

Nuclear fusion

Fast heating scalable to laser fusion ignition

Rapid heating of a compressed fusion fuel by a short-duration laser pulse is a promising route to generating energy by nuclear fusion¹, and has been demonstrated on an experimental scale using a novel fast-ignitor geometry². Here we describe a refinement of this system in which a much more powerful, pulsed petawatt (10^{15} watts) laser creates a fast-heated core plasma that is scalable to full-scale ignition, significantly increasing the number of fusion events while still maintaining high heating efficiency at these substantially higher laser energies. Our findings bring us a step closer to realizing the production of relatively inexpensive, full-scale fast-ignition laser facilities.

In advanced laser ignition of fusion^{3,4}, high-density energetic electrons generated by petawatt lasers instantaneously heat a compressed fusion fuel to its ignition temperature with high coupling efficiency⁵. We tested fast heating by a petawatt laser and the GEKKO XII laser systems on targets in which a hollow gold cone (30° or 60° angle) was inserted into a deuterated polystyrene ('CD') shell (500 μm diameter, 7 μm thick)².

The shell was imploded using nine beams of the laser system operated at a wavelength of 0.53 μm and with an energy of 2.5 kJ for 1.2-ns flat-top pulses. The fast-heating laser was injected into the cone's interior and generated energetic electrons at the end of the cone, at the stagnation of the shell compression with a power of 0.5 petawatts (PW). The imploded core plasma was created near to the centre of the shell, close to the tip of the cone; the compressed density was estimated by using an X-ray backlight method² as 50–100 g ml^{-1} for cores of diameter 30–50 μm . A single laser oscillator⁷ was used for both laser systems to provide perfect synchronization between shell compression and fast electron heating.

To quantify the heating of these highly compressed plasmas, we measured the increase in thermonuclear neutron production as a function of the injection timing of the heating pulse, with respect to the time of peak compression. Neutrons are generated by fusion of two deuterium nuclei to form a helium nucleus (atomic configuration, $d(d,n)^3\text{He}$) in the compressed CD plasma.

Neutron energy spectra were obtained using time-of-flight scintillator/photomultiplier detectors. The coincidence of signals from detectors at different distances and angles confirmed that the neutrons were thermonuclear in origin. Neutron enhancement was about three orders of magnitude

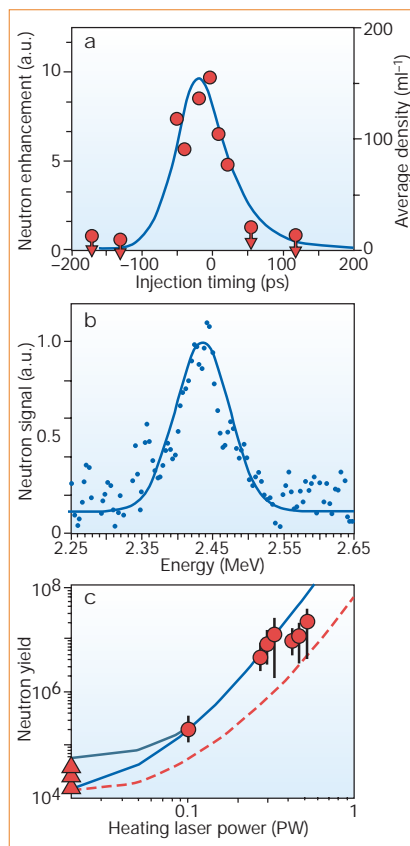


Figure 1 Fast heating of highly compressed plasmas with a petawatt (PW)-class laser pulse. **a**, Neutron enhancement (a.u., arbitrary units) as a function of injection timing (in picoseconds) of the heating pulse. Line represents the temporal profile of the average density of the compressed plasma from a hydrodynamic simulation. Arrows denote data points that fall below the background noise level ($S/N < 1$) or that correspond to the noise level. **b**, Neutron spectrum observed from an angle of 42° for a 0.5-PW laser heating at maximum compression. Line is a Gaussian fit to the data points, indicating an ion temperature of 0.8 keV. **c**, Yield of thermonuclear neutrons from the compressed plasma as a function of heating laser power for the pulse duration of 0.6 ps. Solid and dashed lines, neutron yields for an energy coupling from laser to core of 30% and 15%, respectively; neutron yields obtained without a heating pulse are shown in the 0.02-PW position.

at 0.5 PW, compared with neutrons obtained with no heating pulse ($2\text{--}5 \times 10^4$ for a 1.2 flat-pulse implosion).

Figure 1a shows this enhancement as a function of injection timing of the heating pulse. The timing of heating was checked with X-ray streak images, as well as the injection timing of the pulse to maximum compression, from hydrodynamic simulations of the shell implosion. Enhancement was evident during ± 40 ps, which corresponds to the stagnation time of the imploded plasma; the heating pulse is 0.6 ps, which is two orders of magnitude shorter than the stagnation time. These results indicate that heating for ignition might be achieved by using pulses that are close to the duration of stagnation.

