Picosecond lasers: the next generation of short-pulsed lasers

Joshua R Freedman, MD;[1] Joely Kaufman, MD;[1,2] Andrei I Metelitsa, MD, FRCPC;[3,4] Jeremy B Green, MD[1,2]

Abstract

Selective photothermolysis, first discussed in the context of targeted microsurgery in 1983, proposed that the optimal parameters for specific thermal damage rely critically on the duration over which energy is delivered to the tissue. At that time, nonspecific thermal damage had been an intrinsic limitation of all commercially available lasers, despite efforts to mitigate this by a variety of compensatory cooling mechanisms. Fifteen years later, experimental picosecond lasers were first reported in the dermatological literature to demonstrate greater efficacy over their nanosecond predecessors in the context of targeted destruction of tattoo ink. Within the last 4 years, more than a decade after those experiments, the first commercially available cutaneous picosecond laser unit became available (Cynosure, Westford, Massachusetts), and several pilot studies have demonstrated its utility in tattoo removal. An experimental picosecond infrared laser has also recently demonstrated a nonthermal tissue ablative capability in soft tissue, bone, and dentin. In this article, we review the published data pertaining to dermatology on picosecond lasers from their initial reports to the present as well as discuss forthcoming technology.

Semin Cutan Med Surg 33:164-168 © 2014 Frontline Medical Communications

Lasers capable of delivering optical pulse widths of less than 1 nanosecond (10^{-9} sec) are referred to as Picosecond (10^{-12} sec) lasers. These devices have the ability to deliver energy to tissue in a shorter duration of time than antecedent technologies; which enables higher energy density, more specific targeting of smaller particles, more efficient delivery of energy, and lower thermal diffusion to surrounding tissues. Picosecond lasers have been largely reported in terms of their utility in tattoo removal, but reports of efficacy in "cold" tissue ablation studies may herald new applications in dermatology. Although picosecond laser technology has been available in the nonclinical setting for decades, the first FDA-approved picosecond laser for cutaneous use (Picosure, Cynosure, Westford, Massachusetts) has only been available since 2012. Consequently, much of the clinical data is recent and more devices are currently in the FDA approval process (PicoWay, Syneron-Candela, Wayland, Massachusetts and Enlighten, Cutera, Brisbane, California). In this article, we review the published data pertaining to dermatology on picosecond lasers from their initial reports to the present and discuss forthcoming technology.

[1]University of Miami Leonard M. Miller School of Medicine Department of Dermatology & Cutaneous Surgery, Florida
[2]Dr. Brandt Dermatology Associates, Coral Gables, Florida
[3]Institute for Skin Advancement, Calgary, Alberta, Canada
[4]Section of Dermatology, University of Calgary, Alberta, Canada
Disclosures: Dr Freedman indicates no conflicts of interest. Drs Kaufman, Green and Metelitsa have performed research for and have served on the speaker's bureau of Cutera Lasers and Cynosure.
Correspondence: Jeremy B. Green, MD; Dr Brandt Dermatology Associates, 4425 Ponce de Leon Boulevard, Suite 200; Coral Gables, FL 33146. E-mail: jgreen@drfredricbrandt.com

Background

Selective photothermolysis (SP) was initially described as a means by which thermally mediated radiation damage might be confined to selected tissue.[1] The incident wavelength is selected to maximize absorption by the target while minimizing optical absorption of surrounding tissue. The small diameter of tattoo particles, typically in the range of 10 nm - 100 nm, leads to a lower fractional absorption relative to larger organic targets. The incident wavelength influences optical attenuation of the laser as it propagates through the tissue, affecting the tissue depth at which SP can be achieved. The pulse width, or the duration of laser exposure each period, is critical to creating specific thermal damage. To attain specific thermal damage, the pulse width must be less than the thermal relaxation time of the target molecule, which is defined as the time required for the central temperature of a Gaussian temperature distribution with a width equal to the target's diameter to decrease by 50%. For spherical targets of diameter d, $T_R = d^2/27K$, where K equals the thermal diffusivity of target and surroundings. The thermal relaxation time rapidly decreases proportional to particle size. Solving this equation for particles on the order of 100 nm yields either nanosecond or shorter pulses which is the required pulse width to achieve SP. Thus, the necessity of picosecond lasers to specifically target small particles such as tattoo ink had been noted long before the realization of this technology.

