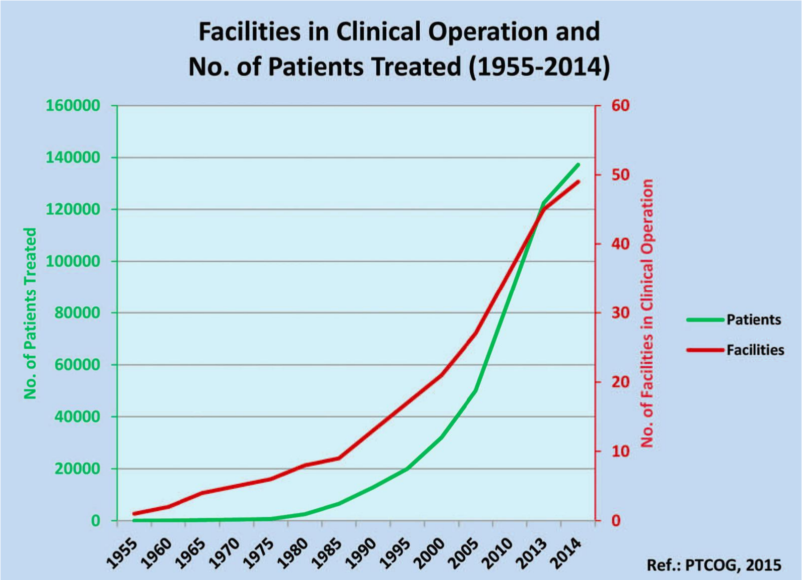

Figure 1. Growth of hadron therapy in treatment centers and treated patients worldwide (image from Reference 20).

Though the total number of treatments is still a small fraction of the total number of radiation treatments, this impressive growth demanded a huge capital investment which could be afforded only by medical institutions from rich countries[‡]. RF-based ion accelerators have faced an impressive progress, mostly in the synchrotron configuration (Figure 2 shows an overview of the CNAO synchrotron) but typical acceleration gradients still remain of the order of 1MeV/m, so that the typical diameter of an accelerator ring is several tens of meters for energies of clinical interest, namely E ≈ 100-400

[‡] As a matter of fact, a global survey from the the Particle Therapy Co-Operative Group updated at the end of 2015, attributes 27 operating facilities to USA, 23 to European countries, 17 to Japan, 4 to China, 4 to Russia, 2 to Canada, 2 to South Korea, 1 to South Africa.

MeV/u, with severe costs involved[21]. Additional high costs and large spaces are requested by the very heavy gantry systems necessary to guide the particle beam onto the patient body from the right direction(s) and focus it with a millimeter precision[22]. According to a recent review[23], the seven major commercial companies operating in the field are able to deliver systems (based on either Cyclotron or Synchrotron technologies) with "superb reliability records". The same companies are actively engaged in reducing size and cost for the next generation of devices. In fact, size and cost (both for construction and maintenance) of such facilities are presently the major drawbacks for a wider diffusion of hadron therapy.

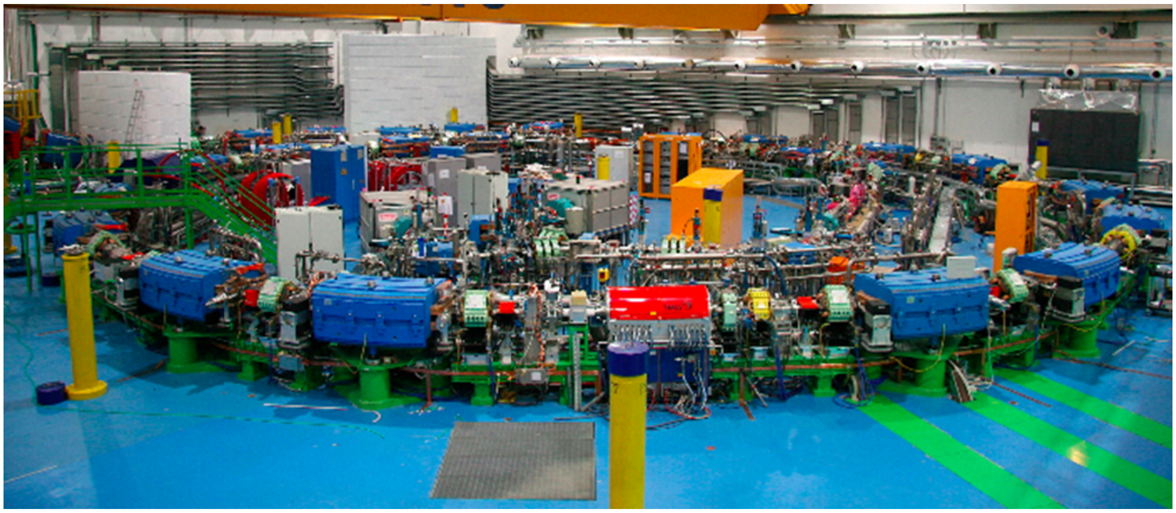

Figure 2. The CNAO Synchrotron, Pavia, Italy.

With such a strong motivation, research on laser-based proton acceleration has been considerably supported in the last decade, mostly in the direction of achieving the challenging performances requested by the clinical standards. A usable device for cancer therapy needs to produce 200-250 MeV protons and /or 400-450 MeV/u carbon ions. In order to really profit of the Bragg peak, no more than 1% energy bandwidth is requested. Further, to release a dose of therapeutic interest in a reasonable time, more than 10^{10} particle/s have to reach the tissue under treatment. None of these performances has been achieved so far with laser techniques. Some of them seem still hard to achieve with existing lasers or even with the next generation lasers, at least in a configuration practically usable in a hospital context. Someone can define today the goal of laser-driven ion therapy as an "unrealistic expectation"[23] but the impressive crop of knowledge[24], the preliminary successful biological tests already performed[25] and some exciting new ideas[26] strongly encourage the community of laser-driven ion acceleration in its serious effort aimed at that long-term goal.

Historically, ion acceleration in plasmas was proposed before the invention of optical lasers, as early as 1956[27] and initially tested with electrons propagating in plasmas. Apart from initial observations related to fusion studies with infrared CO_2 lasers, the laser driven ion acceleration studies with optical lasers could really start only after some decisive breakthrough towards high peak power lasers, like mode-locking (ML) for picosecond pulses and chirped pulse amplification (CPA) for femtosecond pulses[15]. About 1-MeV ions were produced in the early Nineties with picosecond laser pulses[28]. Subsequently, a continuous progress towards higher kinetic energies was continuously driven by both innovation in laser technology and better comprehension of the complex physics involved in the ion acceleration processes. Several proposals raised for a variety of schemes of laser-matter interaction at ultra-high (ultra-relativistic) intensities able to drive protons and light ions to near-relativistic energies. Most of them can be attributed either to *target normal sheath acceleration* (TNSA) or *radiation pressure dominated acceleration* (RPDA). This matter has been recently discussed by Borghesi and Macchi[24].

In a general view, considering the present state of the art, we can say that laser-driven acceleration to kinetic energies suitable for radiotherapy of cancer is well consolidated in the case of electrons and bremsstrahlung photons (with bunches delivering the requested dose). Effort is being invested towards achievement of corresponding energies for protons and light ions. In the case of electrons most of the work to be still done, in order to achieve clinical standards, has to address the control of the electron energy, as well as stability and reliability of the laser-linac. In the case of protons and light ions the work to be done still includes the identification of an acceleration regime able to produce particles of suitable energy (and energy spread) in bunches delivering the right dose.

However, there is a major scientific issue which deserves to be addressed from now, concerning potential radiobiological effects of the extremely different duration of bunches produced by laser with respect to bunches produced by conventional accelerators. A factor exceeding 1,000,000 is involved, from μs to sub-ps timescale. The ultrashort duration of laser-produced particle bunches may involve unexpected consequences for cancer therapy. In fact, it is not known if delivering the same dose with particles of the same kinetic energy but at much higher instantaneous dose-rate may lead to a different tissutal effects with possible consequences on therapeutic strategy and protocols[29]. From the physical point of view we can expect that the extreme particle density we can produce in a bunch with laser acceleration could behave "collectively" and/or lead to non-linear effects which cannot be described by the usual single-particle Monte Carlo simulation. In other words it is possible that each ultradense bunch of electrons could produce not only the statistic sum of the effects of each low-LET particle but also some high-LET effect due to the total charge involved. If this would be true, the biological action could not only concern DNA but also some structural cellular feature, like membrane. This major issue, in turn, calls for a dedicated research on radiobiological effects to be performed with the ultrashort particle bunches produced by laser technology. It is evident that such a research also has a high conceptual value since it enables, for the first time, the investigation of very early processes occurring in the timescales of physical, chemical, biological responses of the living matter to ionizing radiation[30]. Investigation of very early effects arising from ultrashort ionizing pulses at nanometric scale become possible in a framework of advanced *femtochemistry*. This opportunity move also the interest of biologists, aimed at improving the "OMIC" approach to radiation therapy[31]. Finally, it has be be pointed out that the use of laser in combination of an electron beam is capable of creating collimated energy-specific (and energy-tunable) X-rays and γ-rays via the laser Compton scattering process[32]. Such high-energy quasi-monochromatic photon source can be very useful in radiation oncology.

