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Photomodulation

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

Light Accelerated Orthodontics

OrthoPulse™ photobiomodulation enhances and accelerates bone and soft tissue remodeling leading to faster tooth movement and decreased orthodontic treatment time.

Biolux sponsors and supports research at these leading research institutions:
- Forsyth Institute, USA
- University of Alabama at Birmingham, USA
- University of Southern California, USA
- Kyung Hee University, Korea
- European University College, UAE
- University of Sydney, Australia
- Tufts University, USA

Since 2003, Biolux has sponsored over 20 university- and clinician-based in vitro, in vivo studies and clinical trials.

400+ patients treated in clinical trials worldwide.

Clinical Research

Fixed Appliances

- No clinically significant root resorption
- 46% increase in rate of space closure in adults; 28% increase in rate of space closure in adolescents compared to control
- 54% reduction in time to achieve anterior alignment
- 2.3x faster mean alignment rate

2 Samara et al. Velocity of en-masse space closure with and without Photobiomodulation: a prospective RCT. In review.
4 Kau et al. Photobiomodulation accelerates orthodontic alignment in the early phase of treatment. Prog in Ortho., 14:30. 2013

Aligners

- 66% reduction in the average duration per aligner during OrthoPulse™ treatment as compared to the conventionally recommended aligner wear duration
- No measurable root resorption in 6 months

1 Dickerson, T. The effect of OrthoPulse™ on the rate of progression through Invisalign® aligners: a pilot study. To be submitted for publication.
2 Dickerson, T. A randomized controlled crossover trial on the effect of OrthoPulse™ on the rate of orthodontic tooth movement during alignment with Invisalign® aligners. To be submitted for publication.

Refer to Section 5
**Cellular (in vitro) Research**

- Modulated gene expression in human MSF cells¹
- Increased proliferation of gingival fibroblasts and endothelial cells²
- Stimulated proliferation and mineralization of human osteoblasts³
- Inflamed PDL cell response modulated⁴


⁴ Konerman et al. *Impact of LED photobiomodulation on the gene expression profile of PDL cells under simulated inflammation*. To be submitted for publication.

**Refer to Section 6**

**Animal (in vivo) Research**

- 46% acceleration of tooth movement in 620nm treated animals & 80% less root resorption¹
- Significantly more mature bone in expanded sutures²
- Significantly lower failure rate of immediately loaded TADs³
- 2.8 – 3.7x faster rate of tooth movement⁴


⁴ Chiari S et al. *Photobiomodulation-induced tooth movement using extra-oral transcutaneous phototherapy on the rat periodontium*. To be submitted for publication.

**Refer to Section 6**
Introduction

Orthodontic therapy is predictable\(^1\) where conventional methods result in the completion of treatment in 12 to 24 months and a variable follow-up period for retention. One of the common deterrents to orthodontic treatment is the length of time in which a patient needs to commit. Thus, there has been a continuous search for methods to enhance the rate and efficacy of orthodontic tooth movement\(^2,3\). At present, there are three main strategies to improve treatment efficiency.

The first approach is to create an accurate road map of the end point of orthodontic treatment and utilize sophisticated three-dimensional virtual plans to simulate and predict the possible pitfalls in a case\(^4\). Often, these provide the shortest pathway between the initial, malaligned tooth position and its final, corrected position, providing an excellent visualization for the delivery of the best biomechanical plan and serving for patient education.

A second approach aims to increase the rate of orthodontic tooth movement through biologically-based techniques\(^6,7\). One of the best-characterized methods is surgical corticotomy-accelerated orthodontics\(^8-11\). Clinicians raise surgical flaps around the dentoalveolar complex and create selective buccal and lingual decortications of the alveolar bone using rotary and hand instruments or piezoelectricity\(^12\). Active orthodontic treatment is applied almost immediately. While results from available data have been variable\(^13-16\), the most important finding was that there is a window of intervention for accelerated tooth movement following surgical procedures. Once the wound resolution of the corticotomy sites is completed, the ‘accelerated’ tooth movement returns to the rates of the control sites\(^17-19\). Surgery, even if it is highly effective and predictable, potentially carries the risk for morbidity and needs to be carefully planned with the orthodontic protocol and precisely timed for maximum effect during the course of treatment. In addition, beyond the clinical case series and anecdotal evidence, randomized clinical trials are required for
an accurate assessment of the outcomes of surgical corticotomies in humans. Nonsurgical alternatives to the highly invasive surgical methods have been explored. Endothelial growth factors, osteoclast precursors like osteocalcin, prostaglandins, bone resorptive factors like RANKL, leukotrienes, and macrophage colony-stimulating factors have been tested. Studies in these areas are limited, which makes understanding these mechanisms difficult.