However, photothermolysis is not the primary mechanism responsible for the events observed using picosecond lasers. The different types of laser-tissue interactions may be subdivided into either thermal, photochemical, plasma induced, photomechanical, or a combination of these effects. Carbon dioxide (CO_2) and Erbium: yttrium-aluminum-garnet (Er:YAG) are common lasers that create thermal effects. Thermal ablation relies on tissue melting or sublimating through simplistic heating, often at PW > 10 ns and under thermal, but not stress confinement. Hot, pressurized vapors fracture the tissue resulting in tissue ablation. Considerable thermal tissue damage may occur due to peripheral heating. Some scenarios may benefit from heating; several theoretical mechanisms of nonablative skin resurfacing lasers posit that heat induces cytokine changes and in turn promotes a wound healing response which incorporates fibroblast activation and the deposition of new collagen.[2] There are also undesirable side effects to thermal-induced

1085-5629/13$-see front matter © 2014 Frontline Medical Communications
DOI: 10.12788/j.sder.0117

injury, including the unwanted spread of heat to surrounding nontarget tissues, such as melanocytes.

Photochemical ablation occurs when the laser wavelength is tuned to the molecular states of a major tissue constituent, ultimately resulting in cleavage of chemical bonds with a release of heat that in turn weakens and fractures tissue.[3] Excimer lasers, which target both DNA and proteins, are of this class, although they may additionally cause photoacoustic transients and form shockwaves in the MHz range that can increase the range of damage.

Plasma-induced ablation became plausible with the advent of ultrashort-pulsed lasers and captivated significant interest as a potential idealized laser scalpel.[4] The femtosecond (10^{-15} sec) laser pulses generate hot electron plasma through spatially well-confined avalanche ionization which quickly transitions to heat that removes biological material and cuts tissue with extreme precision and minimal peripheral thermal damage. Unfortunately, the ionization also appears to generate toxic-free radicals.[3] If the femtosecond laser wounds bone, the wound heals slower than mechanically generated wounds, implying biochemical pathway destruction from the reactive species.[5] Nonetheless, these lasers appear particularly well suited for ophthalmological purposes and the first femtosecond laser (Alcon-LenSx Lasers Inc, Aliso Viejo, California) received United States Food and Drug Administration (FDA) clearance in 2009 for cataract surgery.[6]

These mechanisms all include secondary photomechanical effects; however, a primary photomechanical effect, known as the front surface spallation effect, can be used very effectively as the dominant ablative mechanism.[7] This theory describes local irradiation of a tissue volume generating tensile strength which exceeds the tissue's ultimate tensile stress, followed by tissue fracture and ablation. This mechanism is extremely efficient, requiring less energy to fracture a material via spallation than to vaporize it.[8]

A computer simulation of the mechanisms of tattoo removal reported findings which supported photomechanical ablation as the underlying mechanism which explains clinical observations of picosecond laser studies.[9] The simulation was modeled using the picosecond wavelengths clinically studied at that time, 755 nm and 1064 nm, and found that graphite tattoos of particle sizes 10 nm to 1 μm did not reach internal temperatures which exceeded the melting point of graphite. The maximum temperature reached of 900°C at the end of a 35-picosecond pulse was well above the boiling point of water. It resulted in a cavitation bubble forming around the particle in the tissue, while the tattoo particles themselves did not significantly undergo thermal expansion. The rapid temperature spike in the particle causes a very strong pressure wave of a maximal tensile strength well above the graphite's tensile strength, resulting in particle fragmentation. The temperatures reached would also permit endothermic steam carbon reactions to occur, a process which alters the optical properties of some tattoo inks, producing shell-like structures and reducing their visibility.[10]

Picosecond laser clinical trials

At present, clinical reports of picosecond laser devices have included use of Nd: YAG,[11] Titanium: Sapphire,[12,13] a novel 758 nm/500 picosecond model,[14] alexandrite,[15,16] and a picosecond infrared laser (PIRL).[17-21] Greater efficacy in black tattoo clearance has been demonstrated with a picosecond versus nanosecond pulse width using two Nd: YAG (1064 nm) lasers, Titanium: Sapphire (795 nm) versus Q-switched (QS) alexandrite (752 nm), and a novel 500-picosecond laser (758 nm) versus Q-switched alexandrite (755 nm). Additional studies without control arms demonstrated clinical safety and efficacy of a picosecond alexandrite 755 nm in black and blue-to-green tattoos. A novel picosecond infrared laser (PIRL, 2.94 μm) demonstrated considerably less thermal damage during tissue ablation than equivalent wavelength Er:YAG. The findings of these studies are discussed in this section.