2. HADRON THERAPY AND LASER-INDUCED ION ACCELERATION

In the year 1932, E. O. Lawrence (see Figure 3) and his group at University of California - Berkeley were able to accelerate protons to 1 MeV kinetic energy into their Cyclotron, based on a 11 inch magnet. Interestingly, his brother, Dr. John Lawrence, from University's Medical Physics Laboratory, already collaborated with him in studying medical and biological applications of the cyclotron, and himself became a consultant to the Institute of Cancer Research. The Cyclotron technology faced a decade of enthusiastic increase in proton energies with Nobel Prize assigned to E.O. Lawrence in 1939[33] till it was realized that energy was limited by the relativistic effect of the mass growth with velocity. The era started of synchro-cyclotrons and synchrotrons, basically the same big machines in operation today in the hadron therapy facilities.

Just after WWII, in his decisive paper[18], Robert Wilson from Harvard noticed that "The accelerators now being constructed or planned will yield protons of energies above 125 Mev (million electron volts) and perhaps as high as 400 Mev. The range of a 125 Mev proton in tissue is 12 cm., while that of a 200 Mev proton is 27 cm. It is clear that such protons can penetrate to any part of the body." and "the specific ionization or dose is many times less when the proton enter the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest." All the future of the Hadron Therapy was simply depicted in these two sentences. More than 10 years later, John Lawrence published his first clinical study (see Figure 4) on "Proton irradiation of the pituitary" which opened the gate to all the subsequent works slowly leading to the present therapeutic protocols.

While discussing the progress of Laser-induced Ion Acceleration (LIA) towards its application to cancer therapy and possibly complaining about its delays, Figure 5 should be carefully considered. The Radio-Frequency (RF) approach to ion acceleration asked some 25 years before getting kinetic energies suitable to deep tumor irradiation, almost 30 years to produce significant clinical tests. Since then, 30 years were spent to experiment on samples and treat a few thousands patients worldwide inside nuclear laboratories in order to setup suitable protocols and reliable statistics. More than 60 years after the first cyclotron a huge device was built for the first time in a Hospital and devoted to patient treatment.

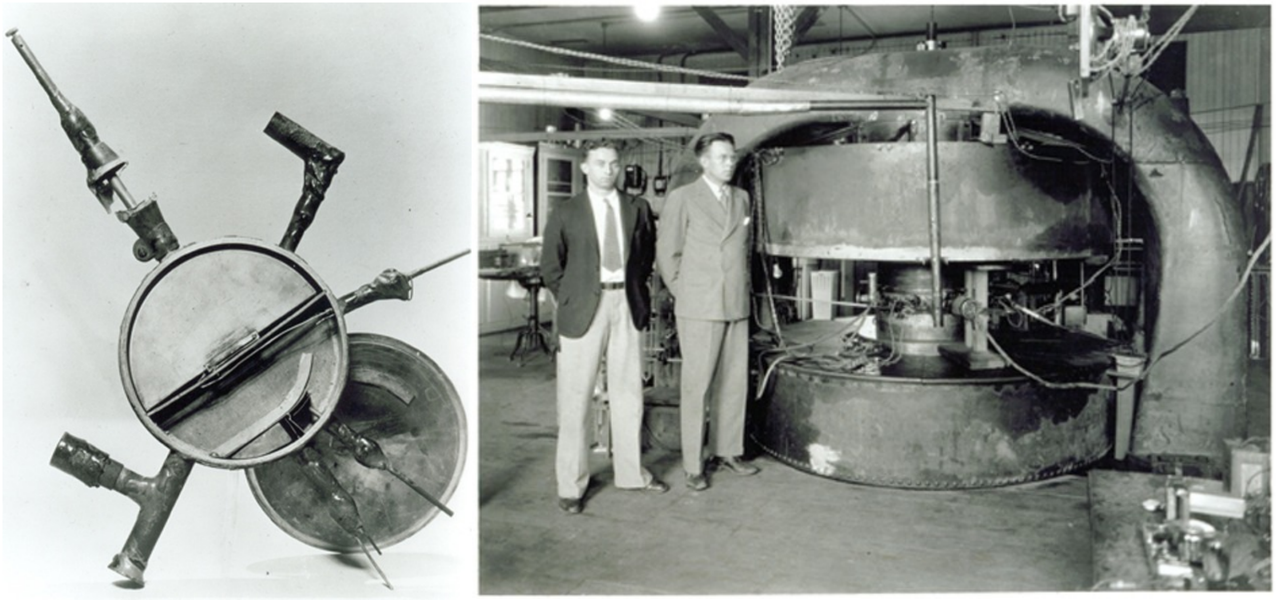

Figure 3. Left: the first 4” Lawrence cyclotron (1930). Right: Lawrence standing close to his 27” cyclotron (1933) at UC-Berkeley.

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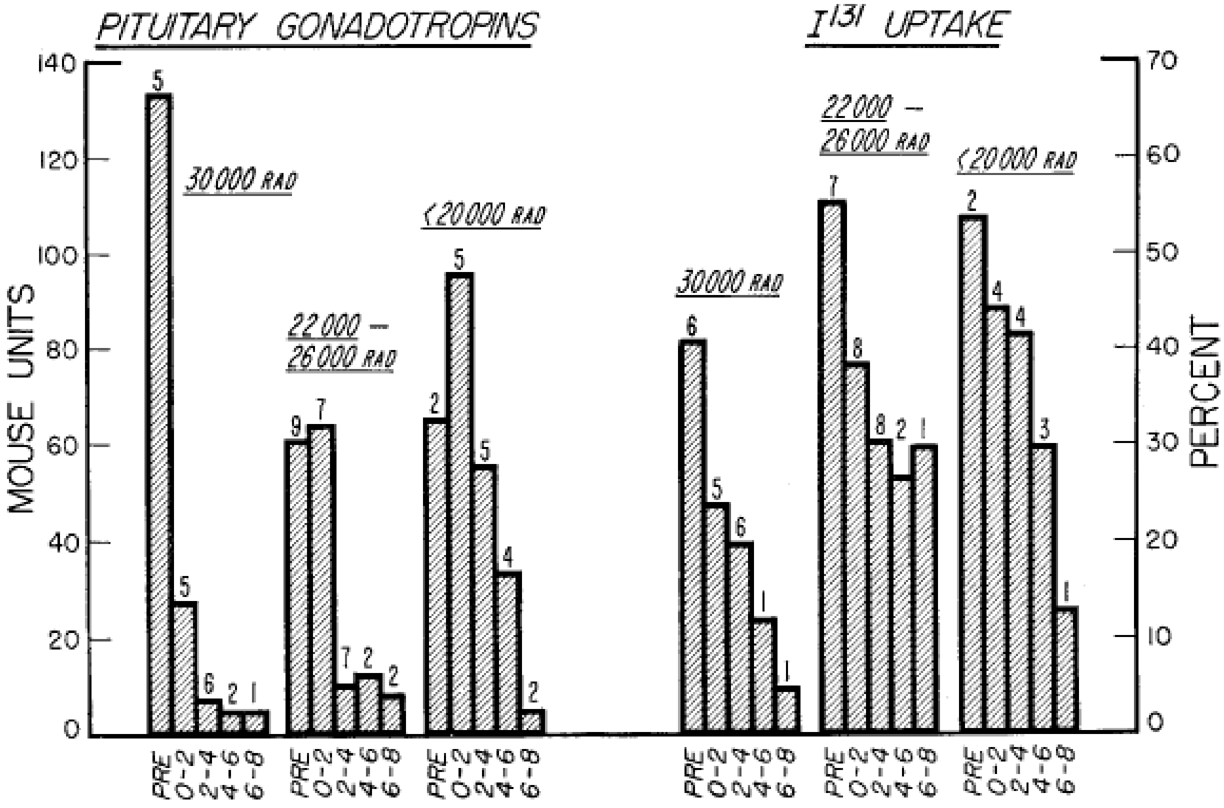


FIG. 4. Decrease in pituitary gonadotropins and I^{131} uptake for months after start of irradiation; grouping is according to three treatment levels—30,000 rads, 22,000 to 26,000 rads, and less than 20,000 rads.