A third approach involves the enhancement of mechanical aspects of tooth movement. Conventional efforts to this end have been focused on enhancing the biomaterial properties and biomechanical interactions of orthodontic brackets and wires based on innovations regarding orthodontic wires and self-ligating systems. Collectively, the progress has reduced the binding interactions of brackets and established constant force systems. Arguably, these enhancements have reached their peak, and any further advancement would result in a minimal impact on the length of orthodontic treatment.

Another recently explored area involves device-assisted therapy to biologically enhance the orthodontic tooth movement. To this end, a number of systems such as light, electrical currents, cyclic forces, and resonance vibration have been introduced. This area is emerging while the majority of these methods have been limited to case reports.

Light Accelerated Orthodontics (LAO) is a technique within the scope of photobiomodulation or low-level laser therapy (LLLT). LAO shows promise in producing a noninvasive stimulation of the dentoalveolar complex with a potential impact on ATP production by mitochondrial cells. The assumption is that an increase in ATP at a localized site will induce cells to undergo remodeling. Cytochrome C oxidase mediates ATP production, which is upregulated two-fold by infrared light. During the tooth movement phase, higher ATP availability helps cells ‘turnover’ more efficiently leading to an increased remodeling process and accelerated tooth movement. LAO may also be functioning through increased vascular activity, which would also contribute to the rapid turnover of the bone. A number of clinical case series have suggested an enhanced impact by LAO, increased velocity of canine movement, decreased pain, and a significantly higher acceleration of retraction of treated canines. However, there are also some studies that show questionable efficacy.


Refer to Section 5.1
3.1. Physiology

- “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.”


There exists an “optical window” between 600 – 1200nm in biologic tissues. This allows for maximum tissue penetration of photons.

- Ex-vivo biopsy tissue study shows higher wavelengths penetrate tissue deeper, Stolik et al, Ex-vivo biopsy tissue study evaluated tissue penetration depths of 632, 675,780 and 835nm light measurement of the penetration depths of red and near infrared light in human ex-vivo tissues.
3.2. Mechanism of Action

Mechanisms thought to be involved in photobiomodulation biological response:

- Mitochondrial chromophores (inc. cytochrome C oxidase) absorb photons, which leads to ↑ proton pumping and ↑ ATP production → *increased energy available to the cell* → *increased / normalized metabolism*

- Reactive Oxygen Species (ROS) production and mitochondrial signaling stimulates/suppresses transcription factors, DNA/RNA synthesis → *plethora of tissue/cellular activity*

- Inducible Nitric Oxide (NO) production through absorption of photons by Nitric Oxide Synthase → *increased micro and regional blood flow and osteoclastic activity*

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

Photobiomodulation activates cytochrome c oxidase and increases mitochondrial electron transport which leads to increased ATP production.

- Eells et al\(^{37}\) showed that cytochrome c oxidase is the photoacceptor in the red to near-infrared spectral range.

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

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

- Karu and Kolyakov\(^ {38} \) performed experiments to find action spectra based on DNA and RNA synthesis rate. HeLa cell mono-layers irradiated with monochromatic light of 580-860 nm.\(^ {38}\)

Exact action spectra for cellular responses relevant to phototherapy.
Oron et al.\textsuperscript{39} showed twofold increase in ATP production with one LLLT treatment

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

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ATP_content.png}
\caption{Adenosine triphosphate (ATP) content in control non-laser-irradiated (dashed column) and laser-irradiated (solid column) human neuronal progenitor cells. Results are expressed as mean ± standard error of the mean (SEM). *p < 0.05 RLU, relative luminescent unit.}
\end{figure}

### 3.3. Genome Activation

Multiple genetic pathways are stimulated by 850nm IR light

- **Deregulation of specific sets of genes detected by microarray analysis of marrow stromal fibroblast cells**

*Refer to Section 6.1*
MECHANISM OF ACTION SCHEMA

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.