The first reported study using cutaneous picosecond lasers demonstrated effective ink removal in cats using an 800 nm Ti:sapphire laser at different fluences and pulse widths (100 femtoseconds, 100 picoseconds, 400 picoseconds) with a spot size of 4 mm.[13] Histologic evidence supported greater clearance with higher fluences, but with no significant differences between pulse widths.

The initial trial of picosecond lasers in human subjects on cutaneous tissue compared the efficacy of a picosecond and nanosecond Nd: YAG laser in 16 black or partially black tattoos.[11] Tattoos were divided into three segments, and treated every 3-4 weeks, for a total of four sessions. Part 1 was treated with a mode-locked Nd: YAG laser (Model YG501, Quantel Technologies, Santa Clara, CA; pulse width (PW) = 35 picoseconds, spot size = 1.4 mm, fluence = 0.65 j/cm2, frequency (f) = 10Hz, beam profile = Gaussian). Part 2 was treated with a Q-switched Nd: YAG (Model NY82-10, Continuum, Santa Clara, CA; PW = 10 nanoseconds, spot size = 1.4 mm, fluence = 0.65 j/cm2, f = 10Hz, beam profile = multimodal). Part 3 was treated with the same laser as part 2, with conventional clinical settings (PW = 10 nanoseconds, spot size = 2.5 mm, fluence = 8.0 j/cm2, f = 10Hz, beam profile = multimodal). Punch biopsies were obtained before and immediately after initial treatment and 30 days after completion. Photographic assessment by blinded physicians scoring demonstrated superior clearance of black ink in picosecond laser treated areas ($P = .02$), insignificant lightening of green areas, and many nonblack tattoo regions with no perceived changes, including red, purple, orange, and yellow pigment. No scarring was noted in the picosecond laser use.

Histological examination with light microscopy demonstrated pretreatment areas with predominant granules as black irregularly shaped clumps at 1-5 μm in diameter, and red or green granules 1-3 μm diameter. Electron micrographs better discriminated pigmented particles in pretreatment areas to range 10 nm to 100 nm in diameter (mean 40 nm), and reside predominantly in fibroblasts. Intertattoo-ink depth varied from 250-1700 μm deep, while within a given tattoo the levels typically showed no morethan a +/-200 μm variability. Immediately after treatment, in clearly demarcated regions (depth range 670+/-96 μm for picosecond pulses, 590+/-107 μm for nanosecond pulses), black particles appeared smudged, transitioning to amorphous light brown bodies with a lacy appearance. Light microscopy also demonstrated suprabasilar clefting and vacuole formation in the dermal interstitium proximal to pigmentation, lined by cellular debris and altered pigmentation. These changes were most pronounced after conventional high-fluence settings and least so using picosecond pulses. Electron micrographs indicated cellular debris in pigment-laden cells and that ~30% of pigmented particles demonstrated a lamellated electron-lucent appearance, which persisted after final treatment. This finding is currently thought to be the result of the steam-carbon reaction.[10]

In summary, this study demonstrated picosecond lasers in com-

parison with nanosecond lasers generated greater clearance of black tattoos at lower energy and had a greater depth of penetration when all other parameters were held constant. On an electron microscopy, there was evidence of an intrinsic optical property change of electron lucent postprocedural particles which were thought to be caused by the steam-carbon reaction. It was theorized that the steam-carbon reaction was responsible for the visible changes more so than particle fragmentation.

A prospective controlled study compared a prototype Titanium:Sapphire (795 nm) versus Q-switched alexandrite (752 nm) in four viable albino guinea pig tattoos. Three parameter sets for the Ti:Sapphire at 500 picoseconds included spot sizes 1.25 mm, 1.5 mm, and 2 mm at fluences of 6.11, 4.24, and 2.39 J/cm^2, respectively. The Q-switched alexandrite laser (Candela Laser Corporation, Wayland, MA) with a pulse width of 50 ns, was set to the same spot sizes and fluences. Clinical evaluation demonstrated two of four tattoos had a significantly greater response in the picosecond laser treated areas. Some evidence of fibroplasia was also noted in the picosecond-treated areas using higher fluences.[12]

