LIGHT-EMITTING DIODE* (LED) RESEARCH ABSTRACTS

THE PHOTOTHERAPY EXPERTS

*SUPER LUMINOUS DIODE (SLD) MEDICAL GRADE LEDs

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Effect of NASA Light-Emitting Diode Irradiation on Wound Healing

Whelan, H.T., Smits R.L., Buchman, E.V., Whelan, N.T., Turner, S.G., Margolis, D.A., Cevenini, V., Stinson, H., Ignatius, R., Martin, T., Cwiklinski, J., Philippi, A.F., Graf, W.R., Hodgson, B., Gould, L., Kane, M., Chen, G., Caviness, J.

Journal of Clinical Laser Medicine & Surgery (2001) 19(6): 305-314

***Objective*:** The purpose of this study was to assess the effects of hyperbaric oxygen (HBO) and near-infrared light therapy on wound healing. *Background Data*: Light-emitting diodes (LED), originally developed for NASA plant growth experiments in space show promise for delivering light deep into tissues of the body to promote wound healing and human tissue growth. In this paper, we review and present our new data of LED treatment on cells grown in culture, on ischemic and diabetic wounds in rat models, and on acute and chronic wounds in humans.

***Materials and Methods*:** *In vitro* and in vivo (animal and human) studies utilized a variety of LED wavelength, power intensity, and energy density parameters to begin to identify conditions for each biological tissue that are optimal for biostimulation.

***Results*:** LED produced in vitro increases of cell growth of 140-200% in mouse-derived fibroblasts, rat-derived osteoblasts, and rat-derived skeletal muscle cells, and increases in growth of 155-171% of normal human epithelial cells. Wound size decreased up to 36% in conjunction with HBO in ischemic rat models. LED produced improvement of greater than 40% in musculoskeletal training injuries in Navy SEAL team members, and decreased wound healing time in crew members aboard a U.S. Naval submarine. LED produced a 47% reduction in pain of children suffering from oral mucositis.

Conclusion: We believe that the use of NASA LED for light therapy alone, and in conjunction with hyperbaric oxygen, will greatly enhance the natural wound healing process, and more quickly return the patient to a preinjury/illness level of activity. This work is supported and managed through the NASA Marshall Space Flight Center-SBIR Program.

Effect of NASA Light-Emitting Diode Irradiation on Molecular Changes for Wound Healing in Diabetic Mice

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Abstract. Objective: The purpose of this study was to assess the changes in gene expression of near-infrared light therapy in a model of impaired wound healing.

Background Data: Light-Emitting Diodes (LED), originally developed for NASA plant growth experiments in space, show promise for delivering light deep into tissues of the body to promote wound healing and human tissue growth. In this paper we present the effects of LED treatment on wounds in a genetically diabetic mouse model.

Materials and Methods: Polyvinyl acetal (PVA) sponges were subcutaneously implanted in the dorsum of BKS.Cg-m +/+ Leprdb mice. LED treatments were given once daily, and at the sacrifice day, the sponges, incision line and skin over the sponges were harvested and used for RNA extraction. The RNA was subsequently analyzed by cDNA array.

Results: Our studies have revealed certain tissue regenerating genes that were significantly upregulated upon LED treatment when compared to the untreated sample. Integrins, laminin, gap junction proteins, and kinesin superfamily motor proteins are some of the genes involved during regeneration process. These are some of the genes that were identified upon gene array experiments with RNA isolated from sponges from the wound site in mouse with LED treatment.

Conclusion: We believe that the use of NASA light-emitting diodes (LED) for light therapy will greatly enhance the natural wound healing process, and more quickly return the patient to a preinjury/illness level of activity.

This work is supported and managed through the Defense Advanced Research Projects Agency (DARPA) and NASA Marshall Space Flight Center-SBIR Program.

The NASA Light-Emitting Diode Medical Program –Progress in Space Flight and Terrestrial Applications

Whelan, H.T., Houle, J.M., Whelan, N.T., Donohoe, D.L., Cwiklinski, J., Schmidt, M.H., Gould, L., Larson, D., Meyer, G.A., Cevenini, V., and Stinson, H.

Abstract. This work is supported and managed through the NASA Marshall Space Flight Center – SBIR Program. Studies on cells exposed to microgravity and hypergravity indicate that human cells need gravity to stimulate cell growth. As the gravitational force increases or decreases, the cell function responds in a linear fashion. This poses significant health risks for astronauts in long term space flight. LED-technology developed for NASA plant grown experiments in space shows promise for delivering light deep into tissues of the body to promote wound healing and human tissue growth. This LED-technology is also biologically optimal for photodynamic therapy of cancer.

