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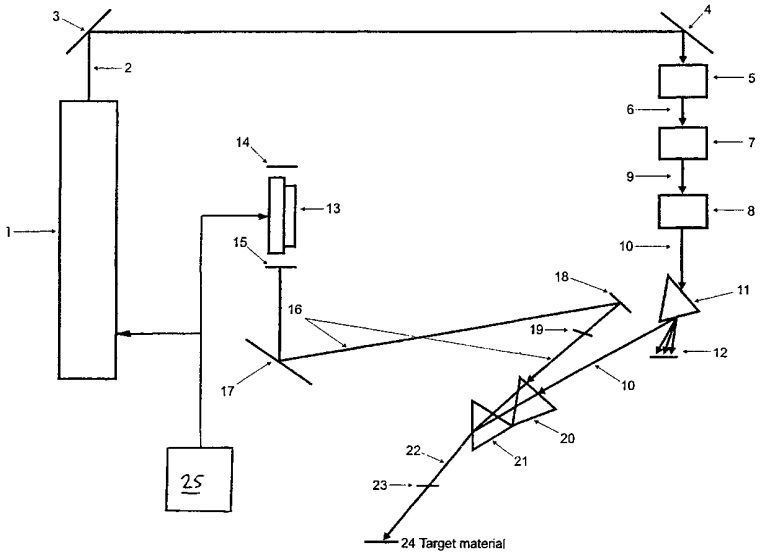
(54) Title: METHOD OF ENHANCED BIOLOGICAL MATERIAL REMOVAL USING SHORT PULSE LASERS



(57) Abstract: Apparatus for ablation of biological tissue includes first laser means (13) for generating a relatively longer pulse infrared laser beam (16), and second laser means (1, 5, 7, 8) for generating a relatively shorter pulse far ultraviolet or infrared laser beam (10). Further included are an optical configuration for directing the beams onto a region of biological tissue, and means (25) to control the respective laser beams to direct the shorter pulse beam (10) onto the biological tissue while the longer pulse beam (16) is incident on the tissue, whereby to ablate the tissue with the shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam. Also disclosed are related methods.

WO 01/26572 A1

METHOD OF ENHANCED BIOLOGICAL MATERIAL REMOVAL USING SHORT PULSE LASERS

Field of the Invention

The present invention concerns a method and apparatus for enhancing the laser ablation of biological tissue. The invention is of particular though not exclusive utility in the ablation of hard tissue such as bone or dental tissue, including carious and healthy dentine, enamel, cementum and bone.

Background Art

The oral cavity contains both soft tissue and hard tissue. The soft tissue component comprises the gingival (gum) tissue, which is firmly anchored to the mandibular & maxillary bones, while the hard tissue consists of the teeth. Teeth are a highly innervated and vascularised tissue, the interior pulpal cavity containing the nerve and blood supply. Dentinal tubules insert from the pulpal cavity to the dentine, a hard, calcified tissue made up of hydroxyapatite. The nerve fibres in the pulpal cavity may shed their myelin sheaths and extend into these dentinal tubules, resulting in sensitivity to pain and temperature. An extremely hard material called enamel, composed mostly of calcium salts, covers the dentine and the tooth surface. Tooth enamel may be damaged due to use or decay processes, such as the development of dental caries, which trigger the need for dental filings. (Junqueira, Carneiro & Kelley (1989) *Basic Histology,* Chapter 15, Digestive Tract. , Appleton & Lange, Connecticut.)

Teeth are usually prepared for fillings, crown work and root canal therapy through the application of a mechanical handpiece or drill. The dental drill brings with its use a fear of pain, unpleasant noise and vibration that can make a visit to the dentist a distasteful experience. There is a perception among dental patients that lasers will be able to replace the drill handpiece with a painless, quick & efficient procedure, without the characteristic noise and vibration associated with the traditional dental visit. 69% of patients surveyed believed a laser would make

a trip to the dentist less traumatic (Wigdor, *Lasers in Surgery and Medicine* (1997) 20: 47-50). Much research has gone into producing a dental laser capable of ablating hard tissue such as dentine and enamel and providing a bloodless cutting implement for periodontal applications. Promising results have come from ultraviolet and short pulse lasers and from lasers operating near 3 microns.

