## Table of Contents

1. Executive Summary .................................................. 5  
2. What is Photobiomodulation? .................................... 7  
3. OrthoPulse® Evidence .............................................. 11  
4. Selected Photobiomodulation Evidence ...................... 25  
5. References .............................................................. 27
Clinical and Scientific Evidence

OrthoPulse® is a Class II medical device and has received FDA clearance, CE mark and regulatory approval in over 40 countries. The OrthoPulse® device is intended to accelerate orthodontic movement of teeth and reduce the overall treatment time for patients. The device is designed to be used in conjunction with traditional orthodontic treatment, with brackets and wires or aligners.

The Science of Photobiomodulation

The application of therapeutic light in the near infrared wavelength (800-1000 nm) has been shown to produce beneficial biological effects in stressed and ischemic tissue (3000+ published peer-reviewed articles). Mitochondrial enzymes absorb these photons and increase the production of adenosine triphosphate (ATP, “energy”), allowing enhanced tissue metabolism.†

In 1903, Niels Ryberg Finsen won the Nobel Prize in Physiology or Medicine in recognition of his contribution to the treatment of diseases with concentrated infrared and red light. Otto Warburg then went on to win the Nobel Prize in Physiology or Medicine in 1931 for discovering Cytochrome c Oxidase (CCO), the terminal enzyme in the mitochondrial oxidative respiration chain. He demonstrated that the mitochondrial CCO was responsive to light stimulation.

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Photobiomodulation Mechanism of Action

- Increases mitochondrial chromophores (including Cytochrome C Oxidase) absorption of photons, proton pumping and ATP production
- Increases Reactive Oxygen Species (ROS) production and mitochondrial signalling
- Induces Nitric Oxide (NO) production through absorption of photons by Nitric Oxide Synthase

Light Accelerated Orthodontics™

OrthoPulse® photobiomodulation stimulates the bone surrounding the roots of teeth, leading to faster tooth movement and decreased orthodontic treatment time. Biolux Research continues to sponsor and support research at leading research institutions including:

- Forsyth Institute, Harvard University affiliate, USA
- University of Southern California, USA
- Tufts University, USA
- University of Alberta, Canada
- University of Alabama, USA
- Boston University, USA

Clinical Research

Fixed Appliances (see page 11)
• No increase to root resorption compared to standard orthodontic treatment¹
• 54% reduction in time to achieve anterior alignment²
• 26% increase in rate of space closure in adults³
• 73% reduction of peak pain compared to sham-controls⁴
• Two-fold faster rate of tooth movement during alignment⁵

Aligners (see page 15)
• 63% reduction in the average time per aligner during OrthoPulse® treatment as compared to conventionally recommended aligner wear time⁶
• No measurable root resorption in six months⁶

Case Reports (see page 16)
• The use of OrthoPulse® allowed for faster aligner change rates compared to conventional protocol⁷
• Two long-distance OrthoPulse® patients, unable to attend frequent and regular appointments, were able to complete treatment more quickly than anticipated⁸
• A patient using OrthoPulse® changed aligners every three days throughout treatment and achieved successful results⁹

Cellular Research (see page 18)
• Increased gene expression in human cells¹⁰
• Increased proliferation of gingival fibroblasts and endothelial cells¹¹
• Increased proliferation and mineralization of human osteoblasts¹²

Animal Research (see page 19)
• Up to 3.7-fold faster rate of tooth movement¹³
• 80% less root resorption¹⁴
• Increased mature bone in expanded sutures¹⁵
• Lower failure rate of immediately loaded temporary anchorage devices (TADs)¹⁶
• Increased mandibular growth stimulation¹⁷
Physiology

“Photobiomodulation (PBM), also known as low-level level laser therapy, is the use of red and near-infrared light to stimulate healing, relieve pain, and reduce inflammation. The primary chromophores have been identified as cytochrome c oxidase in mitochondria and calcium ion channels (possibly mediated by light absorption by opsins). Secondary effects of photon absorption include increases in ATP, a brief burst of reactive oxygen species (ROS), an increase in nitric oxide, and modulation of calcium levels. Tertiary effects include activation of a wide range of transcription factors leading to improved cell survival, increased proliferation and migration, and new protein synthesis.

There is a pronounced biphasic dose response whereby low levels of light have stimulating effects, while high levels of light have inhibitory effects. It has been found that PBM can produce ROS in normal cells, but when used in oxidatively stressed cells or in animal models of disease, ROS levels are lowered. PBM is able to up-regulate anti-oxidant defenses and reduce oxidative stress. It was shown that PBM can activate NF-κB in normal quiescent cells, however in activated inflammatory cells, inflammatory markers were decreased.

One of the most reproducible effects of PBM is an overall reduction in inflammation, which is particularly important for disorders of the joints, traumatic injuries, lung disorders, and in the brain. PBM has been shown to reduce markers of M1 phenotype in activated macrophages. Many reports have shown reductions in reactive nitrogen species and prostaglandins in various animal models. PBM can reduce inflammation in the brain, abdominal fat, wounds, lungs, spinal cord.”


- “Light in the red to near infrared (NIR) range (600–1000 nm), generated by using low energy laser or light-emitting diode (LED) arrays, has been reported to have beneficial biological effects in many injury models. Such photobiomodulation has been observed to increase mitochondrial metabolism, facilitate wound healing and promote angiogenesis in skin, bone, nerve and skeletal muscle in primary neurons.”

- PubMed.gov (US National Library of Medicine | National Institutes of Health) lists over 3,000 peer-reviewed published articles on photobiomodulation (PBM) or low level light (laser) therapy (LLLT).
Mechanism of Action

Mechanisms thought to be involved in photobiomodulation biological response:

- Mitochondrial chromophores (including cytochrome c oxidase) absorb photons, pump protons and increase ATP production, thereby increasing energy available to the cell, and increases/normalizes metabolism.\(^{18}\)
- Reactive Oxygen Species (ROS) production and mitochondrial signalling stimulate/suppress transcription factors and DNA/RNA synthesis.\(^{18}\)
- Production of inducible NO through absorption of photons by nitric oxide synthase increases micro and regional blood flow and osteoclastic activity.\(^{18}\)

Otto Warburg discovered cytochrome c oxidase (CCO), the terminal enzyme in the mitochondrial oxidative respiration chain. He demonstrated that carbon monoxide inhibited CCO function could be displaced by a flash of light. Displacing carbon monoxide allows oxygen to bind again and resume CCO function and respiration.