LED-ENHANCEMENT OF CELL GROWTH

The application of light therapy with the use of NASA LED's will significantly improve the medical care that is available to astronauts on long-term space missions. NASA LED's stimulate the basic energy processes in the mitochondria (energy compartments) of each cell, particularly when near-infrared light is used to activate the color sensitive chemicals (chromophores, cytochrome systems) inside. **Optimal LED wavelengths include 680, 730 and 880 nm**. The depth of near-infrared light penetration into human tissue has been measured spectroscopically (Chance, et al 1988). Spectra taken from the wrist flexor muscles in the forearm and muscles in the calf of the leg demonstrate that most of the light photons at wavelengths between 630-800 nm travel 23 cm through the surface tissue and muscle between input and exit at the photon detector. Our laboratory has improved the healing of wounds in laboratory animals by using NASA LED light and hyperbaric oxygen. **Furthermore, DNA synthesis in fibroblasts and muscle cells has been quintupled using NASA LED light alone, in a single application combining 680, 730, and 880 nm each at 4 Joules per centimeter squared.**

Muscle and bone atrophy are well documented in astronauts, and various minor injuries occurring in space have been reported not to heal until landing on Earth. Long term space flight, with its many inherent risks, also raises the possibility of astronauts being injured performing their required tasks. The fact that the normal healing process is negatively affected by microgravity requires novel approaches to improve wound healing and tissue growth in space. NASA LED arrays have already flown on Space Shuttle missions for studies of plant growth. The U.S. Food and Drug Administration (FDA) has approved human trials. The use of light therapy with LED's is an approach to help increase the rate of wound healing in the microgravity environment, reducing the risk of treatable injuries becoming mission catastrophes.

Wounds heal less effectively in space than here on Earth. Improved wound healing may have multiple applications which benefit civilian medical care, military situations and long-term space flight. Laser light and hyperbaric oxygen have been widely acclaimed to speed wound healing in ischemic, hypoxic wounds. An excellent review of recent human experience with near-infrared light therapy for wound healing was published by Conlan, et al in 1996. Lasers provide low energy stimulation of tissues which results in increased cellular activity during wound healing (Beauvoit, 1989, 1995; Eggert, 1993; Karu, 1989; Lubart, 1992, 1997; Salansky, 1998; Whelan, 1999; Yu, 1997). **Some of these activities include increased fibroblast proliferation, growth factor syntheses, collagen production and angiogenesis.**

Lasers, however, have some inherent characteristics, which make their use in a clinical setting problematic, including limitations in wavelengths and beam width. The combined wavelengths of light optimal for wound healing cannot be efficiently produced, and the size of wounds which may be treated by lasers is limited. **Light-emitting diodes (LED's) offer an effective alternative to lasers.** These diodes can be made to produce multiple wavelengths, and can be arranged in large, flat arrays allowing treatment of large wounds. Our experiments suggest potential for using LED light therapy at 680, 730 and 880 nm simultaneously, alone and in combination with hyperbaric oxygen therapy, both alone and in combination, to accelerate the healing process in Space Station Missions, where prolonged exposure to microgravity may otherwise retard healing. NASA LED's have proven to stimulate wound healing at near-infrared wavelengths of 680, 730 and 880 nm in laboratory animals, and have been approved by the U.S. Food and Drug Administration (FDA) for human trials. Furthermore, near-infrared LED light has quintupled the growth of fibroblasts and muscle cells in tissue culture. The NASA LED arrays are light enough and mobile enough to have already flown on the Space Shuttle numerous times. LED arrays may prove to be useful for improving wound healing and treating problem wounds, as well as speeding the return of deconditioned personnel to full duty performance. Potential benefits to NASA, military, and civilian populations include treatment of serious burns, crush injuries, non-healing fractures, muscle and bone atrophy, traumatic ischemic wounds, radiation tissue damage, compromised skin grafts, and tissue regeneration.

The use of NASA Light-Emitting Diode Near-Infrared (IR) technology for biostimulation

Whelan HT, M.D.

North American Association of Laser Therapy (NALT) Annual Conference (2002) Atlanta, Georgia.