A pilot study compared a novel 758 nm alexandrite, 500-picosecond laser (Cynosure, Westford, MA) to a QS alexandrite laser (755 nm, Candela, Wayland, MA) in India ink (carbon) and iron oxide tattoos applied to the backs of Yorkshire pigs. The picosecond laser parameters varied in spot size and fluence. Results indicated both lasers produced greater tattoo lightening of black carbon tattoos over iron oxide particles. The picosecond laser showed significantly greater lightening at all fluences than the QS alexandrite, with no significant differences between the settings. All lasers were less effective at clearing an iron oxide tattoo, although the QS alexandrite laser was more effective than picosecond pulses, and significantly more so than the high-fluence picosecond setting. Histology demonstrated fibroplasia with no evidence of fibrosis. Electron microscopy of carbon tattoos treated with both lasers revealed electron dense particles within lysosomes and some amorphous material.[14]

A single-center prospective trial of a 755 nm alexandrite picosecond laser (Cynosure, Westford, MA) evaluating black and dark-blue tattoo pigment in 12 patients was assessed via photographic review by a blinded physician as well as rating physician and patient satisfaction. Treatments were performed with a single pass, energy 2.1 to 4.1 J/cm^2, PW of 500-900 picoseconds, spot size from 2.5 – 3.5 mm, f = 5 Hz. Most of the patients (75%) obtained >75% clearance after 2 to 4 sessions. All 12 patients attained 75% clearance after an average of 4.25 sessions. A mean (SD) pain score of 4.5 (2.69) was reported (pain scale 1-10, 10 = worst); two of these patients received topical lidocaine and they reported pain scores of 1- 3. Both patients and physicians rated themselves satisfied or extremely satisfied. Postinflammatory dyspigmentation was noted in 33% of patients, 3 reported hypopigmentation, and 2 reported hyperpigmentation.[15]

The same 755 nm alexandrite picosecond laser was used in treating blue and green tattoo pigment in another center. Twelve tattoos, of which 2 were considered recalcitrant, were treated. Laser parameters varied within parameters pending patient skin type and achievement of epidermal whitening (PW 750-900 picoseconds, spot sizes 3- 3.6 mm, fluence ranging 2.0 – 2.83 J/cm2, f= 5 Hz). After 1 treatment, 92% of patients achieved >75% clearance while the remaining tattoo required 2 treatments to reach that endpoint. Average pain scores reported were 1.08 (pain scale 1-10, 10 = worst). Postinflammatory pigment alteration was observed but resolved in subsequent follow-up visits. One patient reported blistering. There was no control for the study, but the authors indicated that their most efficacious laser in green/blue pigment, the QS-Ruby (Palomar Medical Technologies, Lexington, MA subsequently acquired by Alma), typically required an average of 6-10 treatments in comparison with the 1-2 treatments demonstrated by the picosecond laser.[16]

More recently, a new picosecond laser in the midinfrared spectrum has demonstrated a number of exciting results. The debut study with the 2950 nm wavelength PIRL using a 0.75 J/cm^2, 55 picosecond pulse, demonstrated highly efficient ablation of dental enamel, the hardest substance in the human body.[17] Electron micrographs of treated tissue showing no microfractures supported the theory that the extremely high ablation efficiency is achieved through photomechanical effects. The group then studied the PIRL as a laser scalpel, comparing its efficacy to Er:YAG and a traditional surgical steel scalpel in CD1 mice and measuring subsequent protein signaling.[18] Full thickness incisional and excisional wounds were generated and compared using transmission and scanning electron microscopy, light microscopy, and immunohistochemistry. Analysis of the incised border revealed that the conventional Er:YAG laser created a cutting gap of 650 μm, and damaged the skin border up to 800 μm away from visible wound edge. Surgical scalpel incisions ranged from 40-120 μm, and caused dissociation of extracellular matrix fibers 400 μm from the edge. The PIRL generated a cutting gap of just 8 μm, with a sharp edge and minimal damage to the adjacent tissue. Immediately after incision, comparison of cell viability demonstrated significantly more viable cells and less damage to surrounding tissue using the PIRL laser than either the scalpel ($P < .01$) or Er:YAG ($P < .001$). In order to evaluate tissue damage and the effect on scar formation at different time points, 4 mm circular full thickness excisions were performed. The scar width of PIRL wounds was less than half of the Er:YAG and scalpel wounds at 9 days, and less at all time points measured. KI-67 staining indicated a lower proliferation rate and aniline blue staining showed more collagen in the early stages of PIRL wounds, indicating these wounds have a shorter proliferative phase and faster maturation rate. β-Catenin and TGF-β signaling were assessed due to their role in regulating size and tissue proliferation during wound healing. A significantly lower percentage of β-Catenin and pSmad2 cells ($P < .001$) were noted in PIRL samples compared to Er:YAG and scalpel, suggesting that the tissue damage from the PIRL elicits a different cytokine profile of the wound that alters its healing process to result in a smaller wound size. The authors emphasized remarkably minimal thermally driven fragmentation of tissue in contrast to other laser modalities which are incapable of almost pure photomechanical tissue ablation. In summary, this study demonstrates PIRL lasers are precise, capable of minimal tissue ablation, cause less damage to surrounding tissues leading to reduced activation of β-Catenin and TGF-β signaling, have higher cell viability, have a lower rate of cellular proliferation, and showed more collagen in earlier stages of wound healing, which they posit leads to the accelerated healing response.