As a result of increased energy ATP, mitochondrial signaling, and up/down regulation of genes. A plethora of tissue/cellular activity begins.
4.1. Summary of Key in vitro Bone Metabolism Findings

- Increases osteocyte numbers\textsuperscript{40,41}
- Increases DNA synthesis\textsuperscript{42,43}
- Increases collagen production \textsuperscript{44}
- Increases ALP activity and number of mineral nodules\textsuperscript{45}
- Increases differentiation and proliferation of human osteoblasts\textsuperscript{46}
- Increases bone nodule formation, ALP activity and gene expression\textsuperscript{47}
- Increases osteoblastic activity\textsuperscript{48}
- Increases ostoclastic activity\textsuperscript{49}
- Increases the velocity of tooth movement through the stimulation of the osteoclasts and osteoblasts\textsuperscript{50}
4.2. Summary of Key in vivo Orthodontic Findings

- Low-level laser (LLL) therapy accelerates bone regeneration in the midpalatal suture following palatal expansion in the rat model\textsuperscript{51}
- Kawasaki and Shimizu\textsuperscript{52} 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 LLL therapy was applied to the rabbit model\textsuperscript{53}

Fujita et al\textsuperscript{54} 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 LLL tooth movement in rats\textsuperscript{55}.
- Goulart et al\textsuperscript{56} showed lower dosage (5J/cm\textsuperscript{2}) of LLL accelerates dog premolar tooth movement; higher dosage (35J/cm\textsuperscript{2}) may retard it.
- LLLT accelerates the velocity of tooth movement via stimulation of the alveolar bone remodeling in rats\textsuperscript{57}.
- LLLT facilitates the velocity of tooth movement and MMP-9, cathepsin K, and integrin subunits of alpha(v)beta3 expression in rats\textsuperscript{58}.

LLLT significantly increased PDL cell proliferation, decreased PDL cell inflammation, and increased PDL OC activity.\textsuperscript{59}
5.1. Photobiomodulation accelerates orthodontic alignment in the early phase of treatment

Kau CH1, Kantarci A2, Shaughnessy T3, Vachiramon A, Santiwong P, De la Fuente A, Skrenes D, Ma D, Brawn P. Progress in Orthodontics 2013, 14:30

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2Forsyth Institute, Cambridge, MA, USA
3Shaughnessy Orthodontics, Private Practice, Suwanee, GA

Background: Numerous strategies have been proposed to decrease the treatment time a patient requires in 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. The aim of this study was to determine if photobiomodulation reduces the treatment time in the alignment phase of orthodontic treatment.

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. Multilevel 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 4: Boxplots showing differences in alignment rates (mm/week) between control and test (LAO) patients. The boxplots 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 (8.39mm versus 6.67mm). There were no statistically significant difference between the two groups in terms of destination LII. Outliers (rates greater than 3mm/week) were removed from the test group to make these figures more conservative. The test group's mean alignment rates were 0.99 compared to a control rate of 0.44, with a comparison group of 23 control arches and 111 treatment arches.

This study was supported in part by Biolux Research.

**5.2. The effect of photobiomodulation on root resorption during orthodontic treatment**

Nimeri G¹, Kau CH¹, Corona R¹, Shelly J¹ Clin Cosmet Investig Dent. 2014:6

¹Department of Orthodontics, University of Alabama, Birmingham, AL, USA.

**Abstract:** Photobiomodulation is used to accelerate tooth movement during orthodontic treatments. The changes in root morphology in a group of orthodontic patients who received photobiomodulation were evaluated using the cone beam computed tomography technique. The device used is called OrthoPulse, which produces low levels of light with a near infrared wavelength of 850 nm and an intensity of 60 mW/cm² continuous wave. Twenty orthodontic patients were recruited for these experiments, all with class 1 malocclusion and with Little's Irregularity Index (2 mm) in either of the arches. Root resorption was detected by measuring changes in tooth length using cone beam computed tomography. These changes were measured before the orthodontic treatment and use of low-level laser therapy and after finishing the alignment level. Little's Irregularity Index for all the patients was calculated in both the maxilla and mandible and patients were divided into three groups for further analysis, which were then compared to the root resorption measurements. Our results showed that photobiomodulation did not cause root resorption greater than the normal range that is commonly detected in orthodontic treatments. Furthermore, no correlation between Little's Irregularity Index and root resorption was detected.

