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پروپوزال نویسی
Ultrafast Mid-IR Laser Scalpel: Approaching to Scar-less Surgery

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Lasers have in principle the capability to cut at the level of a single cell, the fundamental limit to minimally invasive procedures and restructuring biological tissues. To date, this limit has not been achieved due to collateral damage on the macroscale that arises from thermal and shock wave induced collateral damage of surrounding tissue. Here, we report on a novel concept using a specifically designed Picosecond IR Laser (PIRL) that selectively energizes water molecules in the tissue to drive ablation or cutting process faster than thermal exchange of energy and shock wave propagation, without plasma formation or ionizing radiation effects. The targeted laser process imparts the least amount of energy in the remaining tissue without any of the deleterious photochemical or photothermal effects that accompanies other laser wavelengths and pulse parameters.

Skin wound healing is a regenerative process requiring the coordinated regulation of a variety of cell types and cell signalling pathways.1 This healing process is comprised of overlapping and linked phases: inflammation, proliferation (new tissue formation), and tissue remodeling.2 Coordination of these phases, together with cellular responses to tissue damage, shapes the outcome of healing tissue, resulting in a scar.3 During the proliferative phase of wound healing, mesenchymal (fibroblast-like) cells migrate into the healing wound, proliferate, and produce a disorganized matrix, providing the initial tensile strength to the wound, and regulating the size of the scar that will form.3

While most wounds heal with a scar that is acceptable to the patient, large scars cause considerable functional and cosmetic deformities, as well as psychological stress, and patient dissatisfaction. The biggest problem is the formation of scar tissue that impairs function, a problem in nearly all surgeries to some extent. Currently available approaches to optimize wound repair include refinements in surgical technique, nutritional supplementation, and the use of local wound care modalities.4 Despite these approaches, there has been little progress in the ability to regulate wound size.

The laser was first used as a surgical tool shortly after its invention as an alternative to mechanical surgical tools.5 In principle, lasers offer the prospect of performing surgery at the fundamental limit by exploiting the spatial phase coherence of laser radiation to focus sufficient intensity for ablation or cutting at the single cell level. Although lasers have emerged as a valuable surgical tool, conventional surgical lasers, having pulse durations longer than nanoseconds, impair the proliferative phase of healing due to thermally-induced cell damage in the surrounding tissue.6 Conventional medical lasers show benefits over mechanical surgical tools only in a very limited number of procedures.7

We recently reported on a novel laser source, the Picosecond IR Laser (PIRL), explicitly designed to exploit a newly discovered ablation mechanism in which the selective excitation of water’s vibrational modes couples directly to translation motions within tissue, the very motions involved in ablation, faster than any other material. By achieving superheating on picoseconds timescales, the nucleation sites for the ablative phase transition have nanometer (molecular) dimensions, avoiding cavitation and associated shock wave induced damage that has been one of the major stumbling blocks in using lasers for surgery. The strong acoustic attenuation at the 100 GHz frequency range further ensures that all the absorbed photon energy ablates tissue on time scales much faster than heat transfer can damage adjacent tissue of the tar-
geted area. The pulse duration and heating rate is also specifically designed to avoid multiphoton ionization effects, that lead to highly reactive species known to be a major problem with other ionizing radiation sources. Using the PIRL system as a surgical tool and comparing it with a conventional laser and mechanical surgical tools, we performed a wound healing study on mice and compared the resultant ablative and tissue damaging characteristics, as well as the final impact on scar size.

To determine how the various modalities ablate tissue differently, the skin of the mouse subject was cut to a linear full thickness cut using the PIRL system, a commercial Er:YAG surgical laser (long pulse) at the exact same wavelength, or a conventional surgical scalpel. Transmission electron microscopy and scanning electron microscopy of the incised border revealed that the conventional laser damaged the skin border up to 800 µm away from the visible edge and the surgical scalpel caused dissociation of extracellular matrix fibres up to 400 µm further from the edge (Figure 1A-C). By comparison, cuts done with the PIRL system had sharp edges and minimal damage to adjacent tissue. The PIRL system generated a cutting gap of 8 µm, smaller than the diameter of a single skin fibroblast which was observed in the same skin sections. In contrast, the measured gap for scalpel incisions ranged from 40 to 120 micrometers and 650 µm for the conventional laser (data not shown). Wounds that were formed using the PIRL system had a higher number of viable skin cells immediately adjacent to the cut as compared to the other modalities (data not shown). Taken together, these results show that PIRL produces substantially less damage to the extracellular matrix and cells surrounding the wound, and ablates a much lower volume of tissue to execute the same function in comparison to a conventional laser and surgical scalpel.

