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Photobiomodulation: A New Dimension to Human Centric Lighting

by Jürgen Honold, Seaborough

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Abstract

Human Centric Lighting (HCL) is an established direction in General lighting, and many companies build products and services around it. It makes use of the interaction between light and photoreceptors in the retina to ultimately improve human wellbeing and productivity. The presence in the market of HCL has encouraged us to look for additional area's where human wellbeing can be improved by light.

A scientific field called Photobiomodulation (PBM) emerged the last decades in medical science and goes by, so far, mostly unnoticed by the General Lighting community. It has developed a detailed understanding of the interaction between light in the visible and near-IR spectral range and human cells. This paper aims to bridge this gap between science and lighting community, and to show the very interesting possibilities that emerge, to create new value add offerings in General Lighting based on the insights generated in the field of PBM for human wellbeing and maintenance of health.

Introduction

Photobiomodulation (PBM) involves the use of red and near-infrared light between 600-1100 nm which is absorbed by mitochondrial chromophores, in order to stimulate, regenerate, and protect tissue caused by photobiochemical interaction with the absorbed light [1]. PBM may be applied as a local therapy to (non exclusively) reduce pain, inflammation, edema, and to regenerate damaged tissues such as wounds, bones, and tendons. Next to these well researched and commonly accepted local effects, there is growing evidence that various systemic (body-wide) responses are caused by a cascade of effects following the initial light absorption [2],[3],[4],[5].

In this paper we explore the option to introduce PBM in the context of General Lighting (GL) with the aim to contribute to human general health and well-being. This results in a brand new dimension to the field of Human Centric Lighting (HCL). All existing GL solutions fall far short of delivering the required parameters (dosimetry) to stimulate the natural photo-acceptors in human tissue responsible for both local and systemic PBM. Our central hypothesis is that if we succeed to reach these required parameters transcutaneously (in and through the skin) with GL equipment, we are entitled to reap the scientifically observed systemic health benefits. We further show that the versatility of LED technology makes this possible with very reasonable power budgets.

We invite interested parties to join our ongoing efforts to develop LED devices, lamps and fixtures for this new and very exciting value-add to GL.

History

The discovery of PBM can be attributed to Endre Mester (1903–1984) in Hungary: Skin incisions made to implant cancer cells in mice appeared to heal faster in ruby laser-treated animals compared to the incisions of control animals that were not treated with light [6],[7]. When PBM (Formerly termed LLLT) was introduced to the public (90ties - early 2000), there was still some uncertainty about the right dosimetry and application parameters, which lead to negative results and misleading conclusions in some of the studies [8]. Since around 2009, dosimetry is far better understood [9],[10], and the scientific evidence in form of an exponentially increasing amount of positive scientific studies [16] supply convincing prove that PBM is safe & efficient [2],[11],[12]. Regarding the recommendation in clinical guidelines the following is the status of today: PBM recommended as first line therapy for oral mucositis [13] (NICE, MASCC); PBM recommended in the majority of guidelines for neck pain; and PBM recommended in some guidelines for achilles tendinopathy, tennis elbow and lower back pain.

However, the rapidly developing insights in dosimetry and application parameters in the last years, the still limited number of papers on systemic effects, and the lack of a structured summary of current scientific findings, might explain why this topic goes by, so far, unnoticed by the GL community. Our organization Seaborough is presumably the first to come up with an approach that translates the latest scientific insights into an economically viable application solution for GL.

Mechanisms of PBM

The generally accepted scientific theory reads as followed: The primary site of light absorption in eukaryotic cells has been identified as the mitochondria and, more specifically, cytochrome c oxidase (CCO; complex IV), which is the terminal enzyme of the electron transport chain (ETC) that mediates the electron transfer from cytochrome c to molecular oxygen. The ETC is formed of five complexes and its main purpose is to produce adenosine triphosphate (ATP); the cell energy. It is understood that photons of light at wavelengths between 600-1100nm excite complex IV, causing the dissociation of nitric oxide (NO) from its binding site, allowing oxygen to bind in its place and therefore allowing the progression of the ETC [2].

In other words, when mitochondira, the so called “powerhouses” or the “batteries” of eukaryotic cells, are in a dysfunctional state (caused by ROS, toxins or aging processes), a photoacceptor called cytochrom c oxidase within these mitochondria can absorb red and near-infrared light, which helps the mitochondria to resume their function, which is to produce ATP (cell energy). As the ETC progresses, complexes I and III of the chain also produce reactive oxygen species (ROS). The production of ROS and ATP then induce the activation of intracellular transcription factors and subsequent gene expression changes, including a

gene whose expression is commonly associated with increased mitochondrial biogenesis, and other effects on transcription of genes in the cell-core which are involved in proliferation, migration and the production of cytokines (associated with the immune response) and growth factors. This network of intra-cellular responses to PBM, and perhaps others not yet identified, combine to enhance cell and tissue resilience and regeneration [14],[15].