This study was supported in part by Biolux Research.
5.3. Intraoral photobiomodulation and orthodontic treatment-induced root resorption: A preliminary study.
Shaughnessy T¹, Kantarci A², Kau CH³, Skrenes D, Skrenes S, Ma D. *In review.*

¹Shaughnessy Orthodontics, Private Practice, Suwanee, GA
²Forsyth Institute, Cambridge, MA, USA
³Department of Orthodontics, School of Dentistry, University of Alabama, Birmingham, AL 35233, USA

**Introduction:** External apical root resorption (EARR) is a common side effect of orthodontic treatment. The aim of our study was to determine the degree of EARR in patients treated with intraoral photobiomodulation (PBM) in conjunction with orthodontic treatment. Furthermore, the correlation between EARR and several potentially contributing factors was investigated.

**Materials and Methods:** Ten patients, aged 12 to 16 years were included in a study to accelerate tooth movement using PBM. The group received daily PBM treatment with an Orthopulse intra-oral LED device in combination with orthodontic treatment. The device produced near infrared light with a continuous 850-nm peak wavelength providing a mean daily energy density of approximately 9.5 J/cm² at the surface of the LED array. Panoramic radiographs were taken before orthodontic treatment (T0) and at the completion of the alignment phase of treatment (T1). EARR of the 4 maxillary incisors was determined by measuring the difference in tooth length between the two images. Length measurements were made from the mesial buccal roots to the distal extent of the crown.

**Results:** The overall mean EARR was found to be 0.74 mm (5th-95th percentile: -1.31-2.96). EARR was only significant at values below 0.32 mm. A multivariate regression analysis was used to determine the relation of EARR with several potentially influential variables.

**Conclusion:** EARR is correlated with Orthopulse PBM dosage, and the duration of treatment. However, it is not linked to ethnicity, sex, degree of initial crowding, or incisor type. No statistically significant changes in root lengths were noted above 0.32 mm.
5.4. Intra-oral photobiomodulation-induced orthodontic tooth alignment: A pilot feasibility study
Shaughnessy T1, Kantarci A2, Kau CH3, Skrenes D, Skrenes S, Ma D. Forthcoming 2015.

Background: 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 intra-oral PBM increases the rate of tooth alignment and reduces the time required to resolve anterior dental crowding.

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 alignment treatment time was significantly faster 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). These results demonstrated that intra-oral PBM increased the rate of tooth movement by 2.9-fold, which resulted in a 54% decrease in alignment duration compared to control.

Conclusions: Our findings suggest that intra-oral PBM could be used to decrease anterior alignment treatment time, which could consequently decrease full orthodontic treatment time.
5.5. The effect of OrthoPulse™ on the rate of progression through Invisalign® aligners: a pilot study
Dickerson T1. To be submitted for publication.
1Dickerson Orthodontics, Private Practice, Phoenix, AZ

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 pilot study was to assess if PBM treatment can reduce the average wearing duration required for 7 and 14 day recommended aligners.

Materials and Methods: Nine patients aged 16-67 who presented for Invisalign treatment were recruited in the study. Implementing a crossover design, each patient established their control aligner wearing duration using a method of self-assessment. Following this control period, patients received daily PBM treatment with an OrthoPulse intra-oral LED device in combination with Invisalign treatment. The device produced near infrared light with a continuous 850-nm peak wavelength. Treatment was divided into two different regimens: 10 minutes of daily treatment (5 minutes per arch), or 20 minutes of daily treatment (10 minutes per arch). The average duration of aligner wearing during treatment was then compared to each patient’s control, and to the conventionally recommended wearing duration.