This work is supported and managed through the NASA Marshall Space Flight Center - SBIR Program. Studies on cells exposed to microgravity and hypergravity indicate that human cells need gravity to stimulate growth. As the gravitational force increases or decreases, the cell function responds in a linear fashion. This poses significant health risks for astronauts in long-term space flight. The application of light therapy with the use of NASA LEDs will significantly improve the medical care that is available to astronauts on long-term space missions. NASA LEDs stimulate the basic energy processes in the mitochondria (energy compartments) of each cell, particularly when near-infrared light is set to activate the color sensitive chemicals (chromophores, cytochrome systems) inside. Optimal LED wavelengths include 680, 730 and 880 nm and our laboratory has improved the healing of wounds in laboratory animals by using both NASA LED light and hyperbaric oxygen. Furthermore, DNA synthesis in fibroblasts and muscle cells has been quintupled using NASA LED light alone, in a single application combining 680, 730 and 880 nm each at 4 Joules per centimeter squared. Muscle and bone atrophy are well documented in astronauts, and various minor injuries occurring in space have been reported not to heal until landing on Earth. An LED blanket device may be used for the prevention of bone and muscle atrophy in astronauts. The depth of near-infrared light penetration into human tissue has been measured spectroscopically. Spectra taken from the wrist flexor muscles in the forearm and muscles in the calf of the leg demonstrate that most of the light photons at wavelengths between 630-800 nm travel 23 cm through the surface tissue and muscle between input and exit at the photon detector. The light is absorbed by mitochondria where it stimulates energy metabolism in muscle and bone, as well as skin and subcutaneous tissue. Long term space flight, with its many inherent risks, also raises the possibility of astronauts being injured performing their required tasks. The fact that the normal healing process is negatively affected by microgravity requires novel approaches to improve wound healing and tissue growth in space. NASA LED arrays have already flown on Space Shuttle missions for studies of plant growth and the U.S. Food and Drug Administration (FDA) has approved human trials. The use of light therapy with LEDs can help prevent bone and muscle atrophy as well as increase the rate of wound healing in a microgravity environment, thus reducing the risk of treatable injuries becoming mission catastrophes. Space flight has provided a laboratory for studying wound healing problems due to microgravity, which mimic traumatic wound healing problems here on earth. Improved wound healing may have multiple applications that benefit civilian medical care, military situations and long-term space flight. Enhancing the soldier's tissue responses to injury may lead to battlefield resilience and medical independence. Counter-measures to chemical, biological and radioactive weapons exposures which are based on biostimulation of natural tissue regeneration mechanisms could be more universally safe and effective than conventional drugs and surgical modalities. Regeneration of wounded organs and limbs may also be possible if biostimulation could re-awaken molecular events leading to re-growth of tissue. Near infrared (IR) light has documented benefits promoting wound healing in human and animal studies. Our preliminary results have also demonstrated two to five-fold increases in growth-phase-specific DNA synthesis in normal fibroblasts, muscle cells, osteoblasts, and mucosal epithelial cells in tissue cultures treated with near-IR light. Our animal models treated with near-IR have included wound healing in diabetic mice and ischemic bipedal skin flap in rats. Near-IR induced a thirty percent increase in the rate of wound closure in these animal models. Dose- and time-dependent increases in vascular endothelial growth factor

(VEGF) and fibroblast growth factor (FGF-2) occurred in animals treated with near-IR. Human studies have included the use of near-IR to prevent ulcerative mucositis resulting from high doses of chemotherapy and radiation. Widely published reports, including those from our laboratory, described accelerated recovery from musculoskeletal injuries, hypoxic-ischemic wounds, burns, lacerations, radiation necrosis, and diabetic ulcers with the use of near-IR. Lasers have some inherent characteristics, which, make their use in a clinical setting problematic, including limitations in wavelength capabilities and beam width. The combined wavelengths of light optimal for wound healing cannot be efficiently produced, and the size of wounds that, may be treated by lasers is limited. Light-emitting diodes (LEDs) developed for NASA manned space flight experiments offer an effective alternative to lasers. These diodes can be made to produce multiple wavelengths, and can be arranged in large, flat arrays allowing treatment of large wounds. We are now investigating new collaborations with the Defense Advanced Research Projects Agency (DARPA) for military applications of LED wound healing technology in military medicine. Several uniquely military situations and indications could be addressed, optimizing near-IR parameters for wound healing via LEDs during extended missions under conditions separated from medical personnel. These include burns, chemical agents, radiation, biological agents and highly infected flesh-eating wounds (with and without extended burns) typical for the hygienic conditions occurring in battle fields, also infectious diseases and external wounds occurring in environments with no solar irradiation, low oxygen and high carbon dioxide (submarines). The dramatic results with use of near-IR LED light to prevent digestive mucosal lesions (mucositis) and pain in cancer patients, after high-dose chemotherapy and radiation, suggest the potential for military use of near-IR light to treat U.S. troops exposed to chemical and radioactive warfare agents in the field. These examples illustrate the many possible military uses for this technology. These life-saving applications require especially accelerated wound healing, rapid reduction of infections and pain modulation. Regeneration of muscles in amphibians has also been produced by near-IR therapy. The potential for regeneration of human tissue also deserves study. Central nervous system regeneration would be of particular benefit. Thus far, we have demonstrated that the best results for wound healing occur at wavelengths of 670 nm and 880 nm using 4 to 8 joules/cm2, applied at power densities of approximately 50 mW/cm2. However, studies to determine molecular mechanisms could lead to the optimization for current uses, as well as open up new applications. Despite numerous reports on the benefits of near-IR on wound healing and rehabilitation over the last decade, the basic mechanisms of its action remain poorly understood. Britton Chance's group has reported that about 50% of near-IR light is absorbed by mitochondrial chromophores, such as cytochrome oxidase. However, the underlying cellular and molecular events are still unknown.