Photobiomodulation activates CCO and increases mitochondrial electron transport which leads to increased ATP production.

- Eells et al.\(^{21}\) showed that CCO is the photoacceptor in the red to near-infrared spectral range.

Activation of CCO by light initiates intracellular signaling cascades, resulting in various cellular responses including ATP production in the mitochondria.

Action spectra of DNA and RNA synthesis rate matches CCO absorption spectra.

- Karu and Kolyakov\(^{22}\) performed experiments to find action spectra based on DNA and RNA synthesis rate. HeLa cell mono-layers were irradiated with monochromatic light of 580-860 nm.

**Exact action spectra for cellular responses relevant to phototherapy**

**Ad et al.**\(^{23}\) showed twofold increase in ATP production with one LLLT treatment

- **Method**: Human neuronal progenitor cells were grown in tissue culture and were treated by Ga-As laser (808 nm, 50 mW/cm\(^2\), 0.05 J/cm\(^2\)). ATP was determined at 10 min after laser application.
- **Result**: LLLT treatment group shows a twofold ATP production

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**FIG. 1.** Adenosine triphosphate (ATP) content in control versus laser treated neuronal progenitor cells. Results are expressed as mean ± standard error of the mean (SEM). \(n=6\). RLU, relative luminescent unit.
ATP production is driven by a high proton concentration in the inner mitochondrial membrane.

Stressed cells have decreased metabolism, thus lower proton concentration and lower ATP production.

Photobiomodulation increases ATP production by stimulating CCO to absorb photons and pump protons.

This increase in energy to the cell leads to greater metabolic activity.

What is Photobiomodulation?

**Mechanism of Action Schema**

**Summary of Key in vivo Orthodontic Findings**

- Low-level laser therapy (LLLT) accelerates bone regeneration in the midpalatal suture following palatal expansion in the rat model.
- Kawasaki and Shimizu concluded that low energy laser irradiation can accelerate tooth movement accompanied with alveolar bone remodeling in the rat model.
- The same effects were observed when the LLLT was applied to the rabbit model.

Fujita et al. demonstrated that laser irradiation stimulates the velocity of tooth movement via induction of RANK and RANKL in rats.

- Increased expression of fibronectin and Type I collagen in LLLT tooth movement in rats.
- Goulart et al. showed lower dosage (5 J/cm²) of LLLT accelerates dog premolar tooth movement; higher dosage (35 J/cm²) may retard it.
- LLLT accelerates the velocity of tooth movement via stimulation of the alveolar bone remodeling in rats.
- LLLT facilitates the velocity of tooth movement and MMP-9, cathepsin K, and integrin subunits of alpha(v)beta3 expression in rats.

LLLT significantly increases PDL cell proliferation, decreases PDL cell inflammation, and increases PDL OC activity.
Summary of Key in vivo Orthodontic Findings

- Low-level laser therapy (LLLT) accelerates bone regeneration in the midpalatal suture following palatal expansion in the rat model.\textsuperscript{24}
- Kawasaki and Shimizu\textsuperscript{25} concluded that low energy laser irradiation can accelerate tooth movement accompanied with alveolar bone remodeling in the rat model.
- The same effects were observed when the LLLT was applied to the rabbit model.\textsuperscript{26}
- Fujita et al.\textsuperscript{27} demonstrated that laser irradiation stimulates the velocity of tooth movement via induction of RANK and RANKL in rats.
  - Increased expression of fibronectin and Type I collagen in LLLT tooth movement in rats.\textsuperscript{28}
  - Goulart et al.\textsuperscript{29} showed lower dosage (5 J/cm\textsuperscript{2}) of LLLT accelerates dog premolar tooth movement; higher dosage (35 J/cm\textsuperscript{2}) may retard it.
  - LLLT accelerates the velocity of tooth movement via stimulation of the alveolar bone remodeling in rats.\textsuperscript{30}
  - LLLT facilitates the velocity of tooth movement and MMP-9, cathepsin K, and integrin subunits of alpha(v) beta3 expression in rats.\textsuperscript{31}

LLLT significantly increases periodontal ligament (PDL) cell proliferation, decreases PDL cell inflammation, and increases PDL OC activity.\textsuperscript{32}
2. Intra-oral photobiomodulation-induced orthodontic tooth alignment: A preliminary study

Shaughnessy T, Kantarci A, Kau CH, Skrenes D, Skrenes S, Ma D.
BMC Oral Health 2016, 16:3

Shaughnessy Orthodontics, Private Practice, Suwanee, GA, USA

Objective: Numerous strategies have been proposed to decrease orthodontic treatment time. Photobiomodulation (PBM) has previously been demonstrated to assist in this objective. The aim of this pilot study was to test if intraoral PBM increases the rate of tooth alignment and reduces the time required to resolve anterior dental crowding.

Materials and Methods: Nineteen orthodontic subjects with Class I or Class II malocclusion and Little’s Irregularity Index (LII) greater or equal to 3 mm were selected from a pool of applicants. The test group (n = 11) received daily PBM treatment with an intra-oral LED device in combination with orthodontic treatment, and the control group (n = 8) received only orthodontic treatment. The PBM device produced near-infrared light with a continuous 850 nm wavelength, generating an average daily energy density of 9.5 J/cm². LII was measured at the start (T0) of orthodontic treatment until alignment was reached (T1, where LII < 1 mm). The rate of anterior alignment and treatment time was determined for both groups.

Results: The mean alignment rate for the PBM group was significantly faster than that of the control group, with rates of 1.27 and 0.44 mm/week, respectively (p = 0.0002). Furthermore, the mean alignment treatment time was significantly shorter for the PBM group, which was achieved in 48 days, as compared to the control group, which was achieved in 104 days (p = 0.0049).

Conclusions: LED photobiomodulation therapy at 850 nm wavelength resulted in 1.7x more rapid maxillary anterior alignment.

1. Effect of photobiomodulation on maxillary decrowding and root resorption: A randomized clinical trial

Al-Okla N, Bader DM, Makki L.
APOS Trends Orthod 2018;8:86-91.

European University College, Department of Orthodontics, Dubai, United Arab Emirates.

Purpose: The effects of low-level laser therapy (LLLT) with light-emitting diode (LED) delivery (Biolux OrthoPulse® device) were tested for no differences from sham-controlled conventional orthodontics in maxillary anterior alignment treatment efficiency and maxillary central incisor root resorption after six months of treatment.