If a gaussian profile is fitted to the neutron

spectrum (Fig. 1b), the spectral width of the 0.5-PW heating shot is 90 ± 5 keV, which is greater than that (60 keV) for 0.1-PW heating. The width of the 0.1-PW-heating spectrum was similar to that for no heating pulse, which was less than, or close to, the spectral resolution corresponding to the ion temperature of 0.4 keV. Taking into account the spectral resolution, the width ($90 \pm \text{keV}$) for 0.5-PW heating corresponds to an ion temperature of 0.8 ± 0.1 keV, indicating that the temperature of core plasmas could be doubled by this heating.

This finding is consistent with the enhancement, by three orders of magnitude, of neutron yield through heating; this indicates that the temperature increases from 0.3–0.4 to 0.8 keV. Our results are also consistent with the change in intensity and spectra of X-rays from heated core plasmas. The intensity increases by a factor of 1.5–2.0 compared with the absence of a heating pulse, and a continuum slope of the X-ray spectra (3–4 keV), temporally resolved with an X-ray streak camera, shows that the increase in temperature (1 ± 0.1 keV compared with 0.4 keV) is more than doubled.

Neutron yields are summarized in Fig. 1c for 0.6-ps laser pulses. Simple predictions of the neutron yield normalized to the yield without heating from energy conservation are also shown as a function of the heated laser energy, for the coupling from laser to the core plasma of 15% and 30%. The yield increases with the energy of the heating laser, implying almost constant coupling from the laser to the core plasma. However, there may be a small decrease in the coupling, from about 30% to 20%, as the laser power is increased from 0.1 PW to 0.5 PW. This could be due to an increase in the energetic electron temperature, resulting in a reduction in the stopping power of electrons for a fixed spot diameter.

Efficient fast heating of imploded plasmas has been accomplished with a petawatt laser at powers that are almost equivalent to those required in fast-ignition conditions. The period for sufficient heating is similar to the stagnation time (± 40 ps), suggesting that the heating laser's energy could be increased to ignite the fuel with a heating pulse of up to 10–20 ps or more at similar irradiance. It may eventually be possible to ignite a compressed deuterium–tritium fusion plasma with a relatively inexpensive fast-ignition facility comprising a petawatt-class laser.

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1. Tabak, M. *et al. Phys. Plasmas* **1**, 1626–1634 (1994).
2. Kodama, R. *et al. Nature* **412**, 798–802 (2001).
3. Norreys, P. *et al. Phys. Plasmas* **7**, 3721–3726 (2000).
4. Kodama, R. *et al. Phys. Plasmas* **8**, 2268–2274 (2001).
5. Key, M. H. *Nature* **412**, 775–776 (2001).
6. Kitagawa, Y. *et al. Phys. Plasmas* **9**, 2202–2207 (2002).
7. Yoshida, H. *et al. Conf. Laser Elec. Opt.* **2002**, 402–403 (2002).

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Tumorigenesis

RAF/RAS oncogenes and mismatch-repair status

Genes of the *RAF* family encode kinases that are regulated by Ras and mediate cellular responses to growth signals. Activating mutations in one *RAF* gene, *BRAF*, have been found in a high proportion of melanomas and in a small fraction of other cancers¹. Here we show that *BRAF* mutations in colorectal cancers occur only in tumours that do not carry mutations in a *RAS* gene known as *KRAS*, and that *BRAF* mutation is linked to the proficiency of these tumours in repairing mismatched bases in DNA. Our results not only provide genetic support for the idea that mutations in *BRAF* and *KRAS* exert equivalent effects in tumorigenesis², but also emphasize the role of repair processes in establishing the mutation spectra that underpin human cancer.

To determine how alterations in *BRAF* and *KRAS* might affect one another, we systematically evaluated mutations in these genes in 330 colorectal tumours (Table 1).

We identified 32 mutations in *BRAF*: 28 cases with thymine-to-adenine (T–A) transversions at nucleotide position 1,796 (corresponding to an amino-acid swap of glutamate for valine at residue 599; V599E), and one case each of a guanine-to-thymine (G–T) transversion at nucleotide 1,382 (R461I), a T–G transversion at nucleotide 1,385 (I462S), a G–A transition at nucleotide 1,388 (G463E), and an A–G transition at nucleotide 1,798 (K600E). All but two of these mutations seemed to be heterozygous, and in all 20 cases for which normal tissue was available, the mutations were shown to be somatic. In the same set of tumours, there were 169 mutations in *KRAS*, including alterations to codons 12, 13, 59 and 61. No tumour exhibited mutations in both *BRAF* and *KRAS*.