Excimer lasers have been used extensively in ophthalmic applications and studies have shown the 193-nm wavelength to be non-mutagenic and non-carcinogenic when applied to biological tissue. This laser ablates tissue through a photochemical reaction, in which thermal heating of adjacent tissue is kept to a minimum. Studies of hard tissue UV interactions have shown that far UV radiation can ablate tooth material without thermal damage to the pulp cavity. A wavelength of around 200-nm could therefore potentially be used for both soft and hard tissue dental operations. However, despite the good ablation characteristics of UV radiation, 193-nm excimer lasers have not been implemented in dental clinics for a number of reasons, including: low ablation rates (not being able to remove dental hard tissue at a rate comparable to the dental drill), large size, and difficulty in providing optic fibre delivery into the oral cavity. In addition, excimer lasers are costly to buy and maintain, are operated through the use of toxic gases and are impractical for dental clinics.

Nd:YAG lasers produce radiation with a wavelength in the 1-micron range. These lasers are used routinely for soft tissue applications including gum resections and other oral soft tissue operations. Harmonic generation can be used to produce the fifth harmonic at 213nm of the Nd:YAG laser. Previous research on the quintupled Nd:YAG reported very good characteristics of ablation (minimal thermal damage) with low ablation rates (H. Sciberras, G. Dair, P. van Saarloos & N. Boyd, "Characteristics of hard dental tissues ablation by a quintupled Nd:YAG", *Biomedical Optics: New concepts in Therapeutic Laser Applications, Novel Biomedical Optical Spectroscopy, Imaging and Diagnostics, Advances in Optical Imaging, Photon Migration, and Tissue Optics, OSA Technical Digest* (Optical Society of America, Washington DC) 1999: 51-53). A quintupled Nd:YAG UV source has the potential to be a practical alternative for the

excimer laser in a dental clinic, as it is smaller, less costly and gas-free, with the added advantage that the fundamental wavelength could be used for soft tissue. Other short pulse Nd:YAG based lasers (eg. optical parametric oscillators) may also be suitable for use in dental ablation processes.

Free-running lasers that have their wavelength situated close to 3-microns are thought to be especially useful in tissue ablation as this wavelength coincides with the water absorption peak of tissue. It is widely believed that the laser wavelength of 2.94μm removes dentine through an explosive mechanism. At high enough fluences the strong absorption in the water within the sub-surface of dentine causes an explosive expansion leading to ablation. The Er:YAG laser, operating at 2.94μm, is the only laser in practical use for the removal of hard tissue due to the high ablation rates it can achieve. However, the disadvantage of the near 3-micron laser is the excessive thermal damage that occurs to the surrounding tissue causing damage to the pulp cavity and cracking in the mineral structure of the tooth. Expensive air and/or water cooling systems are therefore required to prevent collateral damage to adjacent tissues. Also, the need for water cooling can limit access to gingival pockets.

Optical parametric oscillators (OPO) may be another potential source of a practical 3-micron laser. OPO's are tuneable to produce a range of wavelengths suitable for dental ablation. International patent publication WO/98 41177 discloses the use of a KTP generated optical parametric oscillator near 3-microns for use in medical and surgical applications. US patents 5,144,630 and 5,742,626, assigned to LaserSight Technologies Inc and Aculight Corporation respectively, describe lasers in which a Nd:YAG fundamental is used to produce a wavelength around 200 nm. They also have provision for producing longer wavelengths through an OPO arrangement.

The concept of a dual beam laser has been put forward in UK patent number 2313551. This invention, specifically for use on corneal tissue, proposes that two beams, one in the UV and the other in the infrared, be used to simultaneously or separately ablate corneal tissue. Other investigators have used

two beams as a method of increasing the ablation rate of UV lasers. It has also been reported that an increase in the rate of laser ablation can be achieved by a two laser system with one laser running below the threshold for ablation (See for example J. Neev & J.P. Lee, 1996, "Two-lasers assisted ablation: A method for enhancing convention laser ablation of materials", *Lasers in Surgery and Medicine*, 19:130-134).

US patent 5,312,396 to Feld *et al* also describes a process whereby biological material is prepared for removal by the application of a below threshold short wavelength pulse beam (eg 300–400-nm). A second, longer wavelength beam (eg 400-3000-nm) is applied, to effect tissue removal, within a period following the first pulse. Hard body tissue such as bone and teeth enamel is mentioned as a possible application of the concept, and the mechanism proposed is that the initial beam vaporises the soft tissue component inside the hard tissue which entrains and removes the hard component particles that are not vaporised.