Results: Patients experienced a 66% reduction in the average duration per aligner during OPx1 treatment, and a 70% reduction during OPx2 treatment as compared to the conventionally recommended aligner wearing duration. Compared to the control period, patients showed a 51% and 56% decrease in aligner wearing duration for OPx1 and OPx2 treatments, respectively.

Conclusions: OrthoPulse treatment results in a significant reduction in the number of days required per aligner as compared to control, and to what is conventionally prescribed for Invisalign treatment.
5.6. A randomized controlled crossover trial on the effect of OrthoPulse™ on the rate of orthodontic tooth movement during alignment with Invisalign® aligners.

Dickerson T¹. To be submitted for publication.

¹Dickerson Orthodontics, Private Practice, Chandler, AZ

Study Purpose: The primary aim of this crossover study is to determine if daily OrthoPulse™ use affects the rate of orthodontic tooth movement during alignment with Invisalign® aligners in the mandibular arch.

The secondary aim of this study is to determine whether patients treated with OrthoPulse™ demonstrate root resorption beyond what is usually expected during orthodontic treatment.

The study also aims to collect confirmatory evidence on the safety of the device for which no serious adverse events are expected.

Effectiveness Objective: To compare the amount of tooth movement in millimeters per week according to the arch perimeter analysis between the baseline and OrthoPulse™ periods during aligner orthodontic treatment.

Safety Objective: To observe 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 21 patients from 14 to 53 years old received Invisalign® treatment in conjunction with 5-minute daily OrthoPulse™ treatments (OP), per arch.

Results: A total of 17 patients reached the primary outcome of the study, providing complete baseline and OrthoPulse™ tooth movement data. The average tooth movement rates were 0.126 and 0.231 mm/wk for the baseline and OrthoPulse™ periods, respectively. This indicates that the rate of tooth movement for the OrthoPulse™ period was 1.8-fold faster than that of the baseline period, with significance (p-value = 0.02). 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 6 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.

In summary, OrthoPulse™ may be used to increase the rate of orthodontic tooth movement and decrease treatment time with aligner treatment.
5.7. Velocity of en-masse space closure with and without photobiomodulation on root resorption during orthodontic treatment.

Samara et al. In review.

Introduction: The objective of this two-arm parallel-randomized clinical trial was to assess the effectiveness of low-level light therapy (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 orthodontic department of orthodontics at European University College.

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

Trial registration: This trial and its protocol were not registered on a publicly accessible registry. Funding: Biolux Research (Vancouver, Canada) provided the PBM devices used in this study.
Guo J¹, Wang Q, Wai D, Zhang QZ, Shi SH, Le AD, Shi ST, Yen SL.
¹Center 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 Joules/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.

Result: 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 wave-
lengths, 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.

6.2. Light-emitting diode photobiomodulation: effect on bone formation in orthopedically expanded suture in rats-early bone changes.


¹ Faculty of Dentistry, Department of Orthodontics, Erciyes University, Kayseri, Turkey.

Abstract: 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. 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 5 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 sutural 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. New bone formation area (p = 0.024, 1.48-fold), number of osteoblasts (p < 0.001, 1.59-fold), number of osteoclasts (p = 0.004, 1.43-fold), and number of vessels (p = 0.007, 1.67-fold) showed higher values in the experimental group than the control. Bone histomorphometric measurements revealed that bone architecture in the LPT group was improved. The application of LPT can stimulate bone formation in the orthopedically expanded intermaxillary suture during expansion and the early phase of the retention periods.
6.3. Resonance frequency analysis of orthodontic miniscrews subjected to light-emitting diode photobiomodulation therapy.


Abstract: 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). 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, and 300 cN). Osseopulse® LED device (Biolux Research Ltd.) 618 nm wavelength and 20 mW/cm(2) output power 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. 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 cN, P = 0.001; 150 cN, P < 0.001; and 300 cN, P < 0.001). Significant increase was found in ISQ values of LPT applied miniscrews under 0 cN (+11.63 ISQ), 150 cN (+10.50 ISQ), and 300 cN (+7.00 ISQ) force during observation period. By the increase of force levels, it was determined that ISQ values decreased in non-irradiated control miniscrews. 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.

