INTRODUCTION TO PHOTOBIOMODULATION
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In 1967, Endre Mester experimented with the effects of lasers on skin cancer. While applying lasers to the backs of shaven mice, he noticed that the shaved hair grew back more quickly on the treated group than the untreated group.

Figure 3.3  “The historic mice” II. Courtesy: Andrew Mester
Photobiomodulation is an emerging medical and veterinarian application in which exposure to light (usually visible to infrared wavelengths) can stimulate or inhibit cellular function leading to beneficial clinical effects.

The "best" combination of wavelength, irradiance, radiant exposure, and treatment interval is complex and for many treatments still needs to be established.
In the US, the technology received clearance from the FDA in 2002 for hand and wrist pain associated with Carpal Tunnel Syndrome (MicroLight Corp.)
CURRENT SITUATION IN THE US

• Most users are athletic trainers, chiropractors, and practitioners of complementary medicine

• For mainstream medicine, LT is still unpracticed, seldom used, & thought unproven

• The medial and dental community needs to:
  1) understand the mechanism
  2) needs successful, controlled, large scale clinical trial on several Light Based Therapies
MECHANISM OF PHOTOBIOMODULATION

- Mitochondrial Theory
  - S. Passarella (1981-Present)
  - Tina Karu (1984-Present)
- Light induced low concentrations of reactive oxygen species
- Changes in calcium homeostasis
  - Rachel Lubart
    - Trends in Photochemistry and Photobiology 1997: 4; 277-283
    - Drug Development Research 2000: 50; 471-475
  - Moro, Greco, Marra, and Passarella
    - Lasers in Medical Science 2002: 17:A20
MECHANISM OF ACTION

Red and near infrared wavelengths:
- Absorbed by Cu centers in cytochrome C oxidase
- Enhance mitochondrial viability and activity

CcOx is a photoreceptor for red and NIR

Absorption spectrum of CcOx in HeLa cells

MECHANISMS OF LOW-POWER LASER LIGHT ACTION ON CELLULAR LEVEL

Tina Karu
Cytochrome c Oxidase activity increases at 810 nm


Harnessing the cell’s own ability to repair and prevent neurodegenerative disease

H Whelan, K Desmet, E Buchmann, M Henry, M Wong-Riley, J Eells, and J Verhoeve

Cytochrome oxidase and the correlation between the near-IR absorption spectrum of cytochrome oxidase, ATP content, and cytochrome oxidase activity in cultured primary neuronal cells subjected to metabolic inhibition and near-IR light treatment.
Photodissociation of NO from cyt C oxidase

Red or NIR light

4 cyt c (red)
4 cyt c (ox)

4 e-

CuA

Heme a

e-

Heme a3

e-

CuB

4 H

NO

2 H2O

Subunit I

Subunit II

Respiration↑

ATP↑
Cellular Energetics

- Increased activity CcO
- Decreased CcO binding to NO
- Increased Oxygen consumption
- Restoration of mitochondrial electrochemical gradients (PSIm)
- Increased ATP production

Restoration of cellular energy balance & ATP signaling
Mitochondria are also an integral part of multiple cell signaling cascades. Proteins such as GTPases, kinases and phosphatases are involved in bi-directional communication between the mitochondrial reticulum, and the rest of the cell.
Summary of a number of experiments with different cell types, listing the different molecules that are induced by light therapy

<table>
<thead>
<tr>
<th>Classification</th>
<th>Molecules</th>
<th>Biological effects of LLLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth factors</td>
<td>BDNF, GDNF, bFGF, IGF-1, KGF, PDGF, TGF-β, VEGF</td>
<td>Proliferation, Differentiation, Bone nodule formation</td>
</tr>
<tr>
<td>Interleukins</td>
<td>IL-1α, IL-6, IL-8, IL-2, IL-4</td>
<td>Proliferation, Migration, Immunological activation</td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
<td>PGE2, COX-2, IL-1β, TNF-α</td>
<td>Inhibition of inflammation</td>
</tr>
<tr>
<td>Small molecules</td>
<td>ATP, cGMP, ROS, Ca^{2+}, NO</td>
<td>Normalization of cell function, Pain relief, Healing, Mediating cell activities, Migration, Angiogenesis</td>
</tr>
</tbody>
</table>
Relative absorbance

wavelength (nm)

Optical Window

water
Hb
HbO2
Melanin

Relative absorbance

wavelength (nm)

water
Hb
HbO2
Melanin
810 nm CAN PENETRATE TO THE DEPTH OF BRAIN AND SPINAL CORD:
810 nm FOUND TO HAVE HIGH ABSORPTION BY CNS TISSUE
810nm Found to Best Promote Regeneration: 810nm Has Minimal Energy Absorption by Blood and Water
MEDICAL AREAS WHERE PHOTOBIOMODULATION CAN PLAY A MAJOR ROLE

• Wound Healing – Tissue Repair
• Pain – Relief of Inflammation
• Central and Peripheral Nervous System – Injury and Disease
• Metabolic Diseases – Diabetes
• Range of Dental Applications
Microarray Conclusions

Expression of over 200 genes significantly altered after photobiomodulation and spinal cord injury

• Many altered genes involved in:
  – Decreasing inflammatory response
  – Decreasing glutamate receptor
  – Increasing neurotrophic factor receptor
  – Decreasing cell proliferation
INCREASING INTEREST AND ENDORSEMENT OF LIGHT THERAPY IN THE LAST 3 YEARS

Dr. Roberta Chow published in Lancet on efficacy of LT for neck pain

• intense interest in the article and reaches the Lancet Top 20 most downloaded research papers in 2010

Associations Endorsing LT:

• International Association for the Study of Pain (myofacial pain syndrome)
• The American Physical Therapy Association (achilles tendon treatment)
• BMJ sports medical journal (frozen shoulder)
• The World Health Organization (neck pain)
CONCLUSIONS

• Light therapy, whether using low intensity radiation in the visible or infrared region from a laser, an LED, or a filtered incandescent lamp, can be beneficial in a number of clinical situations such as pain remission, wound healing and nervous system repair.

• Mechanism still theoretical – needs to be solved to maximize effectiveness and acceptance of light therapy.

• Selection of proper wavelengths and treatment parameters must be based on solid research and documented clinical observations.

• Establishing action spectra for promising clinical applications would standardize the dose of radiation needed for a specific wavelength.