Materials and Methods: Two prospective clinical trial samples were matched for pretreatment irregularity index with (n = 14) and without (n = 12) photobiomodulation therapy (850 nm wavelength, 0.065 J/cm², 5 min per-arch-per-day) and examined every two weeks for reduction of irregularity index to <1 mm. The sham control sample was provided with LED devices that did not deliver infrared light. Standardized periapical radiographs of maxillary central incisors were compared at initial and six months of treatment.

Results: Photobiomodulation resolved maxillary anterior crowding with 35.2% greater efficiency (41.0 vs. 63.3 days, p= 0.028) at nearly double the tooth movement rate-per-week (1.02 vs. 62 mm/week, p = 0.045). Mean maxillary central incisor root length changes showed no significant difference at the six-month treatment interval after LLLT (0.45 vs. 0.19 mm, p = NS).

Conclusions: LED photobiomodulation therapy at 850 nm wavelength resulted in 1.7x more rapid maxillary anterior alignment.
3. Velocity of orthodontic active space closure with and without photobiomodulation therapy: a single-center, cluster randomized clinical trial


European University College, Department of Orthodontics, Dubai, United Arab Emirates.

N.B. This study utilized an early OrthoPulse® device with half the power density (33mW/cm²) of the current commercial product and only three minutes of treatment time per arch, versus five minutes as for the commercial product. The total energy density delivered in this study was 6 Joules/cm², versus 19.5 Joules/cm² for the commercial OrthoPulse® device.

Objective: The objective of this two-arm parallel-randomized clinical trial was to assess the effectiveness of low-level light therapy (also known as photobiomodulation) using an intra-oral light emitting diode (LED) device with respect to accelerating the rate of premolar extraction space closure during en-masse retraction. This trial was conducted between January 2013 and February 2014 in the department of orthodontics at European University College.

Materials and Methods: The study included 60 orthodontic patients (age range, 11.3 to 47.1 years; mean age, 20.4 years) with premolar extractions. Patients (n = 60) were randomized into the photobiomodulation (PBM) group (n = 30) and a control group (n = 30). Eligibility criteria included no active caries, good oral hygiene and an extraction orthodontic treatment plan. Extraction spaces were closed using NiTi closed springs utilizing (150 g) force. Extraction spaces were measured on study models and the date was recorded at the beginning of en-masse retraction (T1) and at space closure completion (T2).

Blinding: All of the measurements were obtained by a single investigator who was blinded to the allocation of study models to either group.

Outcome: The primary outcome was the velocity of extraction space closure (mm/month) during the period of en-masse retraction.

Randomization: Treatment allocation was implemented using simple randomization by asking each patient to draw from a sealed envelope (n = 60) indicating allocation to the PBM or control group. The allocation ratio was 1:1.

Intervention: PBM group of patients (n = 30) were treated with intra-oral infrared light therapy for three minutes per arch per day using OrthoPulse® (Biolux Research, Vancouver, Canada) during the en-masse retraction phase. Patients were required to maintain over 80% compliance with daily device use. Compliance was monitored by an inbuilt micro-processor embedded within
the device controller.

**Results:** Sixty patients were randomized between the two groups of which 15 patients dropped out during the study period. A total of 45 patients with 123 extraction spaces were included in the primary analysis of the PBM group (n = 23; mean age: 20.7 years) and the control group (n = 22; mean age: 18.3 years). Patients treated with PBM exhibited a statistically significant faster velocity of space closure by 0.276 mm/month, (p < 0.01, 95% CI (0.082 - 0.471)) over that of the control group. The mean velocity of space closure in the PBM group was (1.07 mm/month; SD 0.49) compared with the control group, which had an average velocity of (0.85 mm/month; SD 0.37).

**Harms:** No serious harms due to treatments were encountered during the study period.

**Conclusions:** The results of this study suggest that PBM therapy may accelerate the rate of orthodontic space closure during en-masse retraction.

**4. Pain perception of photobiomodulation treated and sham-controlled patients undergoing orthodontic treatment: A randomized clinical trial**


European University College, Department of Orthodontics, Dubai, United Arab Emirates.

**Objective:** To evaluate the effect of photobiomodulation on pain perception during orthodontic treatment.

**Materials and Methods:** A double-blind, sham-controlled, randomized clinical trial was conducted with 34 patients meeting the study inclusion criteria. Participants were block randomized to one of two groups in a 17/17 split: a photobiomodulation (PBM) group using a functional device or a sham-controlled (SC) group using a non-functional device. Every patient was blinded to whether they received a functional or non-functional device for use at home. Both groups were bonded with fixed orthodontic appliances and instructed to complete 10-minute daily device treatments. The experimental group received light emitting diode (LED) PBM therapy at a wavelength of 850 nm (average of 60 mW/cm² and 18 J/cm²). Patients rated pain intensity immediately after bonding then at 24, 36 and 72 hours after bonding. Two sample t-tests were performed to test the significance of the mean differences between the groups at each time point.

**Results:** Pain perceived was statistically significantly lower at every time point for patients treated with PBM. The PBM group reported 54%, 73% and 73% less pain than the SC group at Day 1, 2 and 3, respectively. Both groups showed peak pain 24 hours after bonding, whereby the mean pain intensity for the PBM group was 2.21 while the SC group reported 4.85.
Conclusions: Daily photobiomodulation self-treatments at home significantly lowered pain throughout the first 3 days of orthodontic treatment.

5. Photobiomodulation accelerates orthodontic alignment in the early phase of treatment

Kau CH, Kantarci A, Shaughnessy T, Vachiramon A, Santiwong P, De la Fuente A, Skrenes D, Ma D, Brawn P. Progress in Orthodontics 2013, 14:30

Department of Orthodontics, School of Dentistry, University of Alabama, Birmingham, AL, USA

Introduction: Numerous strategies have been proposed to decrease the treatment time a patient requires for orthodontic treatment. Recently, a number of device-accelerated therapies have emerged in orthodontics. Photobiomodulation is an emerging area of science that has clinical applications in a number of human biological processes.

Objective: The aim of this study was to determine if photobiomodulation reduces the treatment time in the alignment phase of orthodontic treatment.