The 2.94 μm PIRL laser (AttoDyne Inc, Toronto, Canada) was subsequently evaluated in terms of its ability to ablate tissue with minimal heat generation in comparison with an Er:YAG laser (MCL

29, Aesculap-Meditec GmbH, Heroldsberg, Germany) of the same wavelength.[20,21] Ex vivo porcine skin was ablated with both lasers in 5 mm linear patterns at fluence levels slightly above ablative thresholds (Er:YAG = 2 J/cm^2, PW = 250 µs, f = 24 Hz and PIRL = 0.6 J/cm^2, PW = 300 picoseconds, f = 50 Hz). Thermography was surveyed at 100Hz, measuring epidermal temperatures, and ablation of tissue was confirmed via digital microscopy. Mean peak rise in skin surface temperature for the Er:YAG and PIRL were 15°C and 1.68°C, respectively ($P < .001$). Maximum peak rise was 18.85°C for the Er:YAG laser, and 2.05°C for the PIRL. Inherent limitations of the study include the sampling rate of the camera being insufficient to adequately capture the maximal temperature peaks achieved during the picosecond laser pulses, and the ex vivo nature of the study.[20] The same research group subsequently performed a similar study ablating bone with both lasers, in which electron micrographs demonstrated almost predominantly photomechanical ablation with negligible microfracturing (typically a photothermal effect) and preserved cortical microstructure.[21]

Several new reports of picosecond laser applications were recently presented, which have not yet been published. These include a study of a diffractive lens array with a picosecond laser for treatment of acne scars,[22] reduction of facial photodamage and rhytides,[23,24] as well as data regarding dose optimization.[25,26] The theory behind spatially modulated beams assumes that hundreds of microlenses per square centimeter (each approximately 100 microns) redistribute the picosecond pulse enabling higher concentrations of energy (20x energy per spot compared to a straight-hand piece). Additionally, a novel picosecond 532 nm-Nd: YAG laser was also recently described for the removal of red tattoo pigment and results await substantiation.[27] One study noted clinical improvement in four patients with dermal melanocytosis using a picosecond 755 nm alexandrite laser.[28] Lastly, a separate study analyzed skin which had been treated with the same laser both uniformly and utilizing spatial modulation of the incident beam.[29] Preliminary results indicate that the picosecond pulse may have a role in a number of applications beyond tattoo removal.

Conclusion

Picosecond lasers have demonstrated superiority over antecedent technology in regards to targeted destruction of tattoo inks, which has driven the FDA approval of one picosecond laser, and soon to be followed by two more. These devices appear to offer greater clearance of tattoo ink in a fewer number of treatments for black, blue, green, and purple colors in skin types I-V. Recently, the 755 nm alexandrite picosecond laser (Cynosure, Westford MA) received FDA approval for acne scarring. Recent abstracts related to picosecond lasers presented at an annual conference included utility in acne scars, superficial rhytides, dosing parameters, experiments with spatially modulated beams, and a novel 532-nm Nd: YAG for red tattoo pigment removal.[27] The exponential increase in studies follow the FDA approval of one device, while fueling the approval of others, along with new indications for use. The PIRL currently in development, which demonstrated effectively nonthermal tissue ablation, may have future roles in dermatology as a laser scalpel in scar remodeling or skin resurfacing.

