Photobiomodulation Therapy
- A new tool in Oral Mucositis Management

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## Disclosures

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<th>Company / Entity</th>
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**President,**

**World Association for Laser Therapy**

**Immediate Past President,**

**North American Association for Photobiomodulation Therapy**

**Co-Chair,** **Mechanisms of Photobiomodulation**

**International Society for Optics and Photonics**

**Technical Group on Photobiomodulation**

**Optical Society of America (OSA)**

**Program Chair 2019 (Symposium of Advanced Wound Care)**

**Wound Healing Society (WHS)**
Light Devices in Dentistry

I. Illumination
Operative lights, Fiberoptics in loupes / devices

II. Imaging
Digital imaging, Fluorescence-based diagnostics (Caries, Pre-Cancer), Optical Coherence Tomography, Multi-photon imaging, Spectroscopy

III. Manufacturing
Curing, Welding, Sintering, Milling

IV. Surgical
Hard tissue: Excavation, Bleaching, Prevent demineralization, Dentin desensitization, Bracket bonding / debonding, Photon-Induced Photoacoustic Streaming (PIPS)
Soft tissue: Excisions, Photocoagulation, Field ablation, Recontouring (Esthetics, Snoring, Halitosis), Depigmentation, Curettage

V. Non-Surgical
Photodynamic therapy: Anti-microbial, Anti-tumor
Photobiomodulation therapy: Analgesia, Anti-inflammatory, Immune-modulation, Healing-Regeneration

Arany PR J Dent Res 2016, 95, 9, 977
Can light be a Drug?

A ‘drug’ is a substance that is absorbed and alters bodily function.
Therapeutic use of Light

Niels Ryberg Finsen
Nobel Prize 1903
L.A.S.E.R.

- **Concept of Light Amplification by Stimulated Emission of Radiation**
  Albert Einstein 1917

- **Construction of a working LASER**
  Charles Towne 1954 Theodore Maiman 1960

- Amongst the very first biological effects observed with low power lasers were *stimulation of hair growth* and *promotion of wound healing*.
  Endre Mester 1967, 1973
Photobiomodulation (PBM) Therapy

“Use of non-ionizing source of photonic energy that generates non-thermal, therapeutic effects.”

- **Inhibit**: negative processes
  - Pain, Inflammation, aberrant immune

- **Promote**: positive processes
  - Wound healing, Tissue regeneration, immune system

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Khan I and Arany Adv Wound Care 2015

Anders JJ et al Photomed Las Surg 2015
Applications of Photobiomodulation Therapy

- Hair regrowth
- Tinnitus
- Skin rejuvenation
- Neck pain
- Reduction of heart attack
- Laser lipolysis
- Arthritis
- Wound healing
- Brain, stroke, TBI, Parkinson's, Alzheimer's
- Temporomandibular joint disorder
- Dentistry, pain
- Mucositis
- Non-union fractures
- Lateral epicondylitis
- Carpal tunnel syndrome
- Muscle fatigue
- Achilles tendonitis
- Laser acupuncture

Slide modified from Michael Hamblin
PBM Mechanisms

**#1. Intracellular**
Mitochondria
*Cytochrome C Oxidase*
- ATP, ROS incl'd NO

**#2. Photoreceptors**
Cell Membrane
*Opsins, AHR, TRPV1*
- GPCR signaling, ion flux incl'd Ca^{2+}

**#3. Extracellular**
ECM / Circulating
*TGF-β1*
- Smad, MAPK, NFκB, ATF-4

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*Modified from Khan I and Arany Adv Wound Care 2015, 1, 4, 174*
PBM mechanism 1: Intracellular

Invited Review
Primary and secondary mechanisms of action of visible to near-IR radiation on cells

Tiina Karu *
Laser Technology Research Center of Russian Academy of Sciences, 142992 Troitsk, Moscow Region, Russia
Received 17 March 1998, accepted 9 November 1998

Cellular Effects of Low Power Laser Therapy Can be Mediated by Nitric Oxide

Tiina I. Karu, PhD,1,* Ludmila V. Pyatibrat, MS,2 and Natalia I. Afanasieva, PhD2
1Institute of Laser and Information Technologies of the Russian Academy of Sciences, 142992 Troitsk, Moscow, Russia
2Spectrooptical Sensing, Inc., Portland, Oregon 97205