Materials and Methods: This multicenter clinical trial was performed on 90 subjects (73 test subjects and 17 controls), and Little's Index of Irregularity (LII) was used as a measure of the rate of change of tooth movement. Subjects requiring orthodontic treatment were recruited into the study, and the LII was measured at regular time intervals. Test subjects used a device which produced near-infrared light with a continuous 850 nm wavelength. The surface of the cheek was irradiated with a power density of 60 mW/cm² for 20 or 30 min/day or 60 min/week to achieve total energy densities of 72, 108, or 216 J/cm², respectively. All subjects were fitted with traditional orthodontic brackets and wires. The wire sequences for each site were standardized to an initial round alignment wire (014 NiTi or 016 NiTi) and then advanced through a progression of stiffer arch wires until alignment occurred (LII < 1 mm).

Results: The mean LII scores at the start of the clinical trial for the test and control groups were 6.35 and 5.04 mm, respectively. Multi-level mixed effect regression analysis was performed on the data, and the mean rate of change in LII was 0.49 and 1.12 mm/week for the control and test groups, respectively.
Conclusions: Photobiomodulation produced clinically significant changes in the rates of tooth movement as compared to the control group during the alignment phase of orthodontic treatment.

Figure: Box plots showing differences in alignment rates (mm/week) between control and test (LAO) patients. The box plots were created using arch level data to provide a more accurate weighting of alignment rates over total treatment time. Arch level summaries and Wilcoxon rank-sum tests revealed that the combined LAO arches started at a higher average LII (8.39 mm versus 6.67 mm). There was no statistically significant difference between the two groups in terms of destination LII. Outliers (rates greater than 3 mm/week) were removed from the test group to make these figures more conservative. The test group’s mean alignment rates were 0.99 mm/week compared to a control rate of 0.44 mm/week, with a comparison group of 23 control arches and 111 treatment arches.

CLINICAL RESEARCH
Aligners

6. A randomized controlled crossover trial on the effect of OrthoPulse® on the rate of aligner progression during alignment with Invisalign® aligners

Dickerson T.
Data on file.
Dickerson Orthodontics, Private Practice, Chandler, AZ, USA

Introduction: Photobiomodulation (PBM) has previously been demonstrated to accelerate tooth movement in traditional orthodontic treatment. However, it has not yet been tested in conjunction with Invisalign® aligners. The aim of this study was to assess if PBM treatment can reduce the average wearing duration required for 14-day recommended aligners.

Effectiveness Objective: To compare progression rate in days per aligner during baseline and OrthoPulse® periods during aligner orthodontic treatment.

Safety Objective: To assess the safety of the device by observing the degree of root resorption, as well as by freedom from any significant adverse events during the course of OrthoPulse® treatment.

Study Population: A total of 32 patients, from 14 to 59 years old, received Invisalign® treatment in conjunction with five-minute daily OrthoPulse® treatments (OP), per arch.

Results: The aligner progression rates of the 32 patients were 7.7 and 5.2 days/aligner for the baseline and OrthoPulse® periods, respectively. This indicates that the rate of aligner switching during the OrthoPulse® period was 1.5-fold faster than that of the baseline period, with significance (p-value < 0.0001). The presence of period effects were not supported. Carryover effects were also undetected, likely due to the adequate washout period utilized in our study.

The overall mean EARR was -0.673 mm, indicating marginal root elongation rather than resorption. Thus, no mean root resorption was detected after six months of OrthoPulse® treatment. There was no gingival recession, pathological tooth mobility and post-orthodontic relapse reported by the PI at any point during the course of the study.

There were no patients discontinued from the study due to negative adverse events. There were no adverse events or side effects reported in this study, and none of the patients reported using anything beyond OTC medication to alleviate tooth and mouth discomfort.
Conclusions: OrthoPulse® may be used to increase the rate of aligner progression and decrease treatment time for aligner treatment with no measurable root resorption after six months.

CLINICAL RESEARCH
Case Reports

7. Invisalign with photobiomodulation: Optimizing tooth movement and treatment efficacy with a novel self-assessment algorithm

Dickerson T. 
Dickerson Orthodontics, Private Practice, Chandler, AZ, USA

The two patients presented in this article demonstrate not only the variability among individuals in rates of tooth movement and optimal aligner changes, but the potential benefits of LED photobiomodulation administration in accelerating Invisalign® treatment. By utilizing the new self-assessment algorithm, we can tailor our biomechanics to each patient’s unique biology.

When teeth have moved to their programmed positions, the aligner will no longer apply force, and the patient will perceive a low pressure. This is why aligner pressure as rated by the patient was used to determine the optimal rate of aligner change for that individual. Although an increase in pressure tolerance could have occurred, leading to premature aligner changes, each patient was instructed to remove and clean the aligners before placing them back in the mouth and rating the pressure. Furthermore, the orthodontist consistently monitored aligner tracking to prevent premature switching. Both patients maintained tracking throughout treatment, as demonstrated by their positive results.

In both cases, adjunctive OrthoPulse® use allowed substantially faster aligner changes than under the conventional protocol. The efficacy of this PBM device was confirmed in previous studies by Shaughnessy et al as well as Kau et al. PBM devices using laser light sources have also been shown to be effective in accelerating tooth movement. Although the safety of faster aligner changes may be more of a concern, a previous study of accelerated orthodontic treatment with PBM found no increase in root resorption. Our two patients showed no adverse effects from PBM and neither has experienced any orthodontic relapse.
8. Long distance orthodontic treatment with adjunctive light therapy

Shaughnessy T. 

Shaughnessy Orthodontics, Private Practice, Marietta, GA, USA

Accelerated treatment is not only advantageous for patients concerned about treatment duration, but also for patients who are unable to frequently and regularly attend orthodontic appointments. Efficient tooth movement during the longer appointment intervals becomes even more important in reducing treatment time. This paper chronicles the orthodontic treatment of two long-distance patients who were treated successfully and time-efficiently with LLLT. Both patients used OrthoPulse, a removable intraoral device that emits a continuous light of 850 nm wavelength, in conjunction with comprehensive fixed appliance therapy.

9. Invisalign treatment accelerated by photobiomodulation

Ojima K, Dan C, Kumagai Y, Schupp W.

Hongo Sakura Ortho, Private Practice, Tokyo, Japan.

OrthoPulse® was used in combination with Invisalign® to treat a difficult malocclusion. Although the ClinCheck® was designed for the usual two-week aligner wear period, PBM allowed the aligners to be changed every three days. The patient was instructed to use the appliance for five minutes per arch each day; cooperation was monitored remotely using a unique app in the OrthoPulse® charging base that communicates through the Internet with the doctor’s office. The authors believe the patient's ability to change aligners every three days improved her compliance. Aligner fit was checked at each appointment to ensure the teeth were tracking properly. In this way, an Invisalign® treatment originally planned for 92 weeks (46 sets of aligners) was completed in six months.
CELLULAR RESEARCH

10. Visible red and infrared light alters gene expression in human marrow stromal fibroblast cells

Guo J, Wang Q, Wai D, Zhang QZ, Shi SH, Le AD, Shi ST, Yen SL.