Unfortunately, this was only the tip of the iceberg of the already discovered or hypothesized, involved mechanisms within the field of photobiomodulation, which describes the photochemical interaction of light with human and animal tissue. There is already a large amount of scientific papers and books available about the fundamental science, and it's recommended to the interested reader to reserve some time to dig into the literature [16].

To further prepare for the content below, it is necessary to mention once more that not only the above described, local effects exist, but that there are related systemic effects, eather caused by the migration of metabolic mediators transferred through the bloodstream between the cells, the stimulated migration of stem cells to do repair jobs at damaged sites in the body, or by mechanisms stimulated through irradiation of the blood [2],[3],[4],[5],[17].

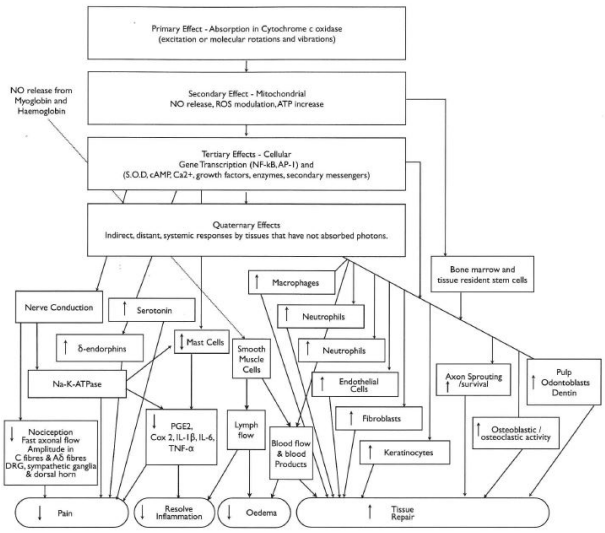

Figure 1: **The intial light absorption in the mytochondria is followed by a cascade of local and systemic effects.**

One step back before we go further: What's all the fuzz about - what's the big picture?

A popular-scientific definition what PBM may be able to achieve when combined with general lighting, is to partly address the "mal-illumination" caused by today's artificial lighting. If one spends every day almost solely in artificial lighting, one simply does not get the "maintenance" effects induced in the human body by certain wavelengths and power densities of sunlight. The photochemical interactions of tissue with such specific light prevent us from developing certain diseases and stimulate local and systemic repair mechanisms. Overall, PBM in general lighting may be able to contribute to the general well-being and maintenance of health.

The core scientific explanation for this "maintenance" effect is that photobiomodulation has mitochondria-boosting and normalizing effects, which addresses mytochondrial dysfunctionality [2],[18].

Today's leading experts in the field of gerontology (science of aging) assume that the cause of aging and its associated diseases is multifactorial [19], and mitochondrial dysfunction is one of the main factors that has been implicated in the aging process and the onset and progression of age-associated disorders, such as dementia, Alzheimer's disease, strokes, Parkinson's disease, transient ischemic attack, coronary artery disease, chronic fatigue syndrome, retinitis pigmentosa, diabetes and certain forms of cancer [20],[21],[22].

Further, mytochondrial dysfunctionality is linked to low-grade inflammation and oxidative stress, which also play major roles in ageing and a variety of chronic diseases [23],[24]. Also these aging factors are adressed by PBM via its anti-inflammatory and anti-oxidative effects [25].

Therefore, it seems very rewarding for the public health and well-being if one would be able to implement photobiomodulation in general lighting.

A fundamental approach to define PBM dosimetry for general lighting

Before we can have a look how to bring the above mentioned scientific insights into applications, we have to ask ourselves where the majority of light absorption happens under natural conditions, which then may cause systemic (and local) effects. This is necessary in the context of the right dosimetry, as we will see later in this text below.

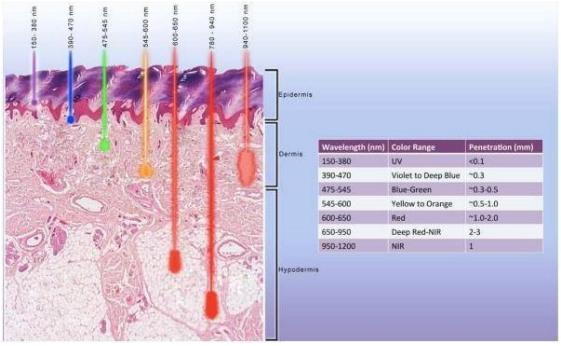

Figure 2: **The majority of light is absorbed in the skin layers.**

First of all, it seems appropriate to speculate that the layers of the skin are causally connected to at least some of the observed systemic effects since they are the main absorbers of light, as shown in the graph above.