Effects of 670-nm Phototherapy on Development

Yeager RL, Franzosa JA, Millsap DS, Angell-Yeager JL, Heise SS, Wakhungu P, Lim J, Whelan HT, Eells JT, Henshel DS

Photomed Laser Surgury (2005) 23(3): 268-72.

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Objective: The objective of the present study was to assess the survival and hatching success of chickens (Gallus gallus) exposed in ovo to far-red (670-nm) LED therapy.

Background Data: Photobiomodulation by light in the red to near-infrared range (630-1000 nm) using low-energy lasers or light-emitting diode (LED) arrays has been shown to accelerate wound healing and improve recovery from ischemic injury. The mechanism of photobiomodulation at the cellular level has been ascribed to the activation of mitochondrial respiratory chain components resulting in initiation of a signaling cascade that promotes cellular proliferation and cytoprotecton.

Materials and Methods: Fertile chicken eggs were treated once per day from embryonic days 0-20 with 670-nm LED light at a fluence of 4 J/cm(2). In ovo survival and death were monitored by daily candling (after Day 4).

Results: We observed a substantial decrease in overall and third-week mortality rates in the light-treated chickens. Overall, there was approximately a 41.5% decrease in mortality rate in the light-treated chickens (NL: 20%; L: 11.8%). During the third week of development, there was a 68.8% decrease in the mortality rate in light-treated chickens (NL: 20%; L: 6.25%). In addition, body weight, crown-rump length, and liver weight increased as a result of the 670-nm phototherapy. Light-treated chickens pipped (broke shell) earlier and had a shorter duration between pip and hatch.

Conclusion: These results indicate that 670-nm phototherapy by itself does not adversely affect developing embryos and may improve the hatching survival rate.

Green light emitting diode irradiation enhances fibroblast growth impaired by high glucose level

Vinck EM, Cagnie BJ, Cornelissen MJ, Declercq HA, Cambier DC

Photomed Laser Surgury (2005) 23(2): 167-71.

Background and Objective: The chronic metabolic disorder diabetes mellitus is an important cause of morbidity and mortality due to a series of common secondary metabolic complications, such as the development of severe, often slow healing skin lesions. In view of promoting the wound-healing process in diabetic patients, this preliminary in vitro study investigated the efficacy of green light emitting diode (LED) irradiation on fibroblast proliferation and viability under hyperglycemic circumstances.

Materials and Methods: To achieve hyperglycemic circumstances, embryonic chicken fibroblasts were cultured in Hanks' culture medium supplemented with 30 g/L glucose. LED irradiation was performed on 3 consecutive days with a probe emitting green light (570 nm) and a power output of 10 mW. Each treatment lasted 3 min, resulting in a radiation exposure of 0.1 J/cm2.

Results: A Mann-Whitney U test revealed a higher proliferation rate ($p = 0.001$) in all irradiated cultures in comparison with the controls.

Conclusion: According to these results, the effectiveness of green LED irradiation on fibroblasts in hyperglycemic circumstances is established. Future in vivo investigation would be worthwhile to investigate whether there are equivalent positive results in diabetic patients.

Increased fibroblast proliferation induced by light emitting diode and low power laser irradiation

Vinck EM, Cagnie BJ, Cornelissen MJ, Declercq HA, Cambier DC

Lasers Med Science (2003) 18(2): 95-9

Background and Objective: As Light Emitting Diode (LED) devices are commercially introduced as an alternative for Low Level Laser (LLL) Therapy, the ability of LED in influencing wound healing processes at cellular level was examined.

Study Design, Materials and Methods: Cultured fibroblasts were treated in a controlled, randomized manner, during three consecutive days, either with an infrared LLL or with a LED light source emitting several wavelengths (950 nm, 660 nm and 570 nm) and respective power outputs. Treatment duration varied in relation to varying surface energy densities (radiant exposures).

Results: Statistical analysis revealed a higher rate of proliferation ($p < 0.001$) in all irradiated cultures in comparison with the controls. Green light yielded a significantly higher number of cells, than red ($p < 0.001$) and infrared LED light ($p < 0.001$) and than the cultures irradiated with the LLL ($p < 0.001$); the red probe provided a higher increase ($p < 0.001$) than the infrared LED probe and than the LLL source.

Conclusion: LED and LLL irradiation resulted in an increased fibroblast proliferation in vitro. This study therefore postulates possible stimulatory effects on wound healing in vivo at the applied dosimetric parameters.

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