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High power laser production of short-lived isotopes for positron emission tomography

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Abstract

Positron emission tomography (PET) is a powerful diagnostic/imaging technique requiring the production of the short-lived positron emitting isotopes ^{11}C, ^{13}N, ^{15}O and ^{18}F by proton irradiation of natural/enriched targets using cyclotrons. The development of PET has been hampered due to the size and shielding requirements of nuclear installations. Recent results show that when an intense laser beam interacts with solid targets, megaelectronvolt (MeV) protons capable of producing PET isotopes are generated. This report describes how to generate intense PET sources of ^{11}C and ^{18}F using a petawatt laser beam. The work describing the laser production of ^{18}F through a (p,n) ^{18}O reaction, and the subsequent synthesis of 2-[^{18}F] is reported for the first time. The potential for developing compact laser technology for this purpose is discussed.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

The history of positron emission tomography (PET) [1] is linked with technological advances in nuclear physics, accelerators, detectors and chemistry since the beginning of modern PET in 1973. PET is a powerful diagnostic/imaging technique requiring the production of short-lived positron emitting isotopes, principally ^{11}C, ^{13}N, ^{15}O and ^{18}F, by proton irradiation of natural/enriched targets using cyclotrons. The technique requires these isotopes to be administered to the patient in the form of a radiopharmaceutical. Many chemical compounds can be labelled with positron emitting isotopes, and their bio-distribution can be determined through PET imaging as a function of time. However, the most commonly used radiopharmaceutical is 2-fluoro-2-deoxyglucose

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(2-[^{18}F]FDG). Various biochemical events including glucose metabolism can be directly assessed in patients to reveal changes in the metabolic activity resulting from disease progression and therapeutic intervention. Over the last few years the value of PET FDG in the management of cancer patients has been widely demonstrated.

One of the main factors limiting the wider use of FDG PET imaging is the requirement for expensive infrastructure, at the heart of which is the cyclotron and the associated extensive radiation shielding. A more simplified approach to isotope production would be to develop a miniaturized, on-site resource with an eventual capability similar to that of a cyclotron. Potentially satisfying this demand, recent results show that when an intense laser beam interacts with solid targets [2–5], beams of megaelectronvolt (MeV) protons capable of producing PET isotopes are generated. In a recent article in Science, Ledingham *et al* [6] have described some preliminary work carried out in order to produce PET isotopes using a high power laser. After an extended programme of research, we report here how to generate the intense, short-lived PET sources, ^{11}C and ^{18}F, using the VULCAN petawatt laser beam and also for the first time, the synthesis of 2-[^{18}F]-fluorodeoxy glucose, the 'workhorse' of PET technology from laser-driven ^{18}F using an enriched water target. In the conclusion to this report the potential for developing this for on-site, easy to shield, compact laser technology for this purpose will also be discussed.

Recent advances in laser technology with the introduction of 'chirped pulse amplification' (CPA) [7] have led to the development of multi-terawatt pulsed laser systems in many laboratories worldwide. In CPA, a laser pulse of the order of femtoseconds or picoseconds is temporally stretched by three to four orders of magnitude using dispersive gratings, thus preventing damage to the laser amplifying medium from non-linear processes at high intensities. After amplification, these laser pulses are recompressed to deliver 10^{18} to 10^{20} W cm^{-2} on target. Proposed techniques, including optical parametric chirped pulse amplification (OPCPA) [8, 9] promise to extend the boundaries of laser science into the future and also reduce large lasers used at present to compact table-top varieties.

High intensity laser radiation may now be applied in many traditional areas of nuclear science. As the laser intensity and associated electric field are increased, the electron quiver energy, the energy that a free electron has in the laser field, increases dramatically. When laser radiation is focused on to solid and gaseous targets at intensities $>10^{18}$ W cm^{-2}, electrons quiver with energies greater than their rest mass (0.511 MeV), creating relativistic plasmas [10].