A further disclosure of dual laser ablation is to be found at Pratisto et al, 1996, "*Tissue treatment underwater with simultaneously fiber guided Erbium and Holmium laser radiation*" SPIE 2624, 10-14.

Summary of the Invention

It is an object of the present invention to provide an improved method and apparatus for enhanced biological material removal using short pulse lasers, while minimising collateral damage to surrounding tissue structures.

It is a further object of the present invention to provide a method and apparatus that maintain the damage-inhibiting characteristics of short pulse laser ablation while increasing the ablation rate of the biological material.

In a first broad aspect, the invention provides apparatus for ablation of biological tissue, that includes first laser means for generating a relatively longer pulse infrared laser beam, and second laser means for generating a relatively

shorter pulse far ultraviolet or infrared laser beam. Further included are an optical configuration for directing the beams onto a region of biological tissue, and means to control the respective laser beams to direct the shorter pulse beam onto the biological tissue while the longer pulse beam is incident on the tissue, whereby to ablate the tissue with the shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam.

The invention further provides, in a second aspect, a method of providing a dual laser beam suitable for ablating biological tissue, including: directing a relatively longer pulse infrared laser beam along a guided light path, and, while the longer pulse beam is traversing said path, directing a relatively shorter pulse far ultraviolet or infrared laser beam along the path, whereby to form a dual laser beam that, if incident on biological tissue, ablates the tissue with the shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam.

Preferably, the method further includes directing the dual laser beam onto biological tissue, whereby to ablate the tissue with the shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam.

Preferably the tissue is hard tissue such as bone or dental tissue, including carious or non-carious dentine, enamel or cementum.

Preferably, the longer pulse beam is at a wavelength in the region of 3-microns, most preferably in the range of 2.75 to 3.2 microns. The first laser means for generating the longer pulse beam may conveniently include an erbium: YAG laser.

Advantageously, the fluence of the longer pulse laser beam is below that required to ablate the tissue, eg in the range of 0.24J/cm^2 to 0.93J/cm^2. The duration of the longer pulse is preferably in the range 60-150 μsec, eg about 100 μsec. Fluence may be higher but the preferred upper limit is conservatively estimated at 0.93 J/cm^2 to minimise the risk of tissue damage.

The shorter pulse beam is preferably at a wavelength in the region of 200 nm. Its duration is preferably in the range 1 to 25 nsec, most preferably 1 to 10 nsec, eg around 5 nsec. Suitable laser sources for the second laser means include a quintupled Nd:YAG laser emitting at 213 nm, or an excimer laser at 193 nm. Preferably, in the former case, the maximum fifth harmonic energy is 55mJ.

Preferably, the shorter pulse beam is delivered during the second half of the longer pulse, most preferably towards the end of the pulse, eg in the final ¼ of the pulse. Preferably the shorter pulse laser beam is directed onto the tissue at a time 80-95 microseconds after commencement of the longer pulse first striking the tissue.

In certain applications the biological tissue is non-human biological tissue, in other applications human biological tissue.

Brief Description of the Drawings

In order that the invention be more fully understood, a preferred embodiment will be described by way of example with reference to the following illustrations in which:

Figure 1 is a schematic diagram of a first embodiment of the present invention; and

Figure 2 is a schematic diagram of a further embodiment of the present invention.

Preferred Embodiment

In the embodiment depicted in Figure 1, non-linear optical (NLO) crystals 5, 7, 8 are used to produce, at 10, the fifth harmonic (213nm) of an Nd:YAG laser 1 with an output beam 2 of fundamental wavelength 1064-nm. A commercial Nd:YAG laser engine may be used, such as the Surelite II supplied by Continuum

(Santa Clara, California), which has the capacity to produce 660mJ of energy at a repetition rate of 10Hz. The pulse duration of the laser 1 is preferably 5ns FWHM. To produce the 213-nm fifth harmonic at 10, the 1064nm beam 2 is steered by two high reflectance mirrors 3 and 4, positioned at 45° angles, to pass through a first NLO crystal 5, preferably a beta barium borate (BBO) or potassium titanyl phosphate (KTP) or a caesium lithium borate (CLBO) crystal, which doubles the frequency of the infra-red fundamental laser beam 2 to green light 6 at 532nm. Two CLBO crystals, 7 and 8, produce the fourth (266-nm) harmonic 9 and fifth harmonic 10 at 213-nm. The CLBO crystals 7 and 8 are preferably maintained, in mutual optical or non-optical contact, in sealed, temperature-regulated housings containing an inert gas such as argon (not shown). These environmental conditions are utilised to prolong the life of the crystals and maintain optimal output at 213nm.