Light-emitting diode treatment reverses the effect of TTX on cytochrome oxidase in neurons

Margaret T. T. Wong-Riley, CA Xuetao Bai, Ellen Buchmann1 and Harry T. Whelan1
Departments of Cell Biology, Neurobiology and Anatomy, and 1Neurology, Medical College of Wisconsin, 8761 Watertown
Plank Road, Milwaukee, WI 53226, USA
*Corresponding Author
Received 19 July 2001; accepted 24 July 2001

Mechanisms and applications of the anti-inflammatory effects of photobiomodulation

Michael R Hamblin1,2,3,*
1Wellman Center for Photomedicine, Massachusetts General Hospital, BAR414, 40 Blossom Street, Boston, MA 02114, USA
2Department of Dermatology, Harvard Medical School, Boston, MA 02115, USA
3Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139, USA
Red (660 nm) or near-infrared (810 nm) photobiomodulation stimulates, while blue (415 nm), green (540 nm) light inhibits proliferation in human adipose-derived stem cells

Yuguang Wang1,2,3*, Ying-Ying Huang1,2, Yong Wang1,2, Peijun Lyu1,2 & Michael R. Hamblin1,2,3

A New Path in Defining Light Parameters for Hair Growth: Discovery and Modulation of Photoreceptors in Human Hair Follicle

Serena Buscemi, 1,2,3, Andrea N. Mardaryev, 1,2,3, Bianca Raukas, 1,2,3, Jan W. Bikker, 1,2,3, Carsten Sticht, 1,2,3, Norbert Gretz, 1,2,3, Nilofor Forjaz, 1,2,3, Natalija L. Uzumbajakava, 1,2,3 & Natalia V. Botchkareva, 1,2,3

Gene expression profiling reveals aryl hydrocarbon receptor as a possible target for photobiomodulation when using blue light

Anja Becker1, Anna Klapczynski1, Natalia Kuch1, Fabiola Arpino1, Katja Simon-Keller1, Carolina De La Torre1, Carsten Sticht1, Frank A. van Abeelen2, Gerrit Oversluizen3 & Norbert Gretz1

Melanopsin mediates light-dependent relaxation in blood vessels

Gautam Sikk1, G. Patrick Hussmann2, Deepesh Pandey2, Suyi Cao2, Daijio Hori1, Jorg Taek Park2, Jochen Steppan2, Jee Hyung Kim, Vlasheesu Barokka2, Allen C. Myers2, Lakshmi Santhanam2, Daniel Nyhaver, Mark K. Hakskialla, Raymond C. Koehler3, Solomon H. Snyder1,4, Larissa A. Shimoda2, and Dan E. Berkowitz2,4


Opsin 3 and 4 mediate light-induced pulmonary vasorelaxation that is potentiated by G protein-coupled receptor kinase 2 inhibition

Sébastien Barretto Ortiz1,2, Daijio Hori1,2, Yoshinori Nomura2,3, Xin Yang2, Hadyang Fang2, Huanmei Ye2, James Chen3, Sam Pock2, Deepesh Pandey2, Gautam Sikk1, Anh Bui4, Andrew Gillard1, Jochen Steppan2, Jee Hyung Kim, Hideo Aida1, Vishnulakshana M. Baroka2, Lewis Romer1,2, Steven S. An2, Larissa A. Shimoda2, Lakshmi Santhanam2 and Dan E. Berkowitz1,3

Am J Physiol Lung Cell Mol Physiol 314: L129-L139, 2018
First published September 7, 2018, doi:10.1152/ajplung.00391.2017

RESEARCH ARTICLE

*Corresponding author.

Submitted 28 February 2017, accepted in final form 1 September 2017

PBM mechanism 2: Cell Membrane
PBM mechanism 3: Extracellular

RESEARCH ARTICLE

REGenerative Medicine

Photoactivation of Endogenous Latent Transforming Growth Factor–β1 Directs Dental Stem Cell Differentiation for Regeneration

Praveen R. Arany,1,2,3,4,5 Andrew Cho,5 Tristan D. Hunt,1 Gursimran Sidhu,1 Kyungsup Shin,1,3 Eason Hahm,1 George X. Huang,1 James Weaver,2 Aaron Chih-Hao Chen,6 Bonnie L. Padwa,7 Michael R. Hamblin,6,8,9 Mary Helen Barcellos-Hoff,10 Ashok B. Kulkarni,5 David J. Mooney1,2*