In the 1970s, it was proposed [11] that laser-driven electron acceleration was possible using intense laser light to produce a wake of oscillations in a plasma. Recently, 200 MeV electrons have been measured using a compact, high repetition rate laser [12]. Laser plasma–based accelerators have the potential to deliver accelerating gradients more than 1000 times higher than that available in conventional accelerator technology, and on a compact scale! This increase in the accelerating gradient is the key to reducing the scale, and, therefore, the associated cost over current conventional accelerators.

Multi-MeV proton beams are also produced when an intense $>10^{19}$ W cm^{-2} laser pulse interacts with the surface of a solid target [2]. Proton energies with an exponential distribution of up to 58 MeV have been observed [13] for a laser pulse intensity of 3×10^{20} W cm^{-2}, and production of greater than 10^{13} protons per pulse has been reported [14]. With the VULCAN laser at the Rutherford Appleton Laboratory (RAL) delivering close to petawatt powers, it is now possible to demonstrate the potential for high power lasers to produce intense radioactive sources.

2. Experimental

The new petawatt arm of the VULCAN Nd : Glass laser at RAL was used in this experimental study. The 60 cm beam was focused on to a 5.5 μm diameter spot using a 1.8 m focal length off-axis parabolic mirror in a vacuum chamber evacuated to $\sim 10^{-4}$ mbar. The average pulse duration was 750 fs and the energy on target was between 220 and 300 J. The peak intensity was of the order of 2×10^{20} W cm^{-2}. Aluminium, gold and mylar foil targets of various thicknesses have been irradiated by the p-polarised laser beam incident at an angle of 45°. The protons emanated from water and hydrocarbon contamination layers on the target surfaces.

Nuclear activation techniques to measure the proton energy spectra, namely copper stacks (5 cm × 5 cm), were positioned along the target normal direction and exposed to the protons accelerated from both the front and back surfaces of the target foil. The activity in the foils from the ^{63}Cu(p,n)^{63}Zn with a half-life of 38 min [4] was measured in a 3″ × 3″ NaI coincidence system.

The copper stacks were replaced by boron samples (5 cm diameter and 3 mm thick) to produce ^{11}C. After irradiation, the boron targets were removed from the vacuum chamber and the ^{11}C activity produced by the (p,n) reaction on ^{11}B was measured in the coincidence system up to 2 h after the laser shot, a safety precaution because of the high activity. The counting rate was determined at time zero and converted to becquerels using a calibrated ^{22}Na source.

3. Results and discussion

The measured activity in the foils from the ^{63}Cu(p,n)^{63}Zn, convoluted with the reaction cross-section and proton stopping powers was used to produce the energy distributions shown in figure 1. The ^{11}C activity generated in the secondary ^{11}B targets at the front and back of the primary target was measured in becquerels as a function of the target thickness and material. The ratio of the back to front activities is shown in figure 2. A number of points must be made in connection with figures 1 and 2. First, figure 1 indicates that the end point of the proton spectrum has increased from about 30 MeV for a 100 TW [4] laser to about 50 MeV for the close to petawatt laser. It also shows that contrary to the mono-energetic spectrum from a cyclotron, the laser proton spectrum is quasi-exponential. However, high quality proton beams are not required for isotope production. The importance of figure 2 is that it is needed in order to determine the thickness of the target that generated the highest activity sources. This was carried out using the production of the PET isotope ^{11}C rather than the more novel ^{18}F because the cost of doing systematic work using the very

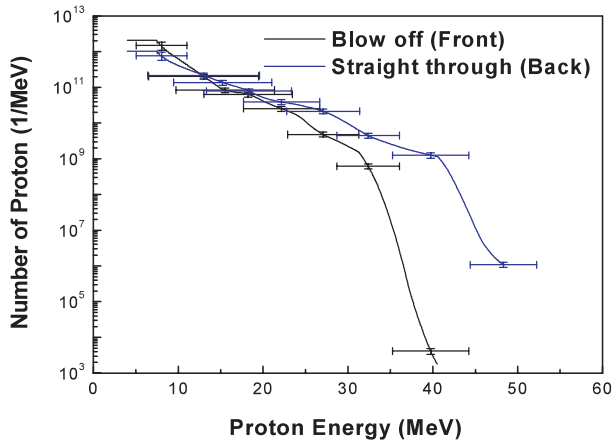

Figure 1. Typical proton spectra in front of and back a 10 μm Al target. The spectra are quasi-exponential, with the highest energy protons measured behind the target. The number of protons generated per laser shot at about 300 J and 2×10^{20} W cm^{-2} was typically 10^{12}.