The fundamental and harmonic beams are all collinear until separated by a dispersing prism 11 which guides the 213nm beam 10 and removes the unwanted wavelengths which are captured by a beam block 12. Overall conversion efficiency is preferably in the range of 8-10%, most preferably around 10%, to give a maximum fifth harmonic energy of 50mJ from the 500mJ fundamental beam.

A free running Er:YAG laser 13, consisting of a very basic cavity design set up for stable operation, with one high reflector 14 and a 85% partial reflector output coupler 15, may be used to produce the infra-red beam 16 at or near 3-microns (2.94-μm). An alternative near three-micron source, such as an optical parametric oscillator, is a second embodiment of the present invention and may produce wavelengths in the range of 2.75-3.2-μm. The Nd:YAG laser 1 can be used to pump an OPO in potassium titanyl phosphate (KTP), periodic poled lithium niobate (PPLN) or any other suitable non-linear material. The output from the 3-micron laser 13 ideally has a pulse duration of 100μs and a maximum energy of 750mJ. The flashlamp pumping the Er:YAG (not shown) may be controlled with a "Fixed Sync" signal from the Nd:YAG laser so that the UV and infrared laser outputs can be appropriately superimposed. This confines the pulse

repetition rate of the Er:YAG to the pulse repetition rate of the Nd:YAG laser.

The near 3-micron beam 16 is directed via a number of high reflectance mirrors 17, 18, 19. To ensure the short pulse UV beam 10 and long pulse infra-red beam 16 are spatially aligned, the 213-nm and 2.94μm wavelengths 10, 16 are passed through a pair of CaF_2 combining prisms 20, 21. Alternatively sapphire or suprasil prisms may be used. The prisms are set so as to combine the 213nm and 2.94-μm paths into a final dual laser beam guided path 22, with the 213nm having minimum deviation. A focus lens 23 in light path 22 may be an achromat or non-achromat set up, as only the 213nm pulse is required to have its focal point close to the target.

A controller 25 is provided for running and controlling the respective lasers 1, 13 so as to direct the shorter pulse beam onto the target tissue 24 while the longer pulse beam 16 is incident on the tissue. This controller may also control the variable optics components for steering and focusing the beams.

The near 3-micron long pulse laser 13 is preferably run at a fluence below the ablation threshold of the tissue. While infrared beam 16 is incident on the tissue, the short pulse ultraviolet beam 10 is directed onto the tissue. This simultaneous application of the beams is found to be effective to achieve ablation of the tissue with the shorter pulse beam 10 at an ablation rate enhanced by the application of the longer pulse beam 16. In this way, thermal damage to the tissue is prevented while increasing the ablation effectiveness of the short pulse irradiation.

A study conducted for the present applicant has demonstrated that the embodiment just described almost doubled the ablation rate of dentine by the UV radiation. The 213nm, 5ns radiation had a fluence of 7.6 J/cm^2 for all data points and the repetition rate was 10Hz. The 213nm, 5ns pulse was located at the 65μs point within the 100μs Er:YAG pulse. This point was chosen arbitrarily. With no Er:YAG energy (single 213nm beam) the average ablation rate achieved was 3.4μm/pulse which closely matches the previous data obtained on the quintupled

Nd:YAG laser. As the Er:YAG energy was introduced and increased the ablation rate increased. Noticeable differences in the ablation rate of the dentine started at a Er:YAG fluence of 0.24J/cm^2. Thermal damage became visually apparent at fluences of 0.93J/cm^2 and upward. Even though this is a very low fluence, discolouration of the tissue (yellow hues) pointed to a heat build up at this point. Keeping the Er:YAG fluence below 0.89J/cm^2 prevented discolouration of the tissue. An ablation rate of 5.8μm/pulse was achieved with the addition of a Er:YAG fluence of 0.89J/cm^2.