Rapid advancements in the field of stem cell biology have led to many current efforts to exploit stem cells as therapeutic agents in regenerative medicine. However, current ex vivo cell manipulations common to most regenerative approaches create a variety of technical and regulatory hurdles to their clinical translation, and even simpler approaches that use exogenous factors to differentiate tissue-resident stem cells carry significant off-target side effects. We show that non-ionizing, low-power laser (LPL) treatment can instead be used as a minimally invasive tool to activate an endogenous latent growth factor complex, transforming growth factor–β1 (TGF-β1), that subsequently differentiates host stem cells to promote tissue regeneration. LPL treatment induced reactive oxygen species (ROS) in a dose-dependent manner, which, in turn, activated latent TGF-β1 (LTGF-β1) via a specific methionine residue (at position 253 on LAP). Laser-activated TGF-β1 was capable of differentiating human dental stem cells in vitro. Further, an in vivo pulp capping model in rat teeth demonstrated significant increase in dentin regeneration after LPL treatment. These in vivo effects were abrogated in TGF-β receptor II (TGF-βRII) conditional knockout (DSPP<sup>Cre</sup> TGF-βRII<sup>fl/fl</sup>) mice or when wild-type mice were given a TGF-βRI inhibitor. These findings indicate a pivotal role for TGF-β in mediating LPL-induced dental tissue regeneration. More broadly, this work outlines a mechanistic basis for harnessing resident stem cells with a light-activated endogenous cue for clinical regenerative applications.

Michael Hamblin, MGH
Mary-Helen Barcellos Hoff, NYU

Arany PR et al/ Sci Transl Med 2014, 6, 238, 1
Jobling MF et al/ Rad Res 2008, 166, 839
Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients

Cesar Mignani* - Ian Howson - Rajesh V. Lulla - Halim Spinola Antunes - Cherry L. Fatti - Brian Hodgson - Nilda Nelly Fontana Lopes - Mark M. Schubert - Joanne Bowen - Sharon Elad - For the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO)

Received: 21 June 2012 / Accepted: 10 September 2012 / Published online: 22 September 2012
© Springer-Verlag 2012

Abstract
Background: The aim of this study was to review the available literature and define clinical practice guidelines for the use of laser and other light therapies for the prevention and treatment of oral mucositis.

Methods: A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology. The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level, based on

Dr. Elad’s talk next.......
Rationale: PBM for Pain Relief in OM

- Depolarization nerve conduction
- Direct modulation of TRPV1
- Reduced axonal transport of Mitochondria in neurons

Chow R et al Lancet 2009, 374, 1897
Bjordal J et al BMC Musculsket 2008, 9:75
**Rationale:** PBM in OM for healing

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1. Arany et al/ WRR 2007  
3. Arany et al/ PMLS 2016
PBM promotes Keratinocyte migration

Khan et al in preparation
PBM increases eCFUs

A. Skin eCFU

B. Oral Mucosa eCFU

Khan and Arany Photomed Laser Surg 2016
PBM promotes Burn Wound Healing

Khan et al in preparation
Lasers can destroy tissues.
Are they Genotoxic-Mutagenic?

THE ELECTROMAGNETIC SPECTRUM

- Sub-lethal
- Lethal
- Direct DNA damage
- Thermal
- ROS
Sub-lethal laser doses are Non-Genotoxic

In vitro

In vivo

Khan I et al Sci Reports 2015, 1, 510581
Gene expression Arrays

DNA damage-repair

γ-Radiation

ER stress

Khan I et al Sci Reports 2015, 1, 510581
Cytotoxic laser dose induces ER stress

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Untreated

Laser (Sub-lethal)

Khan and Arany Arch Tranl Med 2015
HR6, Public Law 115-271 that mandates examination of current evidences (clinical practice guidelines, insurance), further research and funding on alternative pain treatments.
Reimbursement

Billing Codes: 97026, S8948
Can light be a drug?
Yes, A *photoceutical* approach for PBM Therapy

**Photokinetics** *(Pharmacokinetics)*
‘What body does to the light (drug)’

**Photodynamics** *(Pharmacodynamics)*
‘What light (drug) does to the body’