Center for Craniofacial Molecular Biology, Ostrow School of Dentistry, University of Southern California, Los Angeles, CA, USA; Department of Orthodontics, School of Stomatology, Shandong University, Jinan, China.

Objectives: This study tested whether or not gene expression in human marrow stromal fibroblast (MSF) cells depends on light wavelength and energy density.

Materials and Methods: Primary cultures of isolated human bone marrow stem cells (hBMSC) were exposed to visible red (VR, 633 nm) and infrared (IR, 830 nm) radiation wavelengths from a light emitting diode (LED) over a range of energy densities (0.5, 1.0, 1.5, and 2.0 J/cm²). Cultured cells were assayed for cell proliferation, osteogenic potential, adipogenesis, mRNA and protein content. mRNA was analyzed by microarray and compared among different wavelengths and energy densities. Mesenchymal and epithelial cell responses were compared to determine whether responses were cell type specific. Protein array analysis was used to further analyze key pathways identified by microarrays.

Results: Different wavelengths and energy densities produced unique sets of genes identified by microarray analysis. Pathway analysis pointed to TGF-beta 1 in the visible red and Akt 1 in the infrared wavelengths as key pathways to study. TGF-beta protein arrays suggested switching from canonical to non-canonical TGF-beta pathways with increases to longer IR wavelengths. Microarrays suggest RANKL and MMP 10 followed IR energy density dose-response curves. Epithelial and mesenchymal cells respond differently to stimulation by light suggesting cell type-specific response is possible.

Conclusions: These studies demonstrate differential gene expression with different wavelengths, energy densities and cell types. These differences in gene expression have the potential to be exploited for therapeutic purposes and can help explain contradictory results in the literature when wavelengths, energy densities and cell types differ.

11. Photobiostimulation of gingival fibroblast and vascular endothelial cell proliferation

Iscan D, Mendes R, Kantarci A.
Presented at Annual Meeting of Turkish Society of Orthodontics, October 26-30, 2014 Ankara, Turkey.

ForSyth Institute, Cambridge, MA, USA
Marmara University, Istanbul, Turkey

Objective: Photobiomodulation is a non-invasive method for accelerated orthodontic tooth movement. LED treatment (LEDT) increases the rate of tooth movement by more than twofold, compared to the conventional techniques. The mechanism of action at the cellular level however, is unclear. The aim of this study was to investigate the impact of LEDT on the proliferation of human gingival fibroblasts (HGF) and vascular endothelial cells (HUVEC) in vitro.

Materials and Methods: HGF and HUVECs were plated in 96 well-plates with a concentration of 104 cells per well. The setup was designed to irradiate the cell layer directly, with a distance of 2.5 cm below the plate. The near infrared light source had a continuous wavelength of 850 nm and a power density of 60 mW/cm². Group 1 samples were irradiated every day for one minute while Group 2 samples were irradiated for 10 minutes during eight days of experiment. Proliferation and viability of the cells were evaluated by the MTT assay.

Results: The impact was mostly similar for both cell lines. Viable number of HGF cells increased for irradiated groups in 24 hours, while HUVEC cells were not affected for the first 72 hours. There was an increase in cell proliferation in response to one-minute irradiation and a decrease in the 10-minute irradiation group in comparison with control groups.

Conclusions: This data suggests that while a low dose exposure to LEDT stimulates the proliferation of gingival fibroblasts and endothelial cells, higher exposure inhibits their growth and the impact of LEDT is dose-dependent.
12. Human osteoblast response to LED photobiomodulation

Le A, Mendes RT, Iscan D, Pamuk F, Hasturk H, A. Kantarci A.  

**Objectives:** Photobiomodulation is a non-invasive method for accelerated orthodontic tooth movement. Photobiomodulation is known to increase the rate of tooth movement by more than twofold compared to conventional techniques. The mechanism of action at the cellular level however, remains unclear. The aim of this study was to investigate the effect of photobiomodulation on the proliferation and mineralization of human osteoblasts *in vitro*.

**Methods:** Human osteoblasts were seeded and cultured in a concentration of 104 cells per well. A near infrared light source with a continuous wavelength of 850 nm and a power density of 60 mW/cm² was used to irradiate the cell layer directly, with a distance of 2.5 cm below the plate. The samples were divided into three groups per plate: Group 1 – one-minute daily radiation for nine days; Group 2 – 10-minute radiation only at Days 1 and 5 and Group 3 – control (no radiation). MTT assay was used to study the proliferation and viability of cells for 9 days over the course of the experiment (5 weeks). Alkaline phosphatase (ALP) activity was measured once a week.

**Results:** Photobiomodulation increased osteoblast proliferation in a dose-dependent manner. Ten-minute radiation resulted in a significantly higher proliferation compared to control and one-minute radiation (*p* < 0.05). At Day 5, proliferation in Group 1 was 1.8-fold higher than the control and remained higher up to Day 8 (*p* < 0.05). After Day 8, all groups showed a decrease in proliferation. Photobiomodulation also dose-dependently increased the ALP activity, which was higher for Group 2 during the first three weeks. At Week 5, however, one-minute radiation resulted in the highest ALP activity (1.8-fold higher than Group 2 and 4.4-fold higher than the control; *p* < 0.05).

**Conclusions:** The data suggests that photobiomodulation stimulates the proliferation and mineralization of human osteoblasts by modulating their activity.

13. Photobiomodulation-induced orthodontic tooth movement

Chiari S, Baloul S, Goguet-Surmenian E, Dyke T, A. Kantarci A.  
*Data on file.*

**Objective:** The study has been designed to assess the effect of LED radiation versus NIR-laser radiation phototherapy on the rate of the orthodontic tooth movement and the biological impact in the rat model.

**Materials and Methods:** Nineteen healthy adult CRL-CD male rats with a body weight of 350-400 g were used as experimental animals. The orthodontic appliances were placed to mesially move the left maxillary first molar. The test animals in phototherapy groups received LED or laser applications daily while the stability of the orthodontic appliances were constantly checked under isoflurane anesthesia. All animals were constantly monitored for 21 days. Two different application times were selected to deliver the two different doses: 333 seconds (5 minutes and 33 seconds) or 1000 seconds (16 minutes and 40 seconds) and the photobiomodulation test groups were designated as LED-Short, Laser-Short, LED-Long, or Laser-Long accordingly. For animals in the LED-Short group, the device was applied for a cumulative energy dose of 10 J/cm²; for the LED-Long group for 30 J/cm²; for animals in the Laser-Short group for 10 J/cm²; and for the Laser-Long group for 30 J/cm².