Figure 4. Taken from the historic paper of Ref. 19.

Only 10 years later both the numbers of installed clinical facilities and treated patient showed a really fast growth rate with a weak but sensible decrease in the last few years, possibly due to the global economical crisis. Presently the number of treatments performed with ions are a few percent of the total radiation treatments, while the ordinary X-ray radiotherapy based on electron linacs covers more than 90% of the cases. The story of LIA and its steps towards medical application is obviously shifted forward of several decades and could conventionally start with the invention of lasers delivering short pulses and more exactly when those pulses reached a suitable power, namely early Nineties. Whether the progress towards the medical application is comparable to the one performed by RF accelerators in a comparable period of time is hard to say, also because physical processes to be studied and applied were well assessed in the RF case, while laser acceleration in plasmas created from a variety of targets involves a number of physical processes and regimes almost never explored so far, whose modeling requires sophysticated, not always fully reliable, numerical calculations. This complex matter has been reviewed recently by several authors[24,34,35] in the framework of the physics of laser-matter interaction at extreme intensities[36].

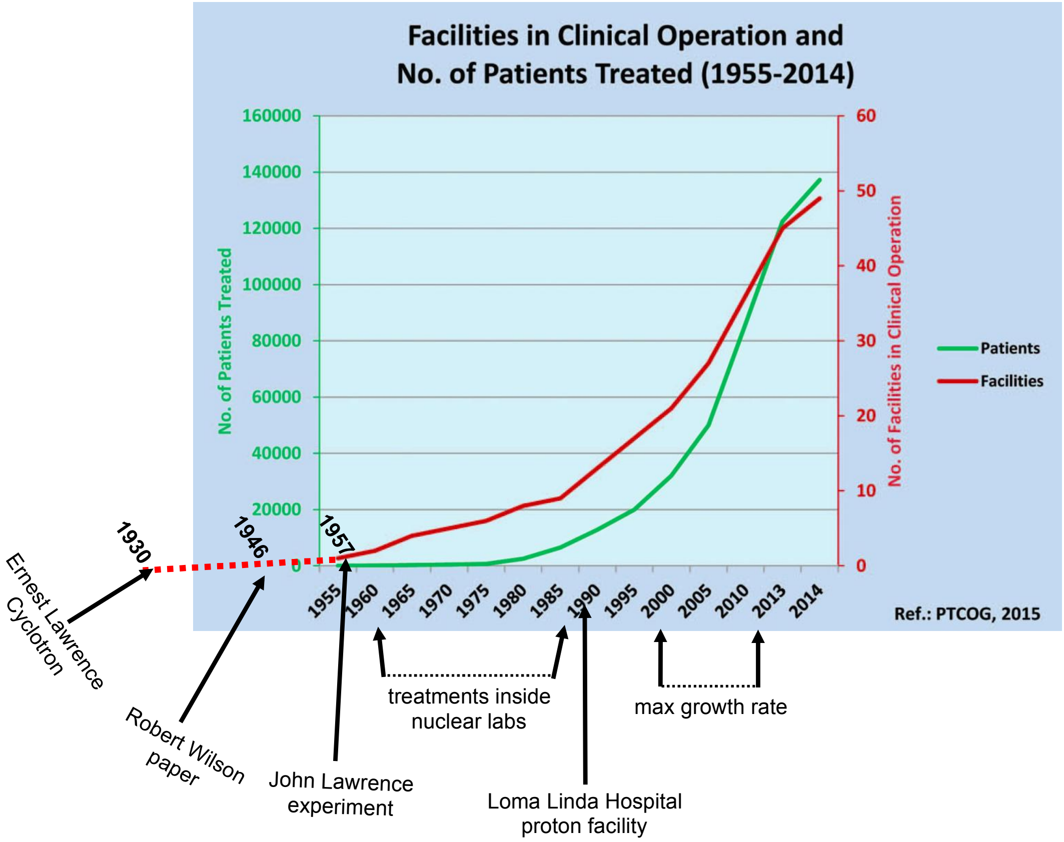


Figure 5. Milestones on the hadron therapy road.

Target Normal Sheath Acceleration (TNSA) is by far the most studied acceleration mechanism also in view of medical applications. Typical proton spectra produced via TNSA are exponential-like up to a cut-off energy which has been so far well below 100 MeV with the largest available lasers. 67 MeV protons were obtained at LANL using a) 80 J pulse energy and b) hollow-cone microtargets[37] a record result but both experimental features are not suitable for a Hospital device. The more suitable *table-top* lasers, typically having a few joule energy, presently allow to reach up to few tens of MeV. The use of targets with limited mass[38] or surface structuring[39] has recently moved the cut-off towards higher energies.

A few years ago the exploitation of radiation pressure in laser plasma interaction at ultra-high intensity emerged from simulations as a brilliant solution to get quasi-monochromatic bunches of energetic ions[40]. The regime of Radiation

Pressure Acceleration (RPA) is usually split in two, namely Hole Boring (HB) and Light Sail (LS), depending on the thickness of the foil used as interaction target. The HB regime applies to thicker targets where the radiation pressure pushes as a piston the interaction surface causing its recession and the steepening of the density profile. A first experiment used a CO_2 infrared laser (□□$\simeq$ 10 μm), for which $n_c \simeq 10^{19}$ cm^{-3}, at a density approaching n_c, using circularly polarized pulses at intensities up to 10^{16} W cm^{-2}. A high-charge proton bunch, whose spectrum peaked at 1 MeV was obtained[41], with a substantial agreement with theory. Production of ion energies useful for medical applications requires substantial advances in CO2 laser technology[42]. Optical lasers ($\lambda \simeq 1$ mm) require the development of targets with suitable density values and profiles, by engineering high density gas jets[43] or using low-density foams[44]. Differently from most of the acceleration regimes, the presence of a low-density plasma produced by the laser prepulse in front of solid targets may favor HB acceleration. The LS regime applies when very thin foil targets are used and the whole mass of the irradiated portion of the foil is pushed by radiation pressure. The LS's scaling with pulse energy for ultrashort pulses is quite promising[24], and quasi-monochromatic spectra are expected. However, first experimental investigations (see Ref. 45 and references therein) showed some promising results but also a number of optimization and stability issues. Recently, extremely intense and sharp rising fs pulses were focused on thin foils covered by a few-micron Carbon nanotube foam in order to induce self-focusing and self steepening of the pulse at a plasma density close to n_c. Enhanced acceleration of carbon ions (up to •20 MeV energy per nucleon) with RPA-LS features has been obtained[46].

Collisionless shock acceleration (CSA) has been invoked as the mechanism leading to the generation of highly monoenergetic proton spectra (up to • 20 MeV energy) in the interaction of CO_2 laser pulses with gaseous hydrogen jet targets[47]. The laser pulse was a sequence of 3 ps pulses with peak intensity $I \simeq 6\ 10^{16}$ Wcm^{-2}. The energy spread of less than 1% is the narrowest one observed in laser-plasma acceleration experiments. However, the number of accelerated protons is very low, apparently about three orders of magnitude lower than produced via HB acceleration in similar laser and target conditions[41]. Simulations[47] suggest that CSA could scale with laser intensity in order to produce > 100 MeV protons, although this will require at least substantial upgrades in the laser system to allow an increase by two orders of magnitude in intensity. Demonstrating CSA with optical lasers requires the development of target media with suitable density profiles. Although often confused in the literature, HB and CSA are different processes, the latter being effective in the presence of hot electrons. As stated above, a very relevant difference is the number of ions accelerated per shot. In CSA, such number must be low in order to preserve a monoenergetic spectrum.