The effect of the temporal position of the 213nm pulse within the 2.94μs pulse was also investigated. For the temporal position trials the fluence of the quintupled Nd:YAG was kept constant at 6.8J/cm^2, and the Er:YAG fluence was set to 0.89J/cm^2. The best ablation results came from the 213nm pulse being located at the end of the 100μs Er:YAG pulse, eg in the final quarter of the pulse duration and preferably in the final 10% of the pulse duration. The averaged data at the 90μs point and the 100μs point give an ablation rate of 4μm/pulse. This is more than double the rate achieved with the single 213nm beam, which was 1.8μm/pulse. The UV pulses that were located earlier in the 2.94μm pulse did show slight increases in the ablation rate, but these increases were not as pronounced as the UV pulses located near the end of the 100μm pulse.

The introduction of a dual beam technique to enhance the rate of ablation on dentine was successful, in that the time taken to optically drill through 1mm of dentine was halved without the onset of visible thermal damage. It was also found that the temporal position of the laser pulses did have an influence on the ablation rate. This is despite the fact that the low fluence Er:YAG laser did not produce any tissue removal effects at all when it was solely pulsed onto the target. Considering the mechanism of ablation, which the Er:YAG is reported to have, we propose that the improved ablation rates comes from a build up in sub-surface pressure resulting in a weakening of the dentine structure, possibly through micro-explosions in the hard tissue layer. If this is the case then the possibility of the short pulse UV laser having a photomechanical ablative effect on dentine should

be considered. The thermal damage to surrounding tissue was not visibly present when the Er:YAG was kept to very low fluences; however, micro cracks were present in dual beam ablation. Nevertheless, the surface damage produced after dual beam ablation was negligible compared to that produced by the common dental drill, and thermal damage to the pulpal cavity is unlikely using this technique.

A third embodiment of the present invention, involving the use of two infrared 3-micron beams in a dual beam arrangement, is depicted in Figure 2. Referring to Figure 2, a Er:YAG laser 126, operating within the parameters described in the first embodiment above and producing a long pulse output beam 124 around 2.94-microns, is combined with another infrared beam from a short pulse Nd:YAG based optical parametric oscillator (OPO) 108. A short pulse OPO will not produce thermal damage to the tooth surface due to the short pulse duration and could therefore be used in place of a short pulse UV laser.

The fundamental wavelength (1064 nm) output beam 100 of Nd:YAG laser 101 is directed via high reflectance mirrors 102 and 104 through an aperture 106 to the OPO arrangement 108. Two mirrors 110, 112 surround a non-linear optical crystal 114, preferably potassium titanyl phosphate (KTP) or lithium niobate ($LiNO_3$, Magnesium Oxide 5%). The first mirror 110 is highly transmissive to the 1064-nm beam 100 from the Nd:YAG pumping laser, and is highly reflective of the OPO signal and idler wavelengths of 1650-nm and ~3000-nm. The second mirror 112 is highly reflective at 1064-nm, and transmits greater than 80% of the 1650-nm radiation and greater than 85% of the 3000-nm radiation.

The signal and idler beams produced from the OPO 108 are directed to a 45° mirror 116, which transmits the 3-micron idler beam 118 and reflects the 1650-nm signal beam 120 into a beam dump. After passing through an aperture 122, the near 3-micron short pulse OPO beam 118 is combined with the long pulse 2.94-micron beam 124 from the Er:YAG laser 126 through the use of a polarising beam splitter 128, to form a dual laser beam 129 on a guided light path downstream of beamsplitter 128. A combination of the long pulse Er:YAG laser

running below ablation threshold and the short pulse optical parametric oscillator arrangement as described above therefore has the potential to produce good ablation rates with minimal thermal damage to the tooth.

Claims

1 Apparatus for ablation of biological tissue, including:

first laser means for generating a relatively longer pulse infrared laser beam;

second laser means for generating a relatively shorter pulse far ultraviolet or infrared laser beam;

an optical configuration for directing said beams onto a region of biological tissue; and

means to control said respective laser beams to direct the shorter pulse beam onto the biological tissue while the longer pulse beam is incident on the tissue, whereby to ablate the tissue with the shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam.

2 Apparatus according to claim 1 adapted to ablate hard tissue.

3 Apparatus according to claim 2 wherein said hard tissue is bone or dental tissue, including carious or non-carious dentine, enamel or cementum.