**Results:** The Faxitron analyses demonstrated that mesial movement of the first molar in three (LED-Long, Laser-Short, Laser-Long: 1.46 to 1.88 mm) of the four test groups with light application compared was significantly enhanced compared to the tooth movement (0.51 ± 0.05 mm) alone (*p* < 0.05). The magnitude of movement in the fourth group (LED-Short) was also higher (1.17 ± 0.70 mm) compared to the TM group but the difference was not statistically significant. Collectively, all light application groups resulted in significantly more tooth movement compared to the TM group (*p* < 0.05). When NIR (LASER) groups were compared to LED-treated groups, there was no statistically significant difference.
Conclusions: Both phototherapy methods have the potential for accelerating orthodontic tooth movement with an increase of bone remodeling in the interradicular area. NIR-Laser irradiation and an increased application time per day lead to a more predictable tooth movement. LED application, however, provides a lower velocity compared to laser application but the tooth movement can be considered of a higher quality, as indicated by the high bone regeneration and the bodily movement of the mesialized tooth, and the less resorptive activity in the distance, in the third molar region. No negative effects due to light penetration could be found in any group.

14. Effect of LED-mediated-photobiomodulation therapy on orthodontic tooth movement and root resorption in rats

Ekizer A, Uysal T, Guray E.

Faculty of Dentistry, Department of Orthodontics, Erciyes University, Kayseri, Turkey.

Objective: The aim of this experimental study was to evaluate the effects of light-emitting diode-mediated-photobiomodulation therapy (LPT), on the rate of orthodontic tooth movement (TM) and orthodontically induced root resorption, in rats.

Materials and Methods: Twenty male 12-week-old Wistar rats were separated into two groups (control and LPT) and 50 cN of force was applied between maxillary left molar and incisor with a coil spring. In the treatment group, LPT was applied with an energy density of 20 mW/cm², over a period of 10 consecutive days, directly over the movement of the first molar tooth area. The distance between the teeth was measured with a digital caliper on days 0 (T0), 10 (T1), and 21 (T2) on dental cast models. The surface area of root resorption lacunae was measured histomorphometrically using digital photomicrographs. Mann–Whitney U and Wilcoxon tests were used for statistical evaluation at $p < 0.05$ level.

Results: TM during two different time intervals (T1–T0 and T2–T1) were compared for both groups and a statistically significant difference was found in the LPT group ($p = 0.016$). The TM amount at the first time period (1.31 ± 0.36 mm) was significantly higher than the second time period (0.24 ± 0.23 mm) in the LPT group. Statistical analysis showed significant differences between two groups after treatment/observation period ($p = 0.017$). The magnitude of movement in the treatment group was higher (1.55 ± 0.33 mm) compared to the control group (1.06 ± 0.35 mm). Histomorphometric analysis of root resorption, expressed as a percentage, showed that the average relative root resorption affecting the maxillary molars on the TM side was 0.098 ± 0.066 in the LPT group and 0.494 ± 0.224 in the control group. Statistically significant inhibition of root resorption with LPT was determined ($p < 0.001$) on the TM side.

Conclusions: The LPT method has the potential of accelerating orthodontic tooth movement and inhibitory effects on orthodontically induced resorptive activity.
15. Light-emitting diode photobiomodulation: Effect on bone formation in orthopedically expanded suture in rats-early bone changes


Faculty of Dentistry, Department of Orthodontics, Erciyes University, Kayseri, Turkey.

Objectives: The aim of this experimental study was to evaluate histomorphometrically the effects of light-emitting diode (LED) photobiomodulation therapy (LPT) on bone formation in response to expansion of the intermaxillary suture in rats.

Materials and Methods: Twenty male, 50- to 60-day-old Wistar rats were divided into two equal groups (control and experimental). Both groups were subjected to expansion for five days, and 50 cN of force was applied to the maxillary incisors with helical spring. An OsseoPulse® LED device, 618 nm wavelength and 20 mW/cm² output power irradiation, was applied to the intermaxillary suture for 10 days. Bone formation in the sutured area was histomorphometrically evaluated, including the amount of new bone formation (in square micrometers), number of osteoblasts, number of osteoclasts, and number of vessels. Mann-Whitney U test was used for statistical evaluation at \( p < 0.025 \) level. Significant differences were found between groups for all investigated histomorphometric parameters.

Results: New bone formation area \( (p = 0.024, 1.48\text{-fold}) \), number of osteoblasts \( (p < 0.001, 1.59\text{-fold}) \), number of osteoclasts \( (p = 0.004, 1.43\text{-fold}) \), and number of vessels \( (p = 0.007, 1.67\text{-fold}) \) showed higher values in the experimental group than the control. Bone histomorphometric measurements revealed that bone architecture in the LPT group was improved.

Conclusions: The application of LPT can stimulate bone formation in the orthopedically expanded intermaxillary suture during expansion and the early phase of the retention periods.

16. Resonance frequency analysis of orthodontic miniscrews subjected to light-emitting diode photobiomodulation therapy


Department of Orthodontics, Faculty of Dentistry, Erciyes University, Kayseri, Turkey.

Objective: The aim of this prospective experimental study was to evaluate the effect of light-emitting diode (LED) photobiomodulation therapy (LPT) on the stability of immediately loaded miniscrews under different force levels, as assessed by resonance frequency analysis (RFA).

Materials and Methods: Sixty titanium orthodontic miniscrews with a length of 8 mm and a diameter of 1.4 mm were implanted into cortical bone by closed flap technique in each proximal tibia of 15 New Zealand white adult male rabbits \( (n = 30) \). The animals were randomly divided into irradiated and control groups under different force levels \( (0, 150, \text{ and } 300 \text{ cN}) \). OsseoPulse® LED device (Biolux Research Ltd.), of 618 nm wavelength and 20 mW/cm² power output irradiation (20 minutes/day), was applied to the miniscrews for 10 days. The RFA records were performed at miniscrew insertion session \( (T1) \) and 21 days after surgery \( (T2) \). Wilcoxon and Mann-Whitney U-tests were used for statistical evaluation at \( p < 0.005 \) level.