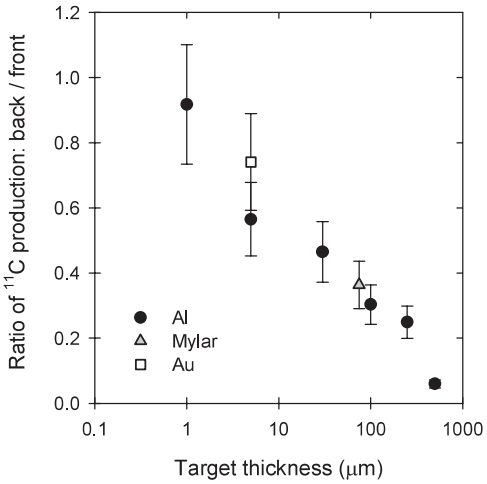

Figure 2. The Back/front ratio of ^{11}C from the (p,n) reactions on ^{11}B as a function of target thickness. It was found that at the highest pulse energy on target ~300 J, the ^{11}C activity maximally was about 6×10^6 Bq per shot on each side. This is greater than 10^7 Bq in total. Behind the target the ^{11}C activity decreased with increasing thickness, while for similar energy values on target the activity in front of the target was largely independent of the target thickness or, indeed, of the material.

expensive separated ^{18}O isotope as target is prohibitive. It is clear from figure 2 that very thin targets provide the highest activity sources when the total activity produced per laser shot is the sum of the back and front activities.

It was reported earlier that ^{18}F is the most widely used tracer in clinical PET today due to its longer half-life allowing the synthesis of a number of samples within a half-life decay of the isotope and because fluorine chemistry is readily introduced in many organic and bioinorganic compounds. It was necessary to determine how much ^{18}F could be produced per laser shot. The isotope is generated from a (p,n) reaction on an ^{18}O enriched (96.5%) target. The enriched ^{18}O targets were irradiated in the form of 1.5 ml of [^{18}O]H_2O placed in a 20 mm diameter stainless steel target holder. The holder was assembled with a 100 μm aluminium window and secured