A few experiments have investigated ion acceleration during the interaction with underdense gas jet targets, which would be suited to high repetition rate operation. In these experiments, ion acceleration typically occurs in the radial direction with respect to the laser propagation axis, as the result of the drilling of a low-density channel (see e.g. Ref. 48 and references therein); such uncollimated ion emission has low brilliance and is not ideal for applications. Collimated, longitudinal ion emission from a gas jet has been observed by focusing a 40-fs a laser pulse at 7 10^{17} W cm^{-2}, achieving a surprisingly high cut-off of 20 MeV[49]. The interpretation of these results is still not well assessed. It has to be mentioned that next generation lasers might allow a super-relativistic regime of efficient acceleration in underdense plasmas which has been foreseen theoretically almost two decades ago[50]. Once the quiver velocity reaches a given value, the electron mass equals the rest mass of proton, so that protons stick to electrons and are accelerated in a "snow-plow" mode with high efficiency. The simulations of Ref. 50 show that hundreds of MeV ions, collimated by self-generated magnetic fields, may be generated. Finally, for laser intensities above the relativistic transparency threshold for ultrathin targets, it is also possible to remove target electrons completely in a region with a size of the order of the focal radius. In such conditions, ions undergo a Coulomb explosion, i.e. they are accelerated by the electrostatic field generated by themselves which is the highest field attainable for a given target size. Differently from the same process undergoing in clusters[51], Coulomb explosion in thin foils accelerates ions in a preferential direction[52].

Excluding the case of HB acceleration, in all the ion acceleration schemes a crucial role is played by the *laser pulse contrast*[53], more exactly by the ratio between the main pulse peak *power* and the power associated with the light emitted by the laser chain *before* the main pulse itself. In Figure 5 the emitted power vs. time is sketched in a log-log diagram. Though all the early emission is often indicated as *prepulse*, the actual prepulse (left hand peak in Figure 5) is an ultrashort pulse, similar to the main pulse but much weaker, leaking from the electro-optical shutter out of the oscillator. This prepulse usually carries a negligible amount of energy (and power). More dangerous is the *amplified spontaneous emission* (ASE), also called *ASE pedestal*, which lasts typically a few nanosecond and then carries a considerable amount of energy, comparable with the main pulse energy if the contrast is worse than 10^6. In most of the previous experiments on laser-driven proton acceleration this *ns-contrast* had to be increased above 10^9, with several means, including the "plasma mirror" technique[54]. Early emission a few picosecond before the main pulse involves the *ps-contrast* which is

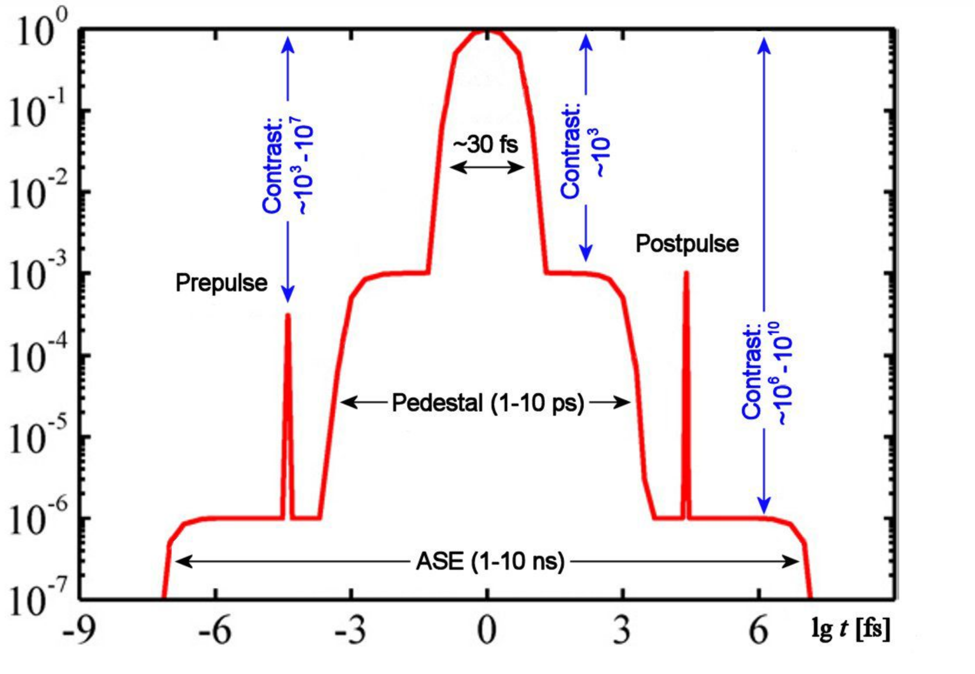


Figure 5. Time evolution of parasitic laser emission before and after the main pulse (image from Ref. 53).

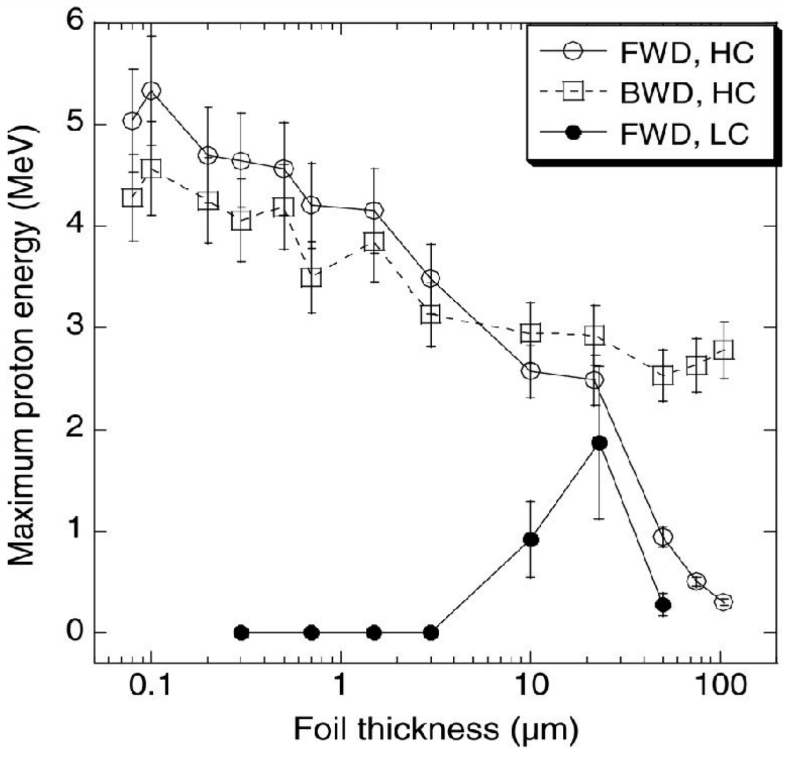


Figure 6. Proton energy vs. foil thickness for high-contrast (HC) and low-contrast (LC) laser pulses (image from Ref. 55).

usually 3-4 orders of magnitude worse than the ASE-contrast, but carries much less energy. It can be nevertheless dangerous as well. It can be reduced only assuring high quality and accuracy in the optical compression of the stretched amplified pulse at the end of the laser chain. A critical feature of the pre-pulse problem is that most of the undesired effects depend on the absolute value of the pre-pulse energy and power and not from the value of the contrast. In other words, increasing the laser power, as requested by most of the advanced schemes of acceleration, the contrast has to be increased correspondingly. This technical point deserves a special attention for the future of laser-driven ion accelerators. A clear example of the relevance of ultrashort laser pulse contrast was provided by the crucial experiment performed by Ceccotti et al. on thin targets[55], as shown in Figure 6.

Back to the ion accelerators presently operating in clinical background, their census at the end of the year 2015 was about 80 worldwide, possibly they raised close to one hundred today. Though the spectrum of these devices is quite rich and varied, most of them deliver only protons and are based on standard design of cyclotrons, still the true "workhorse" of the proton therapy of tumors. Nevertheless synchrotron, the first machine implemented in a hospital at Loma Linda, is gaining positions in the race, also for his capability of accelerating both protons and C ions, like in the case of CNAO machine shown in Figure 2. A number of alternative devices are under intensive study and test, including the fixed-field alternating-gradient accelerators, proton linacs and dielectric wall accelerators. In the meantime also cyclotrons and synchrotrons are facing a true revolution in their design, in some case already introduced in the market. Most of novelties are due or linked to the use of superconductive materials in the construction of magnets both for the circular machines and for dipoles and quadrupoles assembled in the gantries, with a significant reduction of their weight and footprint. As for the actual costs reduction, the scenario is still controversial. An excellent, concise review of the status of the art in this field has been published recently[56].