Photothermal damage, which predominated considerations in nanosecond lasers, is no longer believed to be the primary method of tissue or exogenous particle destruction in picosecond lasers. Rather, photomechanical or photoacoustic fragmentation is responsible for destruction of some tattoo particles, and the steam-carbon reaction is theorized to underlie the conversion of others to less visible, electron lucent shelled structures. PIRL lasers are the most efficient means of tissue ablation occurring through photomechanical spallation. As picosecond lasers take the forefront of technology, resident education should be updated to reflect the evolution of collective knowledge, so that future clinicians may better understand and develop new technologies.

Very few adverse events have been reported using picosecond lasers. These include edema noted after Nd: YAG tattoo treatment, as well as transient dyspigmentation, persistent hypopigmentation, and rare blister formation using the 755-nm alexandrite laser. These lasers appear to be as safe as their Q-switched nanosecond pulse duration predecessors.

Histological findings after picosecond laser use in tattoos demonstrated suprabasilar clefting, vacuolization with varying degrees of cellular debris at their periphery, and alteration of tattooed pigment particles at depths near 670 µms (using Nd: YAG). Vacuole formation was theorized to be the result of cavitation caused by vaporized water in proximity to heated tattoo particles.[10] Alteration of carbon-based tattoos to the electron lucent, less visible form may be due to the steam-carbon reaction. It has not been demonstrated that iron oxide particles neither respond as well nor form this reaction. Fibroplasia without evidence of fibrosis was also reported.

Study findings associated with the PIRL have demonstrated efficient tissue ablation with narrower tissue gaps than surgical steel, minimal thermal damage to surrounding tissue, creation of smaller scars, and altered expression of cytokines. It may be too soon to extrapolate all of the implications of this laser for use in dermatology, but certainly speculation should include laser surgery, scar revision, and laser resurfacing.

References

1. Anderson RR , Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. *Science.* 1983;220(4596):524-527.
2. Freedman JR, Greene RM , Green JB. Histologic effects of resurfacing lasers. *Facial Plas Surg.* 2014;30(1):40-48.
3. Vogel A, Venugopalan V. Mechanisms of pulsed laser ablation of biological tissues. *Chem Rev.* 2003;103(2):577-644.
4. Tibor J, Kurtz R, Raksi F, Suarez C, Horvath C, Spooner G. The femtosecond blade: applications in corneal surgery. *Optics Photonics News*. 2002;13(1):24-29.
5. Girard B, Cloutier M, Wilson DJ, Clokie CM, Miller RJ , Wilson BC. Microtomographic analysis of healing of femtosecond laser bone calvarial wounds compared to mechanical instruments in mice with and without application of BMP-7. *Lasers Surg Med.* 2007;39(5):458-467.
6. Nagy ZZ. New technology update: femtosecond laser in cataract surgery. *Clin Ophthalmol.* 2014;8:1157-1167.
7. Dingus, RS, Scammon RJ. Grüneisen-stress-induced ablation of biological tissue. *Proc. SPIE*. Laser-Tissue Interaction II. 1991;1427:45-54.
8. Paltauf G, Dyer PE. Photomechanical processes and effects in ablation. *Chem Rev.* 2003;103(2):487-518.
9. Ho DD, London R, Zimmerman GB, Young DA. Laser-tattoo removal--a study of the mechanism and the optimal treatment strategy via computer simulations. *Lasers Surg Med.* 2002;30(5):389-397.
10. Chen H, Diebold G. Chemical generation of acoustic waves: a giant photoacoustic effect. *Science*. 1995;270(5238):963-966.
11. Ross V, Naseef G, Lin G, et al. Comparison of responses of tattoos to picosecond and nanosecond Q-switched neodymium: YAG lasers. *Arch Dermatol.* 1998;134(2):167-171.
12. Herd RM, Alora MB, Smoller B, Arndt KA , Dover JS. A clinical and histologic prospective controlled comparative study of the picosecond titanium:sapphire (795 nm) laser versus the Q-switched alexandrite (752 nm) laser for removing tattoo pigment. *J Am Acad Dermatol.* 1999;40(4):603-606.
13. Kilmer SL, R. E. Fitzpatrick, L. B. Da Silva, R. Marshall, R. Ghiselli. "Picosecond