Mutations in either *BRAF* or *KRAS* occurred in all Duke's stages of cancer (results not shown) and also in premalignant lesions. Mutations in both genes seemed to be more common in adenomas larger than 1 cm across than they were in smaller adenomas.

There was also a striking difference in the frequency of *BRAF* mutations between cancers with and without mismatch-repair (MMR) deficiency ($P < 10^{-6}$, χ^2 test; Table 1). All but one of the 15 *BRAF* mutations identified in MMR-deficient cases resulted in a V599E substitution.

These results provide strong support for the hypothesis that *BRAF* and *KRAS* mutations are equivalent in their tumorigenic effects². Both genes seem to be mutated at a similar phase of tumorigenesis, after initiation but before malignant conversion. Moreover, we found no tumour that concurrently contained both *BRAF* and *KRAS* mutations. In view of the large number of mutations of both genes found in colorectal cancers, this observation is highly statistically significant ($P < 10^{-6}$, χ^2 -test) and cannot be easily explained in other ways. This conclusion

could not have been reached through the study of melanomas or of most other tumour types in which only one of the two genes is commonly mutated. It is consistent with biochemical observations³ and was suggested by Davies *et al.*¹.

Our results also show that MMR-deficient tumours have a very high incidence of *BRAF* mutations and a lower incidence of *KRAS* mutations compared with MMR-proficient colorectal cancers. This is consistent with the idea that both tumour types progress through the same biochemical pathways, but that the mutation spectrum depends on the nature of the underlying genetic instability⁴. The V599E mutation is the most frequent nucleotide substitution ever identified in a repair-deficient tumour.

The only other tumour type with a *BRAF*-mutation frequency as high as that seen in MMR-deficient colorectal cancers is melanoma¹. Melanomas and MMR-deficient colorectal cancers also share a high incidence of mutations in the oncogene that encodes β -catenin^{5,6}. It will be interesting to see whether melanomas have a repair defect that makes them susceptible to the types of mutation found in MMR-deficient colorectal cancers, and to determine what structural or sequence elements surrounding *BRAF* codon 599 make it prone to mutagenesis in a repair-deficient background.

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Table 1 *BRAF* and *KRAS* mutations in colorectal tumours

Tumours	No. of cases	<i>BRAF</i> mutation	<i>KRAS</i> mutation
All types	330	32 (10%)	169 (51%)
<i>BRAF</i> mutants	1	R461I	WT
	1	I462S	WT
	1	G463E	WT
	28	V599E	WT
	1	K600E	WT
<i>KRAS</i> mutants	169	WT	MUT
Other	129	WT	WT
Clinical cancers	276	30 (11%)	154 (56%)
Adenomas > 1 cm	20	2 (10%)	12 (60%)
Adenomas ≤ 1 cm	34	0 (0%)	3 (9%)
MMR-deficient cancers	49	15 (31%)	21 (43%)
MMR-proficient cancers	227	15 (7%)	133 (59%)

DNA was purified from microdissected primary tumours ($n=54$), first-passage xenografts ($n=189$) or cell lines ($n=87$) as described⁷. The complete coding sequences of exons 11 and 15 of *BRAF* and exons 2 and 3 of *KRAS* were amplified by polymerase chain reaction using intronic primers and the products were sequenced as described⁸. Mutations were identified using the Mutation Explorer package (SoftGenetics). This strategy allowed us to identify all mutations previously known to occur in these two genes. Mismatch-repair (MMR) deficiency was assessed by analysis of microsatellite instability, using the BAT26 marker and at least 12 microsatellite repeat markers⁹. WT, wild-type sequence; MUT, mutations in codons 12, 13, 59 or 61 in *KRAS*.

1. Davies, H. *et al. Nature* **417**, 949–954 (2002).
2. Storm, S. M. & Rapp, U. R. *Toxicol. Lett.* **67**, 201–210 (1993).
3. Marais, R., Light, Y., Paterson, H. F., Mason, C. S. & Marshall, C. J. *J. Biol. Chem.* **272**, 4378–4383 (1997).
4. Kinzler, K. W. & Vogelstein, B. *Cell* **87**, 159–170 (1996).
5. Sparks, A. B., Morin, P. J., Vogelstein, B. & Kinzler, K. W. *Cancer Res.* **58**, 1130–1134 (1998).
6. Rubinfeld, B. *et al. Science* **275**, 1790–1792 (1997).
7. Thiagalingam, S. *et al. Proc. Natl Acad. Sci. USA* **98**, 2698–2702 (2001).
8. Wang, T. L. *et al. Proc. Natl Acad. Sci. USA* **99**, 3076–3080 (2002).
9. Markowitz, S. J. *Clin. Oncol.* **18** (suppl.), 75–80 (2000).

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