Try to compete *just now* with such a rich offer of clinical solutions would be frustrating for the Laser-induced Ion Acceleration (LIA) community. Nevertheless crude pessimism[23] has to be rejected. It is clear that the possible application of LIA to Ion Beam Therapy (IBT) is still far away and that a long term research and development effort is needed to evaluate its real potential. Several projects are currently active worldwide[57]. For sure a great deal of innovation is required at each stage of the design of a future LIA-IBT facility, once standard beam parameters and reliability will be reached. Strict monoenergeticity may not be required a priori for IBT since the energy spectrum must be modulated in order to obtain the optimal "spread-out Bragg peak" distribution for an optimal dose delivery over the tumor region. Methods to obtain directly such distribution from the native spectrum of laser-accelerated ions have been investigated[58]. The possible success of LIA as an option for IBT also relies on exploiting the peculiar properties of laser-driven ion beams. One of the main advantages would be the option of optical transport to the treatment rooms rather than transporting and steering high energy ion beams with large magnets, so that all costs related to ion beam transport and radiation shielding on the way to the treatment room are removed. Such scenario would benefit further from the development of a compact beam handling system in replacement of the massive and costly gantries used in existing hadrontherapy facilities. Optical control combined with the dose concentration in small-duration bunches may have potential for the irradiation of moving targets[59], which is a major challenge for the IBT of specific organs. Further progress in laser design, not necessarily towards higher pulse energies, together with ideation of new laser coupling and related processes could provide unexpected solutions. In particular production of few-cycle pulses of high energy seems to be a promising option. The recent proposal of a single-cycle high power fiber laser[60] has triggered a new acceleration scheme[26].

Laser-driven ion sources have progressively revealed to be a unique tool for radiobiological studies, for several good reasons. First there is now a variety of facilities, differing each other by relevant features, allowing a broad range of investigations on biological samples with a degree of availability and flexibility unthinkable with ordinary accelerators either operating in nuclear labs or hospitals. Second, the particle energy provided presently by most of the laser-plasma devices ranges between 1 MeV and a few tens of MeV. Though it is too low for therapy of deep tumors, this range of energy includes the energy of particles at Bragg peaks for any kind of tissues. By using thin layers of sensible tissue or cultures, including tumor cells and ill tissues, it is possible to investigate the radiological action straight in the condition occurring around the Bragg region, i.e. the region of therapeutical interest. Third, the particle bunches provided by laser techniques can deliver on sample an unprecedented dose-rate, several orders of magnitude higher than any other device, so allowing to study unexplored regimes of very high specific dose. In this condition each cell can be reached by a number >>1 of particles in a time period much shorter than any DNA repairing time. It is also possible investigate the occurrence of non-linear or collective effects induced by such “dense” ionizing radiation. The high dose rate is partly due to the high charge attainable with laser techniques but mostly to the ultra-short duration of the bunches. This latter feature actually is the fourth good reason for using laser acceleration, since it could allow for the first time to investigate very early processes in the complicate chain of physical, chemical and biological effects leading to either cure of tumors or damage of healthy tissues.

This unique opportunity has also triggered the advance of specific dosimetry[61,62]. In single shot irradiations, on-cell dose rates of the order of 10^9 Gy s^{-1} have been estimated[63] from measurements. Such values are some nine orders of magnitude higher than with conventional means. It is therefore important to assess the biological effect of laser-driven ions with respect to conventional ion beams used in IBT and to other sources of radiation. To this aim, the Relative Biological Effectiveness (RBE) has been measured in several experiments. Two fundamental experiments[64,65] by Yogo et al. at JAEA lab in Japan with • 2 MeV laser-accelerated protons found a RBE value of 1.2 ± 0.1, comparable to that of protons from conventional accelerators[66] having a similar value of Linear Energy Transfer (LET). Those experiments were also relevant for their sophisticated set-up of magnets allowing to separate the protons from electrons and photons, deflect the proton beam first towards an energy selecting pinhole, then towards the sample as shown in Figure 7.

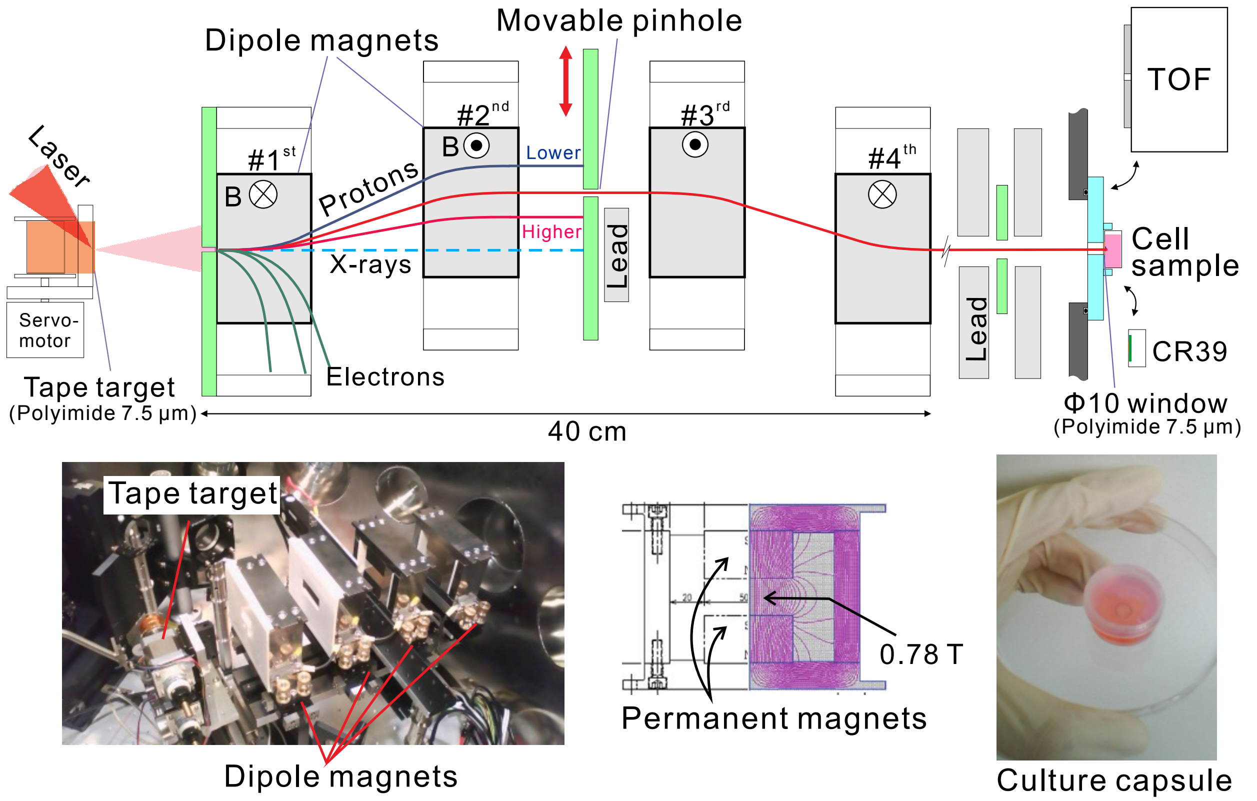


Figure 7. Layout and details describing the second Yogo’s experiment[64] equipped with Energy-Selection System (image from Ref. 25).

Another interesting biological application of energetic protons and ions produced with laser techniques is radiography[2]. In fact, the unique properties of protons, multicharged ions and electron beams generated by high-intensity laser-matter interactions, particularly in terms of spatial quality and temporal duration, have opened up a totally new area of high-resolution radiography. Laser-driven radiographic sources obtained by irradiation of clustered gases were proved to be particularly effective, leading to large-field high-contrast images with 1 μm spatial resolution. Faenov et al.[67] produced > 10^{18} multicharged carbon and oxygen ions per laser shot by irradiating CO_2 clusters from a gas-jet. The ion energy was measured to be ≥ 300 KeV. With such rather divergent but uniform ion beam, ionography of a spider net revealed submicron details, as shown in Fig. 7.

Finally, isotope production by proton-induced nuclear reactions has been achieved with Laser-induced Ion Acceleration and then proposed as a way to produce radionuclides and positron emitters for medical diagnostics[68]. Short-lived positron emitters are of great interest for medical imaging Positron Emission Tomography (PET) and are commonly produced using • 20 MeV protons or deuterons from cyclotrons, i.e. in an energy range currently well accessible with LIA. Reported values of the integrated activity produced using "table-top" femtosecond lasers typically operating at 10 Hz are some two orders of magnitude lower than required for use in PET[69]. Higher activities and a large number of emitters were produced with larger lasers, but their low repetition rate makes them unsuitable for application in PET. On the basis of the extrapolation of present results and additional theoretical and simulation work[70], the activity values required for PET may be reached with table-top lasers (typically delivering a few Joules, 20-30 fs pulses tightly focused to achieve intensities of • 10^{20} W cm^{-2}) working at kHz rate. A recent work reports on laser-driven deuteron beams optimized for isotope production[71]. Nuclear reactions driven by proton or deuteron beams are also of interest for production of neutrons, which has been observed either from direct laser interaction with deuterated targets[72] or by means of a secondary target, i.e. in a "pitcher-catcher" configuration[73].