Results: It was found that initial primer stability of all miniscrews was similar in all groups at the start of the experimental procedure. Statistically significant differences were found for changes in implant stability quotient (ISQ) values between LED-photobiomodulated group and the control \( (0 \text{ cN}, p = 0.001; 150 \text{ cN}, p < 0.001; \text{ and } 300 \text{ cN}, p < 0.001) \). Significant increase was found in ISQ values of LPT-applied miniscrews under 0 cN \( (+11.63 \text{ ISQ}) \), 150 cN \( (+10.50 \text{ ISQ}) \), and 300 cN \( (+7.00 \text{ ISQ}) \) force during observation period. By the increase of force levels, it was determined that ISQ values decreased in non-irradiated control miniscrews.
Conclusions: Within the limits of this in vivo study, the present RFA findings suggest that LPT might have a favourable effect on healing and attachment of titanium orthodontic miniscrews.

17. The effect of light-emitting diode and laser on mandibular growth in rats

El-Bialy T, Alhadlaq A, Felemban N, Yeung J, Ebrahim A, H Hassan A.

Associate Professor, Department of Orthodontics, School of Dentistry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada.

Objective: To evaluate the effect of a light-emitting diode (LED) and/or low-level laser (LLL) with or without the use of anterior bite jumping appliances (also known as functional appliances [FAs]) on mandibular growth in rats.

Materials and Methods: Thirty-six 8-week-old male Sprague-Dawley rats weighing 200 g were obtained from Charles River Canada (St. Constant, QC, Canada) and were divided into six groups of six animals each. Groups were as follows: group 1: LLL; group 2: LLL + FA; group 3: LED; group 4: LED + FA; group 5: FA; and group 6: control (no treatment). Mandibular growth was evaluated by histomorphometric and micro-computed tomographic (microCT) analyses.

Results: The LED and LED + FA groups showed an increase in all condylar tissue parameters compared with other groups.

Conclusions: The LED-treated groups showed more mandibular growth stimulation compared with the laser groups.
Impact of LED photobiomodulation on the gene expression profile of PDL cells under simulated inflammation

Konermann A, Jäger A, Nguyen D, Kantarci A.

*Data on file*

Department of Orthodontics, Medical Faculty, University of Bonn, Bonn, Germany

**Objective:** This study was designed to investigate the impact of LED treatment (LEDT) on the expression of osteogenic differentiation markers, inflammatory cytokines, and molecules involved in tissue metabolism in periodontal ligament (PDL) cells subjected to inflammatory challenge. The hypothesis was that inflammatory processes occurring during orthodontic tooth movement regulate PDL cell responses, which in turn might determine bone turnover.

**Material and Methods:** Human PDL cells were challenged with Interleukin (IL-) 1ß, Tumor Necrosis Factor (TNF) α, or Transforming Growth Factor (TGF) β1. Cells were irradiated with a LEDT device at a wavelength of 850 nm and a power density of 60 mW/cm² for 10 minutes either directly before application of the cytokine stimuli to mimic prophylactic irradiation, or 18 hours after the challenge to simulate therapeutic irradiation in an inflammatory milieu. Quantitative real-time polymerase chain reaction (Q-PCR) was performed for family with sequence similarity 5, member C (FAM5C), osteocalcin, S100A4, IL-1ß, TGFβ1, tissue inhibitor of metalloproteinase-1 (TIMP1), and TIMP2. Statistical analysis was performed using one-way ANOVA and Bonferroni post-hoc test (*p* < 0.05).

**Results:** FAM5C, undetected in resting cells, was induced 4.2-fold by TGFβ1. LEDT increased FAM5C expression by 6.5-fold when applied simultaneously with TGFβ1. Osteocalcin was significantly downregulated by IL-1ß+LEDT. When PDL cells were first challenged with TNFα and exposed to LEDT after 18 hours, osteocalcin was significantly reduced. LEDT did not have any significant impact on the expression of S100A4 or TGFβ1 alone while it decreased the baseline expression of IL-1ß. LEDT further prevented and reduced the upregulation of IL-1ß when cells were challenged with IL-1ß. IL-1ß upregulation by TNF-α was enhanced when LEDT was simultaneously applied (40.7-fold) or when the cells were first challenged with TNF-α and exposed to the LEDT after 18 hours (31-fold). TIMP1 and TIMP2 were significantly reduced by inflammatory cytokines. LEDT further decreased the inflammatory cytokine-suppressed TIMP1 and TIMP2 expression.

**Conclusions:** These data suggest that LEDT modulates the PDL cell response under resting and inflammatory conditions, which could determine the local tissue homeostasis and remodeling processes in the periodontium during orthodontic tooth movement.
The nuts and bolts of low-level laser (light) therapy

Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR. 
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA, USA

Abstract: Soon after the discovery of lasers in the 1960s it was realized that laser therapy had the potential to improve wound healing and reduce pain, inflammation and swelling. In recent years, the field, sometimes known as photobiomodulation, has broadened to include light-emitting diodes and other light sources, and the range of wavelengths used now includes many in the red and near-infrared. The term “low level laser therapy” or LLLT has become widely recognized and implies the existence of the biphasic dose response or the Arndt-Schulz curve. This review will cover the mechanisms of action of LLLT at cellular and tissular levels and will summarize the various light sources and principles of dosimetry that are employed in clinical practice. The range of diseases, injuries, and conditions that can be benefited by LLLT will be summarized with an emphasis on those that have reported randomized controlled clinical trials. Serious life-threatening diseases such as stroke, heart attack, spinal cord injury, and traumatic brain injury may soon be amenable to LLLT therapy.