4 Apparatus according to claim 1, 2 or 3 wherein said longer pulse beam is at a wavelength in the region of 3-microns.

5 Apparatus according to claim 4 wherein said longer pulse beam is at a wavelength in the range of 2.75 to 3.2 microns.

6 Apparatus according to any preceding claim arranged so that the fluence of the longer pulse laser beam at the tissue is below that required to ablate biological tissue.

7 Apparatus according to any preceding claim wherein the duration of the

longer pulse is in the range 60-150 μsec.

8 Apparatus according to any preceding claim wherein said shorter pulse beam is at a wavelength in the region of 200 nm.

9 Apparatus according to any preceding claim wherein the duration of said shorter pulse is in the range 1 to 25 nsec.

10 Apparatus according to claim 9 wherein the duration of said shorter pulse is in the range 1 to 10 nsec.

11 Apparatus according to any preceding claim wherein said means to control said laser beams is arranged to deliver the shorter pulse beam during the second half of the longer pulse.

12 Apparatus according to claim 11 wherein the shorter pulse beam is delivered towards the end of the longer pulse.

13 Apparatus according to claim 11 or 12 wherein the shorter pulse beam is delivered in the final ¼ of the longer pulse.

14 Apparatus according to claim 13 wherein the shorter pulse laser beam is directed onto the tissue at a time 80-95 microseconds after commencement of the longer pulse first striking the tissue.

15 Apparatus according to any preceding claim wherein said control means includes a program for effecting said control.

16 A method of providing a dual laser beam suitable for ablating biological tissue, including: directing a relatively longer pulse infrared laser beam along a guided light path, and, while the longer pulse beam is traversing said path, directing a relatively shorter pulse far ultraviolet or infrared laser beam along the path, whereby to form a dual laser beam that, if incident on

biological tissue, ablates the tissue with the shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam.

17 A method according to claim 16 wherein the biological tissue is hard tissue.

18 A method according to claim 16 or 17 wherein said hard tissue is bone or dental tissue, including carious or non-carious dentine, enamel or cementum.

19 A method according to claim 16, 17 or 18 wherein said longer pulse beam is at a wavelength in the region of 3-microns.

20 A method according to claim 19 wherein said longer pulse beam is at a wavelength in the range of 2.75 to 3.2 microns.

21 A method according to any one of claims 16 to 20, wherein the fluence of the longer pulse laser beam at the tissue is below that required to ablate the biological tissue.

22 A method according to claim 21 wherein the fluence of the longer pulse beam at the tissue is in the range 0.24 to 0.93 J/cm^2.

23 A method according to any one of claims 16 to 22 wherein the duration of the longer pulse is in the range 60-150 μsec.

24 A method according to any one of claims 16 to 23 wherein said shorter pulse beam is at a wavelength in the region of 200 nm.

25 A method according to any one of claims 16 to 24 wherein the duration of said shorter pulse is in the range 1 to 25 nsec.

26 A method according to claim 25 wherein the duration of said shorter pulse is in the range 1 to 10 nsec.

27 A method according to any one of claims 16 to 26, wherein the shorter pulse beam is delivered during the second half of the longer pulse.

28 A method according to claim 27 wherein the shorter pulse beam is delivered towards the end of the longer pulse.

29 A method according to claim 27 or 28 wherein the shorter pulse beam is delivered in the final ¼ of the longer pulse.

30 A method according to claim 29 wherein the shorter pulse laser beam is directed onto the tissue at a time 80-95 microseconds after commencement of the longer pulse first striking the tissue.

31 A method according to any one of claims 16 to 30 further including directing said dual laser beam onto biological tissue, whereby to ablate the tissue with the shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam.

32 A method according to any one of claims 16 to 31 wherein the biological tissue is non-human biological tissue.

33 A method of ablating biological tissue including: directing a relatively longer pulse infrared laser beam onto said tissue and, while said longer pulse beam is incident on the tissue, directing a relatively shorter pulse beam far ultraviolet or infrared laser beam onto the tissue, whereby to ablate the tissue with said shorter pulse beam at an ablation rate enhanced by the application of the longer pulse beam.