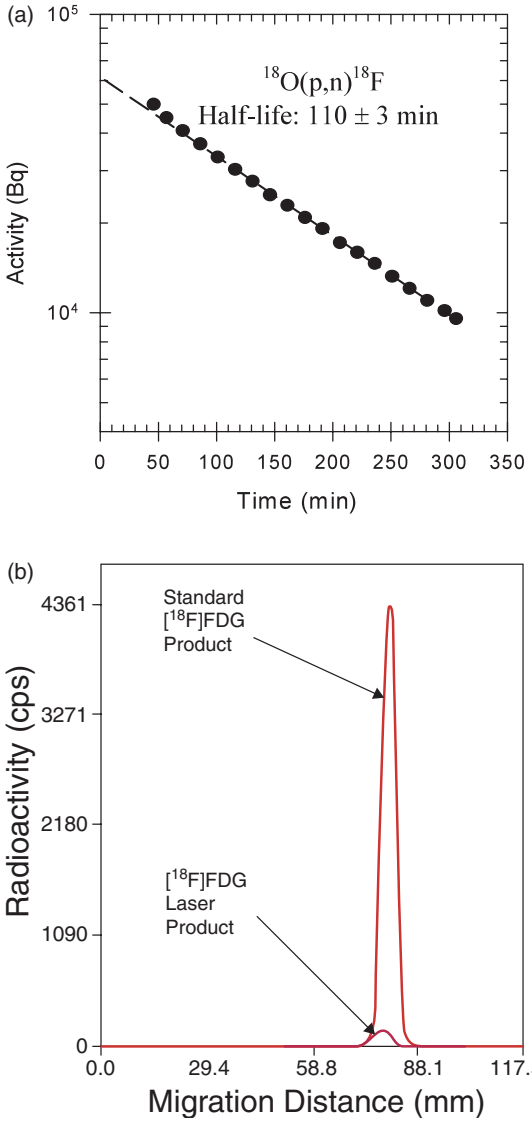

Figure 3. (*a*) The measured half-life for ^{18}F is shown here. The value is close to the accepted one, indicating the purity of the sources produced. The half-life for ^{11}C (20 min) is not shown here but has been discussed in a previous publication [4]. The counting was initiated up to 2 h after the laser shot for ^{11}C due to the radiation hazard from the high activities, although in the ^{18}F case it is normally about 40 min. (*b*) Laser- and cyclotron-induced 2-[^{18}F]FDG showing radiochemical purity. The Radio thin layer chromatogram of 2-[^{18}F]FDG synthesized from either the laser-induced F-18 activity or the cyclotron-induced F-18 activity. The radio TLC was performed on a silica gel 60 (F_{254})-coated aluminium sheet (Merck, UK) using a 90 : 10 acetonitrile, water-mobile phase. The analysis was carried out using an Instant Imager electronic autoradiography system (Packard, USA). Both products show the same migration distance of 75 mm with an R_f value of 0.63. This indicates similar purity.

with a stainless steel clamping plate. At the highest laser pulse energies (300 J), a total activity of ^{18}F of 10^5 Bq was produced. The half-life for the ^{18}F source is shown in figure 3(*a*). The measured half-life of 110 ± 3 min was determined over more than three half-lifes and has been included here to demonstrate the purity of the ^{18}F source and agrees closely with the generally accepted value.

We have demonstrated for the first time the synthesis of 2-[^{18}F]FDG using laser-induced ^{18}F activity. FDG synthesis was initiated 4 h after the irradiation. The synthesis is based on the method developed by Hamacher *et al* [15], adapted for the production of ^{18}F from a remote cyclotron source and the FDG Coincidence-Kit Based Synthesizer (GE Medical Systems). Briefly, a mannose triflate precursor was fluorinated following the recovery of $H_2{}^{18}O$. Subsequent hydrolysis and column purifications yield 2-[^{18}F]FDG. The radiochemical purity and yield were determined by quantitative radio thin layer chromatography (TLC) (figure 3(*b*)).

The laser- and cyclotron-induced peaks on the TLC trace represents a 1 μl sample of 2-[^{18}F]FDG taken from each product for both the laser- and cyclotron-induced activity. The two TLC peaks represent samples taken from vastly different radioactive concentration solutions, and hence the laser peak appears significantly smaller than the cyclotron-induced ^{18}F activity peak. The TLC analysis shows the two peaks' resolving sources are radiochemically pure and identical to each other. Although the laser-induced activity is lower than the cyclotron peak, this activity is only from one laser pulse and it would be possible to achieve integrated nuclear yields over many laser pulses, which would then be comparable with cyclotron technology.

Figure 4 summarizes our measurements to date in this programme of research into laser-driven ^{11}C and ^{18}F PET isotope production on VULCAN. The circular points [^{11}C] correspond to a number of different laser irradiances and pulse energies up to 300 J with a pulse duration of about 750 fs. The single triangular point is the activity from the ^{18}F measurements at the highest laser pulse energy. This graph shows that if the curve is extrapolated linearly on this logarithmic graph, then at 10^{21} W cm^{-2} μm^2 (equivalent to a total pulse energy of 1 kJ), sufficient activity of ^{11}C in one laser shot might be generated equivalent to the required patient dose for PET sources. This statement of extrapolation is made with a great deal of caution because experiments have yet to be conducted at these higher laser irradiances and only refers to the pulse and focal conditions of the VULCAN laser. Other lasers with different pulse and contrast ratio parameters may behave differently.