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


Abstract: 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. 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 teeth 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. Mann–Whitney U and Wilcoxon tests were used for statistical evaluation at p < 0.05 level. 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
6.5. Photobiomodulation-induced orthodontic tooth movement.

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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/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 1st molar. The test animals in phototherapy groups daily received LED or Laser applications 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. Animals in the LED-Short group, the device was applied for a cumulative energy dose of 10J/cm\textsuperscript{2}; for the LED-Long group for 30J/cm\textsuperscript{2}; for animals in the Laser-Short group for 10J/cm\textsuperscript{2}; and for the Laser-Long group for 30J/cm\textsuperscript{2}.

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...

**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 to other groups.

**Conclusions:** The LED-treated groups showed more mandibular growth stimulation compared with the laser groups.

(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 of 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.
6.7. Human osteoblast response to photobiomodulation

Le A\textsuperscript{2}, Mendes RT\textsuperscript{1,2}, Iscan D\textsuperscript{2}, Pamuk P\textsuperscript{2}, Hasturk H\textsuperscript{2}, A. Kantarci A\textsuperscript{2}. Presented at IADR 2015 General Session. Boston, MA. March 14, 2015.

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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 2-fold 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/cm\textsuperscript{2} was used to irradiate the cell layer directly, with a distance of 2.5 cm below the plate. The samples were divided into 3 groups per plate: Group 1– 1 minute daily radiation for 9 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. 10 minutes radiation resulted in a significantly higher proliferation compared to control and 1 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 3 weeks. At week 5, however, 1 min 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).

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

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6.8. Photobiostimulation of gingival fibroblast and vascular endothelial cell proliferation

Iscan D¹², Mendes R¹, Kantarci A¹. *Presented in Annual Meeting of Turkish Society of Orthodontics, October 26-30, 2014 Ankara, Turkey.*

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**Background and Objective:** Photobiomodulation is a non-invasive method for accelerated orthodontic tooth movement. LED treatment (LEDT) increases the rate of tooth movement by more than 2-fold 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 LED on the proliferation of human gingival fibroblasts (HGF) and vascular endothelial cells (HUVEC) in vitro.

**Materials and Methods:** HGF and HUVEC's 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 was with a continuous wavelength of 850nm and a power density of 60mW/cm². Group 1 samples were irradiated every day for 1 minute while group 2 samples were irradiated for 10 minutes during 8 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 1-minute irradiation and a decrease in the 10-minute irradiation group in comparison with control groups.

**Conclusion:** 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.

This study was supported in part by Biolux Research.
6.9. Impact of LED photobiomodulation on the gene expression profile of PDL cells under simulated inflammation

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To be submitted for publication.

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Background and 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-) 1β, 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-1β, 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-1β+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-1β. LEDT further prevented and reduced the upregulation of IL-1β when cells were challenged with IL-1β. IL-1β upregulation by TNF-α (28.6-fold) 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.

This study was supported in part by Biolux Research.
7.1. Mechanism of Action

7.1.1. The nuts and bolts of low-level laser (light) therapy.


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**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 a cellular and at a tissular level 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.
7.1.2. Low-energy laser irradiation facilitates the velocity of tooth movement and the expressions of matrix metalloproteinase-9, cathepsin K, and alpha(v) beta(3) integrin in rats.


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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/its receptor (c-Fms) systems. Matrix metalloproteinase (MMP)-9, cathepsin K, and alpha(v)beta(3) [alpha(v)beta3] 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(v)beta3 integrin during experimental tooth movement. Fifty male, 6-week-old Wistar strain rats were used in the experiment. A total force of 10g 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 7 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(v)beta3 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(v)beta3-positive cells. 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(v)beta3 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(v)beta3 expression in rats.
7.1.3. Metrical and histological investigation of the effects of low-level laser therapy on orthodontic tooth movement.


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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 5 points at the distal side of the tooth root on the first, second, and 3rd days of the experiment. 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 8 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.
7.2. Systematic Review


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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, 5 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.
7.3. Safety Assessment

7.3.1. Long-term safety of low-level laser therapy at different power densities and single or multiple applications to the bone marrow in mice.


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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 8 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 8 months.
8.1. References


References


7.2. Additional Citations


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