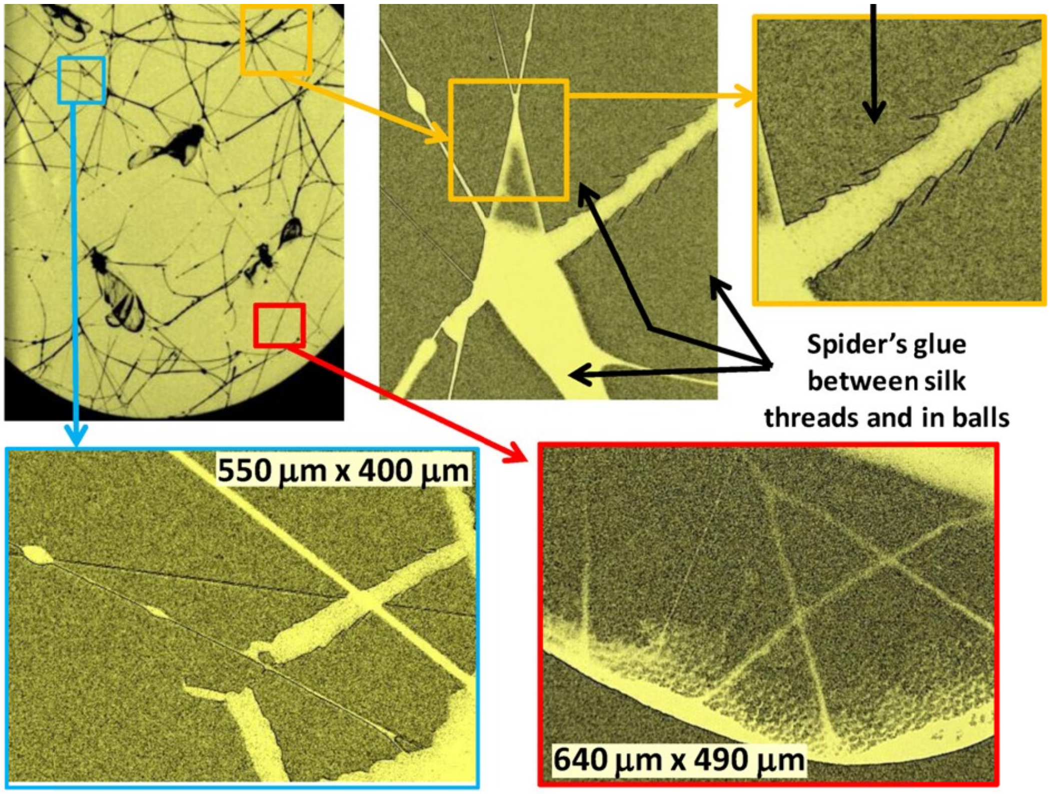


Figure 7. Ion Microscopy with Carbon and Oxygen ions produced by laser interaction with a CO2 clustered jet: contact image of a spider web and magnified details showing high resolution (image from Ref. 67).

3. CURRENT RADIATION THERAPY AND LASER-DRIVEN ELECTRON ACCELERATION

As already noticed in the Introduction, more than 90% of radiation treatments on tumors are presently based on the use of RF-driven linear accelerators of electrons, mostly after conversion of relativistic electrons into hard X-rays. Since the first trials at the end of the 19th Century, the progress of this medical technique was so vaste and deep that cannot be resumed here. There is now a variety of advanced devices and protocols for Hospital practice whose very sofisticated features allow high precision irradiation of the tumor with a minimized detrimental effects on heathy tissues and critical organs. Among them Stereotactic Radiotherapy (SRT)[12] offers a method for delivering high doses of radiation in a single or limited number of fractions to a small volume encompassing the tumor while minimizing the dose to adjacent normal structures due to a large dose gradient and therefore reducing the risk of sequelae. It uses a multitude of small beams requiring extremely precise control of position and movement of the linear accelerator. Moreover, SRT needs a real-time image-guided technique that tracks the target during treatment allowing an automatic reset based on the acquired image. SRT enables hypo-fractionated treatments, i.e strong doses delivered in a small number of fractions, due to its high level of accuracy.

If we limit our consideration to energy and dose, present table-top laser driven electron accelerators can be already considered as competitors of the RF-linac's. In fact, most of the performances usually asked to electron bunches, including energy range and delivered dose have been achieved. Collimation, monochromaticity, pointing stability, etc. are requested at a moderate levels already available with laser techniques, while the main effort has still to be addressed to efficiency, stability and reliability of the process in order to provide clinically acceptable devices. As far as the efficiency is concerned, in an experiment performed at CEA-Saclay (France) a regime of electron acceleration of high efficiency was found, using a 10 TW laser and a supersonic jet of Helium[13]. This *table-top* accelerator delivered high-charge (nC), reproducible, fairly collimated, and quasimonochromatic electron bunches, with peak energy in the range 10–45 MeV. In Figure 8 a typical cross section of the relativistic electron beam at 25 MeV is shown, after de-convolution of experimental data from the SHEEBA radiochromic film stack device[74].

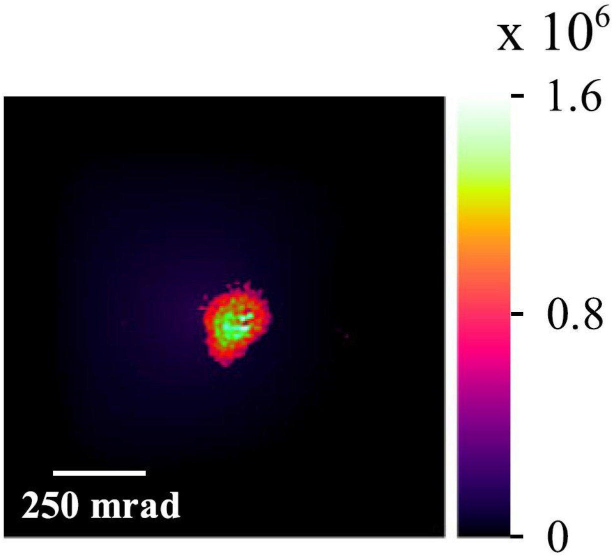


Figure 8 . 25-MeV electron beam cross section (image from Ref. 13).

3D particle-in-cell simulation performed with the numerical code CALDER[75] revealed that the unprecedented efficiency of this accelerator was due to the achievement of a physical regime in which multiple electron bunches are accelerated in the gas-jet plasma during the action of each laser shot. With this experiment, laser driven electron acceleration approached the threshold of suitability for medical uses, in particular for Intra-Operative Radiation Therapy (IORT) of tumors[8,9]. Comparison of the main parameters of electron bunches produced by a commercial RF Hospital accelerator for IORT treatment and those of the that laser driven accelerator is shown in the Table 1. Notice that, while main clinical parameters, including mean current and released energy (proportional to the dose) are comparable, bunch duration is 10^6 times shorter and consequently the peak current (proportional to max the dose-rate) 10^6 times higher. In the same experiment electron bunches of ≈ 40 MeV were converted, via bremsstrahlung in a tantalum foil, into gamma rays with a strong component in the range 10-20 Mev, which matches the Giant Dipole Resonance of nuclei. This gamma rays could in turn activate a foil of gold according to the nuclear reaction $^{197}\mathrm{Au}(\gamma,n)^{196}\mathrm{Au}$. The number of radioactive gold atoms produced in this way was measured[13]. This achievement opens the way to table-top laser-driven nuclear physics and production of radio-isotopes for medical uses.