Low-energy laser irradiation facilitates the velocity of tooth movement and the expressions of matrix metalloproteinase-9, cathepsin K, and \( \alpha(3) \beta(3) \) integrin in rats

Yamaguchi M, Hayashi M, Fujita S, Yoshida T, Utsunomiya T, Yamamoto H, Kasai K. 
Department of Orthodontics, Nihon University School of Dentistry at Matsudo, Chiba, Japan

Abstract: It has previously been reported that low-energy laser irradiation stimulated the velocity of tooth movement via the receptor activator of nuclear factor kappa B (RANK)/RANK ligand and the macrophage colony-stimulating factor (c-Fms) systems. Matrix metalloproteinase (MMP)-9, cathepsin K, and \( \alpha(3) \beta(3) \) integrin are essential for osteoclastogenesis; therefore, the present study was designed to examine the effects of low-energy laser irradiation on the expression of MMP-9, cathepsin K, and \( \alpha(3) \beta(3) \) integrin during experimental tooth movement. Fifty male, 6-week-old Wistar strain rats were used in the experiment. A total force of 10 g was applied to the rat molars to induce tooth movement. A Ga-Al-As diode laser was used to irradiate the area around the moving tooth and, after seven days, the amount of tooth movement was measured. To determine the amount of tooth movement, plaster models of the maxillae were made using a silicone impression material before (Day 0) and after tooth movement (Days 1, 2, 3, 4, and 7). The models were scanned using a contact-type three-dimensional (3-D) measurement apparatus. Immunohistochemical staining for MMP-9, cathepsin K, and integrin subunits of \( \alpha(3) \beta(3) \) was performed. Intergroup comparisons of the average values were conducted with a Mann-Whitney U-test for tooth movement and the number of tartrate-resistant acid phosphatase (TRAP), MMP-9, cathepsin K, and integrin subunits of \( \alpha(3) \beta(3) \) was performed. In the laser-irradiated group, the amount of tooth movement was significantly greater than that in the non-irradiated group at the end of the experiment (\( p < 0.05 \)). Cells positively stained with TRAP, MMP-9, cathepsin K, and integrin subunits of \( \alpha(3) \beta(3) \) were found to be significantly increased in the irradiated group on Days 2-7 compared with those in the non-irradiated group (\( p < 0.05 \)). These findings suggest that low-energy laser irradiation facilitates the velocity of tooth movement and MMP-9, cathepsin K, and integrin subunits of \( \alpha(3) \beta(3) \) expression in rats.
Metrical and histological investigation of the effects of low-level laser therapy on orthodontic tooth movement

Department of Orthodontics, Faculty of Dentistry, Cumhuriyet University, Sivas, Turkey

Abstract: The aim of this study was to evaluate the effects of 820 nm diode laser on osteoclastic and osteoblastic cell proliferation-activity and RANKL/OPG release during orthodontic tooth movement. Thirty-eight albino Wistar rats were used for this experiment. Maxillary incisors of the subjects were moved orthodontically by a helical spring with force of 20 g. An 820 nm Ga-Al-As diode laser, with an output power of 100 mW; and a fiber probe, with spot size of 2 mm in diameter; were used for laser treatment and irradiations were performed on five points at the distal side of the tooth root on the first, second, and third days of the experiment. Group I received no laser energy. Total laser energy of 54 J (100 mW, 3.18 W/cm², 1717.2 J/cm²) was applied to Group II and a total of 15 J (100 mW, 3.18 W/cm², 477 J/cm²) to Group III. The experiment lasted for eight days. The number of osteoclasts, osteoblasts, inflammatory cells and capillaries, and new bone formation were evaluated histologically. Besides immunohistochemical staining of PCNA, RANKL and OPG were also performed. No statistical difference was found for the amount of tooth movement in between the control and study groups (p > 0.05). The number of osteoclasts, osteoblasts, inflammatory cells, capillary vascularization, and new bone formation were found to be increased significantly in Group II (p < 0.05). Immunohistochemical staining findings showed that RANKL immunoreactivity was stronger in Group II than in the other groups. As to OPG immunoreactivity, no difference was found between the groups. Immunohistochemical parameters were higher in Group III than in Group I, while both were lower than Group II. On the basis of these findings, low-level laser irradiation accelerates the bone remodeling process by stimulating osteoblastic and osteoclastic cell proliferation and function during orthodontic tooth movement.

Tooth movement in orthodontic treatment with low-level laser therapy: A systematic review of human and animal studies

Human Anatomy and Embryology Unit, HUBc, University of Barcelona, Barcelona, Spain.

Objective: This review attempts to organize the existing published literature regarding tooth movement in orthodontic treatment when low-level laser therapy (LLLT) is applied.

Background Data: The literature discusses different methods that have been developed to motivate the remodeling and decrease the duration of orthodontic treatment. The application of LLLT has been introduced to favor the biomechanics of tooth movements. However there is disagreement between authors as to whether LLLT reduces orthodontic treatment time, and the parameters that are used vary.

Materials and methods: Studies in humans and animals, in which LLLT was applied to increase the dental movement, were reviewed. Three reviewers selected the articles. The resulting studies were analyzed according to the parameters used in the application of laser and existing changes clinically and histopathologically.

Results: Out of 84 studies, five human studies were selected in which canine traction had been performed after removing a premolar, and 11 studies in rats were selected in which first premolar traction was realized. There were statistically significant changes in four human studies and eight animal studies.

Conclusions: Varying the wavelength with a reasonable dose in the target zone leads to obtaining the desired biological effect and achieving a reduction of the orthodontic treatment time, although there are studies that do not demonstrate any benefit according to their values.
Long-term safety of low-level laser therapy at different power densities and single or multiple applications to the bone marrow in mice


Department of Zoology, The George S. Wise Faculty of Life Sciences, Tel-Aviv University, Tel-Aviv, Israel.

**Objective:** The purpose of this study was to determine the long-term safety effect of low-level laser therapy (LLLT) to the bone marrow (BM) in mice.

**Background Data:** LLLT has been shown to have a photobiostimulatory effect on various cellular processes and on stem cells. It was recently shown that applying LLLT to BM in rats post-myocardial infarction caused a marked reduction of scar tissue formation in the heart.

**Methods:** Eighty-three mice were divided into five groups: control sham-treated and laser-treated at measured density of either 4, 10, 18, or 40 mW/cm² at the BM level. The laser was applied to the exposed flat medial part of the tibia 8 mm from the knee joint for 100 sec. Mice were monitored for eight months and then killed, and histopathology was performed on various organs.

**Results:** No histological differences were observed in the liver, kidneys, brain or BM of the laser-treated mice as compared with the sham-treated, control mice. Moreover, no neoplastic response in the tissues was observed in the laser-treated groups as compared with the control, sham-treated mice. There were no significant histopathological differences among the same organs under different laser treatment regimes in response to the BM-derived mesenchymal stem cell proliferation following LLLT to the BM.

**Conclusions:** LLLT applied multiple times either at the optimal dose (which induces photobiostimulation of stem cells in the BM), or at a higher dose (such as five times the optimal dose), does not cause histopathological changes or neoplastic response in various organs in mice, as examined over a period of eight months.
References


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Biolux Research
230-825 Powell Street
Vancouver BC, Canada V6A 1H7

bioluxresearch.com
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