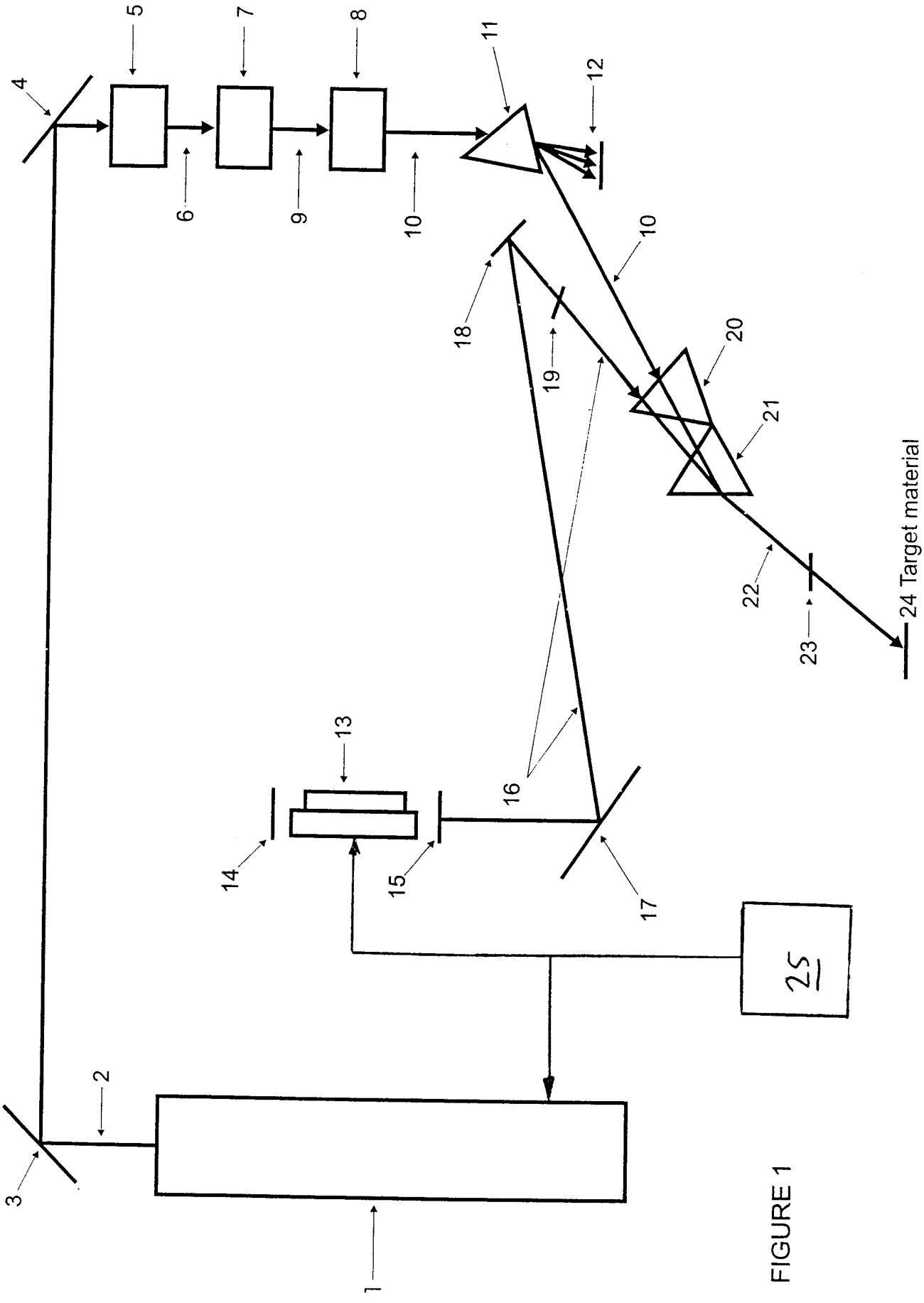

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FIGURE 1

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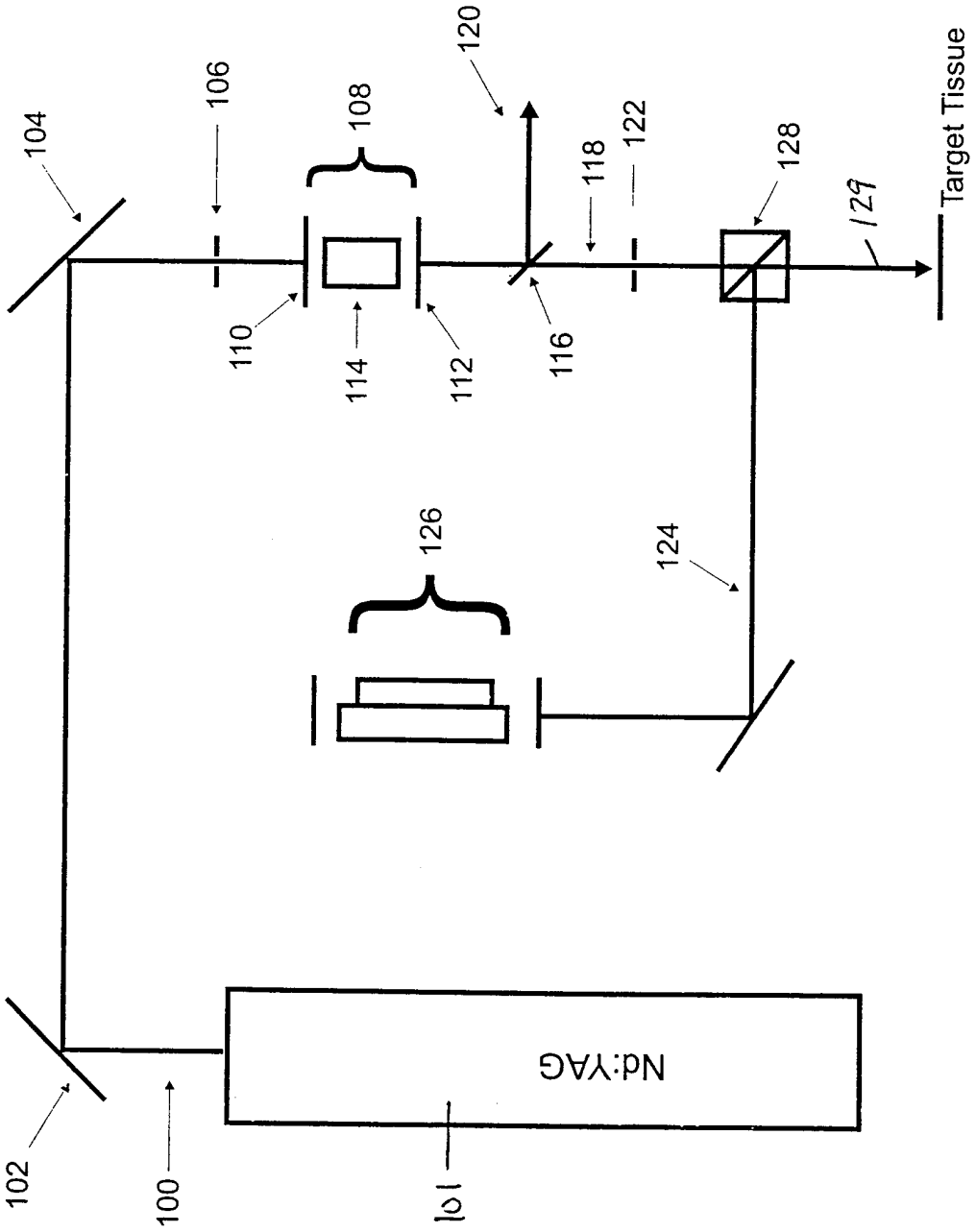
Nd:YAG
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Target Tissue

FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/01181

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61B 18/20 A61C 3/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61B A61C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5172264 A (MORROW) 15 December 1992 Column 2 line 35 to column 3 line 21	1-6,15-21,31-33
X	US 5655547 A (KARNI) 12 August 1997 Column 3 lines 22 to 53	1,8,15,16,24,31-33
X	US 5290274 A (LEVY et al.) 1 March 1994 Column 4 lines 20 to 27	1-5,7,15-20,23,31-33

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/01181

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/27335 A (LIONS EYE INSTITUTE) 12 September 1996 Whole document	1
A	US 5312396 A (FELD et al.) 17 May 1994 Whole document	1

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU00/01181

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member				
US 5172264					
US 5655547	AU 19952/97	EP 807418	JP 10043196	US 5970983	WO 99/05983
US 5290274	EP 575274				
WO 96/27335	AU 47096/96	GB 2313551	US 6056741		
US 5312396	WO 92/03977				

END OF ANNEX