Linac	**IORT-NOVAC7**	**LIAC**	**Laser-Linac (experimental)**
Company	*(SORDINA SpA)*	*(Info & Tech Srl)*	*(CEA-Saclay)*
Max Electron Energy	*10 MeV*	*12 MeV*	*45 MeV*
Available Energies	*(3, 5, 7, 9 MeV)*	*(4, 6, 9, 12 MeV)*	*(5 to 45 MeV)*
Peak current	*1.5 mA*	*1.5 mA*	***> 1.6 KA***
Bunch duration	*4 µs*	*1.2µs*	***< 1 ps***
Bunch charge	*6 nC*	*1.8 nC*	*1.6 nC*
Repetition rate	*5 Hz*	*5-20 Hz*	***10 Hz***
Mean current	*30 nA @5Hz*	*18 nA @10Hz*	***16 nA*** *@10Hz*
Released en. in 1 min.	*18 J @ 9 MeV*	*14 J @12 MeV*	***21 J*** *@20 MeV*

Table 1. Comparison between commercial RF-linac's and the experimental Laser-linac (table from Ref. 53).

As already said in the Introduction, in most cases electrons delivered by a RF-linac currently used in Hospitals, are not sent directly on the tumor but previously converted into photons (hard X-rays) by bremsstrahlung through a suitable target. Of course this is possible also for electrons of comparable energy currently produced in high-power laser labs. Laser-driven electron accelerators would be then ready and produce X-rays for clinical uses provided a suitable stability, uniformity and reproducibility of the electron bunches will be reached. The Laser-driven Electron Accelerator for Radiotherapy of Cancer (LEARC) project[76] aims at speeding up the transfer of a novel laser-based technology to radiotherapy of cancer. The first point to be addressed is to make the driving laser, suitable for efficient acceleration, as reliable and easy to use as possible, with a duty cycle allowing an effective medical use. Second, the laser beam transport to the mini-linac located close to the patient has to be optimized. Third, the most important point, provide the mini-linac with an acceleration process stable and reproducible at each laser shot, also at high repetition rates. This task needs the detailed investigation of both known and novel acceleration schemes and then the optimization of both laser and target parameters. Gas jets are the most investigated targets so far and a special effort will be devoted in making them fully operative at high repetition rate. But other targets can be considered and studied to produce the palsma acceleration path, including gas cells and thin foil stripes. A crucial and difficult task is to deliver electrons of the requested energy and change their energy on demand. Several experiments proved this possibility at some extent but the methods used are hardly transferable in a clinical device which exclude continuous tuning or frequent re-tuning of its components. It has to be recognized that ultrashort laser systems and laser-plasma interactions are not easy to handle and put under complete control.

It is also interesting to consider electrons of energies outside the energy range between 1 and 25 MeV currently provided by commercial accelerators for radiation therapy. Both extremes of sub-relativistic and very high energy electrons (VHEE) are presently studied in view of specific applications. Recently, outstanding performances were obtained with sub-MeV electron bunches produced by the LESM laser-plasma device[77]. This source delivers ultrashort bunches of electrons with kinetic energy around 300 keV, uniformly over a large solid angle. The device is presently setup for radiobiological tests covering a previously untested energy range. Each bunch combines high charge with short duration and sub-millimeter range into a record instantaneous dose rate, as high as 10^9 Gy/s. Both such a high dose rate and high level of Relative Biological Effectiveness, attached to sub-MeV electrons, make this source very attractive for radiobiological tests on thin samples of living cells in similar way as discussed in the previous section for sub-relativistic protons. On the opposite side, very high energy electrons (VHEEs) with energies in the range 150-250 MeV, which penetrate deeply into tissue where the dose can be absorbed within the tumor volume with a relatively small penumbra have been proposed for radiation therapy of tumors a few years ago[78]. Electrons in this range of energy can be produced with plasma acceleration driven by laser of hundreds of TW. Parameters of bunches of such an energy and their dosimetry is under active investigation[79,80].

Electron average energy	260 keV
Spectral shape	exponential
Bunch divergence	20° FWHM
Bunch charge	> 100 pC
Repetition rate	up to 10 Hz
Bunch duration on the sample	3.5 ps
Peak current	> 100A
Non-uniformity on sample	< 10% (over 25 shots)
Stopping power in water	2.49 MeV cm^2/g
Range in water	0.68 mm
Dose per pulse	3.5 ± 0.3 mGy
Peak dose rate	10^9 Gy/s
Average dose rate	35 mGy/s

Table 2 Main features of the laser-driven sub-relativistic electron sources LESM (table from Ref. 77).

Secondary sources of high-energy photons are another exciting by-product of laser-driven electron acceleration. They include the above mentioned bremsstrahlung sources and betatron sources originated during the laser wakefield process itself by the strong restoring forces acting on the electron bunches. Further, the electron beam produced by laser-driven acceleration can be sent to collide with another powerful laser pulse and produce energetic photons by Compton scattering[32,81]. Generation of radiation via Thomson scattering of a laser pulse by energetic counter-propagating electrons was initially proposed in 1963[82,83] as a quasi monochromatic and polarized photons source. With the development of ultra intense lasers the interest on this process has grown and the process is now being exploited as a bright source of energetic photons from UV to gamma-rays and atto-second sources in the full nonlinear regime. In view of medical application, tuneability of the X-ray photon energy may be an important option of an *all-optical* laser-based Thomson source. Recent experiments performed by Sarri et al.[84] and Liu et al.[85] obtained photons of several tens of MeV and opened a new phase of these studies.

We mentioned in the previous Section radiography performed with protons and ions. A similar technique has been used also with electron beams produced by laser-driven accelerators[86]. The laser-driven electron sources included interaction with both ordinary and clustered gas jets[87]. Figure 9 shows an example of test samples and their electron radiography obtained from a laser-produced electron beam. Resolution in this case was better than 60 µm, but 10 µm can be achieved.

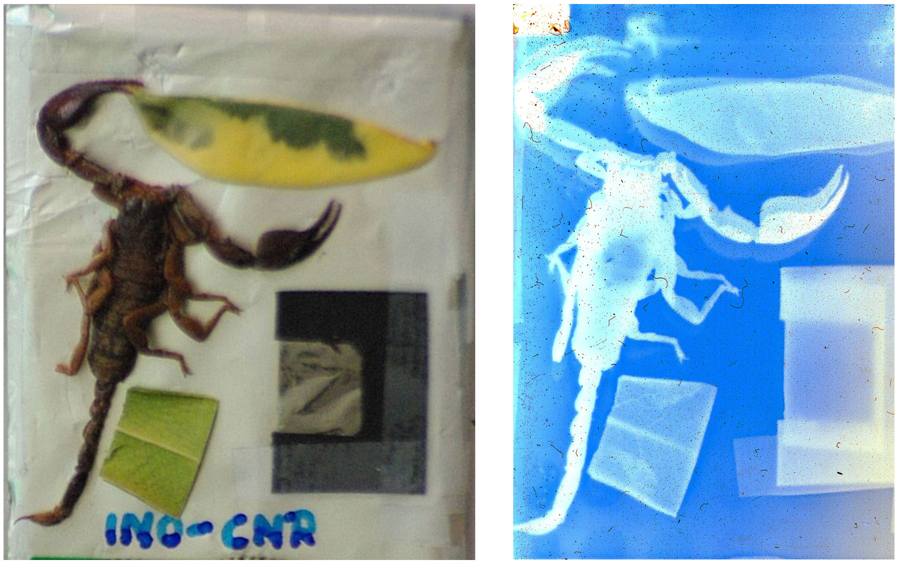


Figure 9. The sample (left) and its own electron radiograph. Overall size: 35 mm x 48 mm (image from Ref. 83).

Radiobiological studies with relativistic electrons generated by laser-plasma interactions, including evaluation of their RBE, have been performed in the last decade. Results have been also compared with RBE of electrons produced with conventional RF-linac's[88,89]. Very recently, a multidisciplinary team of scientists performed an RBE evaluation of electrons from a laser-driven accelerator impinging on several cell lines (including tumor tissues). The experiment included measurements of Micronucleus Frequency, Telomere Shortening and Cell Viability (see Figure 10). The same cell lines were also irradiated with standard reference X-rays and electrons from a RF-linac for IORT. The three series of results were compared, giving comparable values within the error bars, except for a single cell line for which the laser-produced electron bunches resulted slightly more effective[90].