In order to evaluate the amount of tissue damage and its effect on scar formation, we removed the same amount of tissue (excision of 4mm circular, full thickness, wounds) using the three methods and compared scar formation at different time points. Despite the same amount of tissue ablated by all modalities, the width of the scar formed by the PIRL system was half that of the wounds produced using either a conventional surgical laser or a scalpel at 9 days post-wounding (Figure 2 D-F). A similar trend was observed when incision of linear wounds were performed (data not shown). Moreover, there was a lower proliferation rate, as measured using KI-67 staining and aniline blue staining showed higher levels of collagen in the early stages of wounds produced using the PIRL system, suggesting that these wounds mature faster, and thus have a shorter proliferative phase.

These observations show that PIRL ablates the minimal amount of tissue and causes less damage to surrounding tissue (Figure 1G-I). Selective ablation process owes its efficacy to the ultrafast time scale of the ablation process. The process occurs on timescales comparable or faster than even collision induced energy redistribution between molecules within the excited zone. We have observed whole proteins, even weakly bound protein complexes driven into the gas phase as intact neutral species using mass spectroscopy. These molecules, especially the protein complexes, are extremely fragile and heretofore have never been observed in laser ablation without undergoing thermally driven fragmentation. This result shows that even at a molecular level there is minimal heat deposition into the constituent biological molecules. The key factor is the time scale under which the energy is preferentially partitioned within the excited water molecules that act as a propellant to drive the molecules into the gas phase and provide the cutting actions. The choice of pulse duration was made to be in this limit but not so short as to increase the peak power above the threshold for multiphoton ionization effects. In all cases, it is important to note that the forces remain far more localized than those involved in the use of mechanical tools, which need to exceed the shear elastic limit of the tissue in order to cut.

The use of PIRL can open up new surgical methods where scar tissue formation is particularly debilitating. This approach may have general applications in reducing hyperplastic scarring and also cosmetic application in the revision of existing hyperplastic scars. Moreover by decreasing the healing time, this new surgical modality may result in increased patient comfort and decreased risk of infections due to infection in surgery. The PIRL system is a new tool for scar prevention, promising outstanding results and improved surgical outcomes. As stated by Fitz Gibbon: “By your scars you will be judged”.
Figure 1. Minimal tissue ablation with less damage of surrounding tissues by using the PIRL laser.
Scanning electron microscopy (SEM) of skin at the cut borders. (A) The PIRL laser kept the collagen layer intact. (B) The conventional laser damaged (burned) skin and deformed the collagen fibres resulting in a damaged, irregular extracellular matrix surface. (C) The scalpel damaged the skin by shearing between the collagen fibres and exposing individual cells (Arrow shows an adipocytes which is exposed in this image). (D-F) Representative histologic sections of healed skin of excisional 4mm circular full thickness wounds using the three methods at 9 days post wounding. (D) PIRL Laser (E) Conventional Laser (F) Skin Biopsy Punch. (G-I) Schematic of cutting modalities. (G) The well absorbed PIRL pulses cause superheating of water inside the tissue on the picosecond timescale, ejecting the tissue faster than energy can diffuse to the surroundings area. The remaining adjacent tissue shows minimal damage compared to the other two modalities. (H) Conventional surgical lasers cut by depositing heat until the tissue melts or burns away. The damage zone in this case, can reach up to 800 µm away from the ablated edge. (I) The mechanical scalpel cuts skin by producing shear forces which exceed the elastic limit of the tissue. This causes a border of damage around the incision which reaches as far as 400 µm from the borders of the incision.

Conflict of interest statement: the author declares that he has no conflict of interest.

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