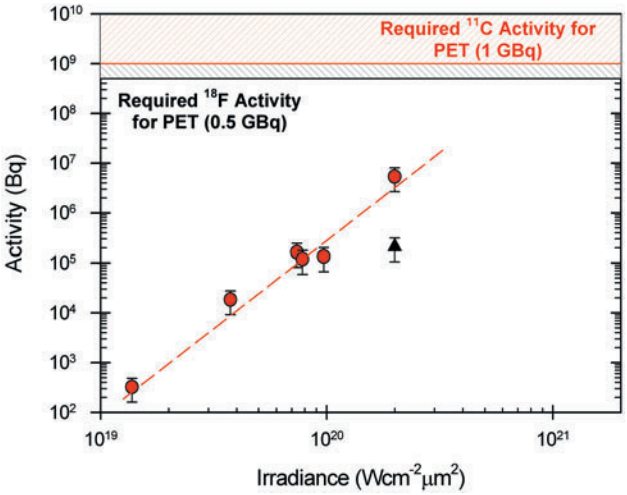

Figure 4. This graph shows the total activity (front + back) generated by a single laser shot for both ^{11}C and ^{18}F as a function of laser irradiance with pulse energies from 15 to 300 J. The circles refer to ^{11}C production, and the single triangular point for ^{18}F was measured at the highest energies. The hatched areas at the top of the graph provide an indication for the level of required ^{18}F activity from which an ^{18}F-FDG patient dose would be generated, the required ^{11}C activity, e.g. in the form of [^{11}C]CO. The activity measured for ^{18}F is lower than that of ^{11}C due to the fact that extra thick protective windows [50 μCu] were placed over the water targets to prevent any possible rupture under vacuum, which reduced the proton energy and hence any (p,n) activity.

These results were obtained from a large single shot laser. Finally, we wish to highlight the progress made using compact high repetition rate lasers. Fritzler *et al* [16] have calculated that 13 MBq of ^{11}C can be generated using the LOA table-top laser (1 J, 40 fs, 6×10^{19} W cm^{-2}) after 30 min at 10 Hz and that this can be extended to gigabecquerels using similar lasers with kilohertz repetition rates. Alternatively, at JanUSP (Livermore), using a single pulse (8.5 J, 100 fs, 800 nm) at 2×10^{20} W cm^{-2}, 4.4 kBq of ^{11}C was generated from a single laser shot [17]. Using a compact laser with similar specifications at 100 Hz after 30 min, this would amount close to 1 GBq. A compact table-top laser system has recently been designed by Collier and Ross [18]. This OPCPA system is envisaged as being capable of delivering 6 J in 50 fs at 100 Hz at optical intensities between 10^{20} and 10^{21} W cm^{-2} μm^2. OPCPA technology is at an early stage of development, but sufficient progress has been made to make one reasonably optimistic that the above specification is attainable. Such a laser would be capable of producing gigabecquerel activities of PET isotopes in 30 min.

4. Conclusions

In conclusion, we have shown that very intense PET sources of ^{11}C and ^{18}F can be produced using a large petawatt laser and also for the first time, the synthesis of 2-[^{18}F]FDG, the workhorse of PET technology. We have also discussed the potential for developing this for on-site, easy to shield compact laser technology. In the very recent conference FIHFP 2004 in Kyoto, April 2004 Nakamura *et al* [19], reported that when a polymer-coated metal target was irradiated with laser pulses of 10^{17} W cm^{-2}, a significant enhancement ($\times$80) of fast protons was produced over the uncoated target and hence there is every likelihood that a significant increase in proton production and hence PET isotope activity will be produced when the layers of contaminants are replaced by controlled surfaces of hydrogen atoms. Recently Esirkepov *et al* [20] have discussed the production of mono-energetic protons using layered targets. Some recent calculations at Strathclyde conclude that if quasi-monoenergetic protons replace the present quasi-exponential distribution, then a further significant increase in PET isotope production may be expected.

Acknowledgments

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