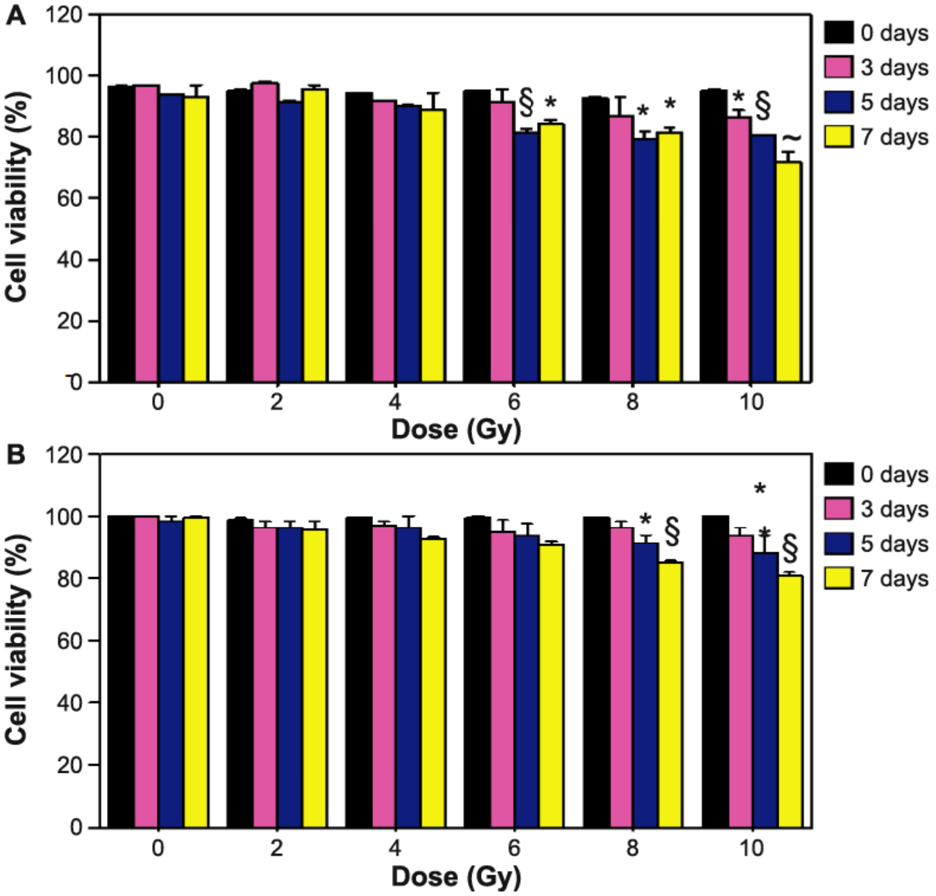


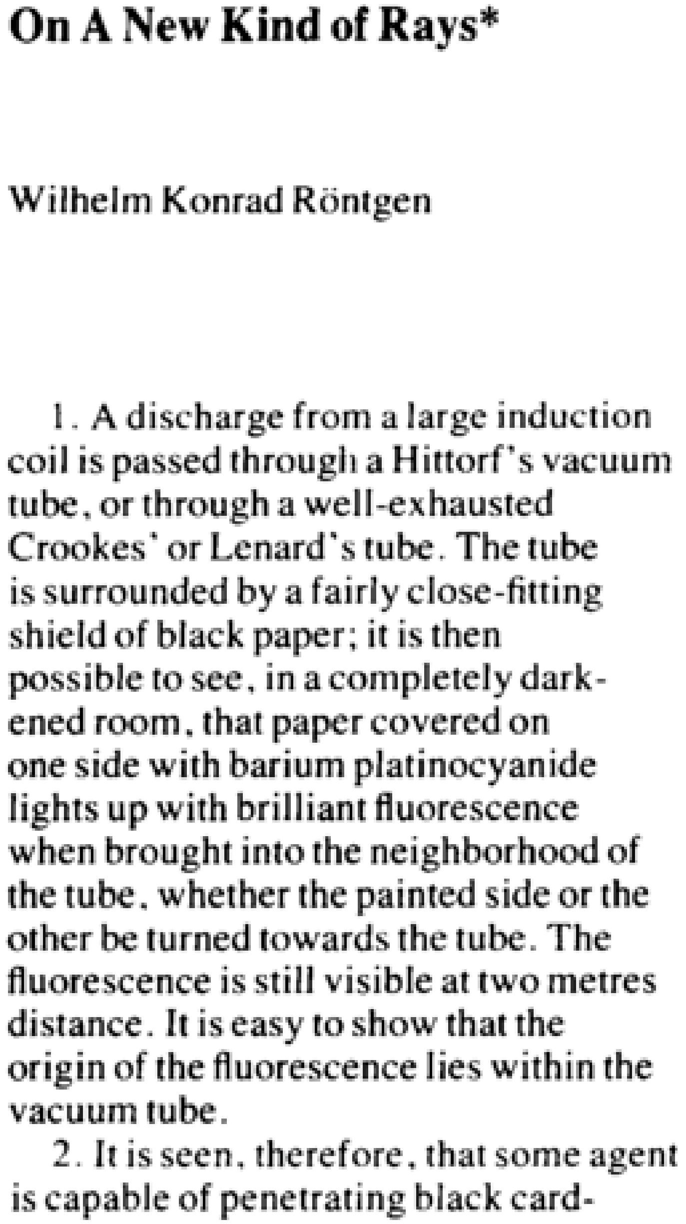
Figure 10. Cell Viability assay in a human cancer cell line after A: exposure to laser-generated electrons and B: conventional accelerated particle beams. All values are expressed as mean ± SD of three independent experiments. Statistical differences SD were assessed for each dose compared to negative control (* $P \leq 0.05$; § $P \leq 0.01$; ~ $P \leq 0.001$) (image from Ref. 90).

Current studies on biological effects of laser-produced electron bunches need a strong support of a) dosimetry, suitably revised in order to take into account the unprecedented features of these bunches, mainly in terms of duration and instantaneous dose rate[3]; b) simulation, mostly with a correct application of the Monte Carlo code based on GEANT4 toolkit[91].

Great deal of research has being devoted to the comprehension of biophysical events triggered by an initial energy deposition inside the first ionization tracks. Ultrashort electron bunches delivered by laser-driven plasma accelerators and secondary femtosecond photon sources are suitable for the development of high energy radiation femtochemistry (HERF)[30] in the prethermal regime of secondary low energy electrons and for a real-time imaging of radiation-induced biomolecular alterations at the nanoscopic scale. It would be possible then to correlate early radiation events triggered by ultrashort radiation sources with the molecular approach of Relative Biological Effectiveness (RBE)[92].

4. A PERSPECTIVE VIEW

The story began more than 120 years ago (see Figure 11). Since then, a continuous progress was made in understanding several kinds of ionizing radiation, produce that radiation in form of photons, electrons and ions, use it for many purposes, first of all for medical applications. More than 50 years ago powerful lasers proved to be another source of ionizing radiation and laser-produced dense plasmas opened a vaste field of novel physics to be investigated. Some 38 years ago[14] a brilliant theory suggested how to use ultrashort laser pulses to accelerate particles in plasmas, whenever they could get enough power and 32 years ago[15] the way was opened to reach that power. Since then, and mostly in the last 25 years, the community of scientists working on laser-driven particle acceleration grew up and many great, somehow unexpected results were obtained.



On A New Kind of Rays*

Wilhelm Konrad Röntgen

1. A discharge from a large induction coil is passed through a Hittorf's vacuum tube, or through a well-exhausted Crookes' or Lenard's tube. The tube is surrounded by a fairly close-fitting shield of black paper; it is then possible to see, in a completely darkened room, that paper covered on one side with barium platinocyanide lights up with brilliant fluorescence when brought into the neighborhood of the tube, whether the painted side or the other be turned towards the tube. The fluorescence is still visible at two metres distance. It is easy to show that the origin of the fluorescence lies within the vacuum tube.

2. It is seen, therefore, that some agent is capable of penetrating black card-

Figure 11. The *incipit* of the 1895 Roentgen paper

This is “from where” we come. This short-review paper try to provide the community with some elements to understand “where we are” and maybe a few indication on “where to go”. For sure the scientific crop of these enthusiastic years was considerable, in laser and plasma physics, radiation physics, radiation biology. How far we are from setting up a prototype device for clinical use is hard to say. Maybe a little closer for electrons (and then photons), a little farer for proton/ions. For sure there is no reason for giving this exciting navigation up, since we have progress of knowledge as our lighthouse: successful landing may be not so far.

ACKNOWLEDGEMENT

Author is deeply grateful to Toshi Tajima for his magistral teaching and friendly support. Author also acknowledges financial support by the ELI-Italy project funded by the Italian Ministry of Research and University. The author also thanks the whole team at the Intense Laser Irradiation Laboratory of INO-CNR in Pisa for reference information and for the continuing enlightening discussions on the subject.

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