and femtosecond laser treatment of tattoo ink." *Lasers Surg Med.* 1996;19(Suppl 8):36.
14. Izikson L, Farinelli W, Sakamoto F, Tannous Z , Anderson RR. Safety and effectiveness of black tattoo clearance in a pig model after a single treatment with a novel 758 nm 500 picosecond laser: a pilot study. *Lasers Surg Med.* 2010;42(7):640-646.
15. Saedi N, Metelitsa A, Petrell K, Arndt KA , Dover JS. Treatment of tattoos with a picosecond alexandrite laser: a prospective trial. *Arch Dermatol.* 2012;148(12):1360-1363.
16. Brauer JA, Reddy KK, Anolik R, et al. Successful and rapid treatment of blue and green tattoo pigment with a novel picosecond laser. *Arch Dermatol.* 2012;148(7):820-823.
17. Franjic K, Cowan ML, Kraemer D , Miller RJD. Laser selective cutting of biological tissues by impulsive heat deposition through ultrafast vibrational excitations. *Opt Express.* 2009;17:22937-22959.
18. Amini-Nik S, Kraemer D, Cowan ML, et al. Ultrafast mid-IR laser scalpel: protein signals of the fundamental limits to minimally invasive surgery. *PLoS One.* 2010;5(9).
19. Böttcher A, Clauditz TS, Knecht R, et al. A novel tool in laryngeal surgery: preliminary results of the picosecond infrared laser. *Laryngoscope.* 2013;123(11):2770-2775.
20. Jowett N, Wollmer W, Mlynarek AM, et al. Heat generation during ablation of porcine skin with erbium:YAG laser vs a novel picosecond infrared laser. *JAMA Otolaryngol Head Neck Surg.* 2013;139(8):828-833.
21. Jowett N, Wöllmer W, Reimer R, et al. Bone ablation without thermal or acoustic mechanical injury via a novel picosecond infrared laser (PIRL). *Otolaryngol Head Neck Surg.* 2014;150(3):385-393.
22. Geronemus RG, Kazlouskaya V, Bae YS, et al. Diffractive lens array with picosecond laser for facial acne scarring: follow up and histology. Paper presented at: 34th Annual Scientific Conference of the American Society for Laser Medicine & Surgery; April 2014; Phoenix, AZ.
23. Weiss RA, Weiss MA, Beasley K. Picosecond laser for reduction of wrinkles. Paper presented at: 34th Annual Scientific Conference of the American Society for Laser Medicine & Surgery; April 2014; Phoenix, AZ .
24. McDaniel D. Treatment of facial photodamage and rhytides using a picosecond pulsed alexandrite laser and specifically designed focus Optico Paper presented at: 34th Annual Scientific Conference of the American Society for Laser Medicine & Surgery; April 2014; Phoenix, AZ .
25. Kilmer SL, Custis, T. Single vs repeat exposure tattoo removal during single sessions with pico-second pulse duration laser technology. Paper presented at: 34th Annual Scientific Conference of the American Society for Laser Medicine & Surgery; April 2014; Phoenix, AZ .
26. Tanghetti E, Tanghetti M. Dose optimization with a picosecond 755nm alexandrite laser for tattoo removal. Paper presented at: 34th Annual Scientific Conference of the American Society for Laser Medicine & Surgery; April 2014; Phoenix, AZ .
27. Alabdulrazzaq H, Bae YSC, Brauer JA, Geronemus RG. Rapid removal of red tattoo pigment with a novel 532nm Nd:YAG picoseconds laser. Paper presented at: 34th Annual Scientific Conference of the American Society for Laser Medicine & Surgery; April 2014; Phoenix, AZ .
28. Diehl J, Chesnut C, Lask G. Treatment of nevus of ota with picosecond alexandrite laser and review of the dermal melanocytoses and treatment options. Treatment of Nevus of Ota with picosecond Alexandrite Laser and review of the dermal melanocytoses and treatment options. American Society for Laser Medicine & Surgery 2014;Annual Conference 2014, Phoenix, AZ.
29. Tanghetti E, Tanghetti M. A clinical and histological study of skin treated with a pico-second alexandrite laser comparing a uniform treatment spot and a spatially modulated spot. Treatment of Nevus of Ota with picosecond Alexandrite Laser and review of the dermal melanocytoses and treatment options. American Society for Laser Medicine & Surgery 2014;Annual Conference 2014, Phoenix, AZ.