This hypothesis can be further supported and amended by a large body of literature: Almost all assumed systemic effects can in theory be attributed to the absorption of light in the layers of the skin (non exclusively):

- potential increase of ATP levels in platelet mitochondria, immunomodulation, vasodilation,... (ec.) by irradiation of the blood in the capillary/artery in the skin [2],[17],[27].
- a variety of effects caused by absorption of light by the cells in the skin [3],[4], for example causing the migration of so called “mitokines” to other cells, following the initial light absorption in the mitochondria
- mesenchymal stem cells may be released from subcutaneous adipose tissue [26]

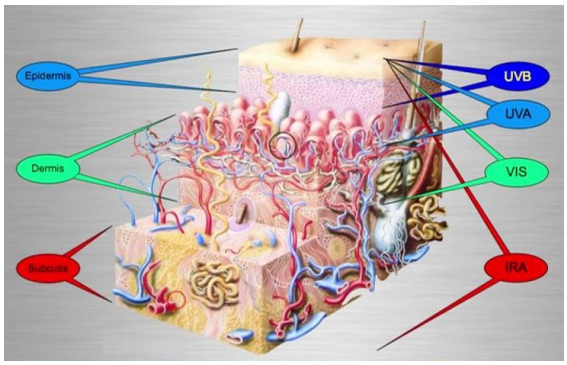

Figure 3: **Almost all discovered systemic effects can in theory be attributed to the absorption of light in the layers of the skin: (1) blood modification (dermis) [2],[17],[27]; (2) various effects following the initial light absorption in mitochondria (dermis) [3],[4]; (3) stem cell release (subcurties). [26]**

The skin is known to interface with the environment, being the first line of defense from external factors. For example, the skin plays a key role in protecting the body against pathogens and excessive water loss. Its other known functions are insulation, temperature regulation, sensation, and the production of vitamin D. However, it may be that the skin is also the main organ to absorb light in a functional way, not only to protect from UV radiation, but to trigger certain PBM related, systemic effects to maintain the functions of the body.

There are many research papers on the effect of light irradiating the skin, but they mostly investigate local effects. Proofs of systemic effects after irradiating the skin *in vivo* are still limited. However, the hypothesis of the central role the skin plays as a functional light absorbing organ to induce systemic PBM effects is directly supported by several scientific publications [17],[28]. Further, indirect but compelling evidence is obtained when one compares the range of the irradiance reached in the relevant skin layers during exposure to daylight with the optimum power densities published for PBM in *in vitro* studies [12],[29].

The above mentioned approach, to compare the power densities occurring during daylight in the relevant skin layers with the power densities which have been found to have the highest dose response in *in vitro* studies, is the key to define the dosimetry for inducing systemic and local PBM effects. This will be explained in more detail in the section below.

Translating scientific insights into today's General Lighting applications

As we move forward in this text, it is inevitable to generalize and to become more abstract to deal with the complexity of the topic and make it accesible for the general audience. Seaborough plans to publish a peer reviewed perspective paper within this year disclosing further details.

Ideal dose and power density in PBM: No law of reciprocity

One of the key scientific insights about PBM dosimetry is the fact that the law of reciprocity is not applicable in PBM. In photochemical processes, usually one can intensify the power density while shortening the time linearly to achieve the same photochemical reaction. Research has found that this law is clearly not applicable in PBM. Both, energy density and power density have distinct peaks, which means that at a certain dose or irradiance, stimulation turns into inhibition. While the power density (irradiance) curve describes kind of an S-shaped ascent, followed by a sharp decline after the maximal effectiveness is reached (see figure 5), the energy density (dose) describes a so called bell-shaped curve as displayed in figure 4. This type of dose-response in PBM is also called hormetic dose-response, biphasic dose response, or "Arndt-Schulz Law" [9],[14].

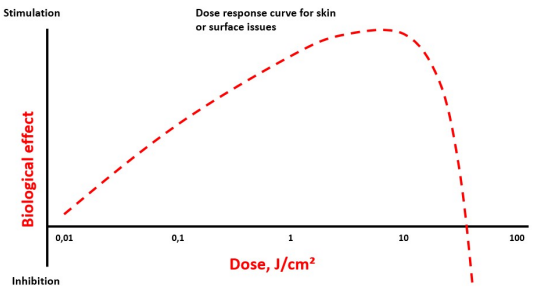

Figure 4: The energy density (dose) describes a so called bell-shaped curve. This type of dose-resonse in PBM is also called hormetic dose-response, biphasic dose response, or "Arndt-Schulz Law" [9],[14].

A good analogy to explain these dosimetric factors is the similarity with cooking: Also when cooking a dish, the applied total energy dose per unit is important to get to a good result (not over- or under-cooked), but it's not the only parameter. If the temperature is too low, the dish will never cook, independent of the time, which means there is a threshold temperature to be met to start the cooking process. This is also true for PBM dosimetry, one needs to reach a certain power density threshold, else the PBM associated photochemical reactions may not be started.

On the other side, coming back to the cooking analogy, the time can't be cut to a few seconds in combination with a thousand degrees of temperature, since the dish will instantly burn. The same is true for PBM, if a certain threshold is exceeded, the PBM effect will turn from stimulation into inhibition (There are applications which make use of the inhibition effect, for example to induce local analgesia against pain).

And finally, of course the dish will succeed best if cooked at the optimal time and temperature, which will be noticeable by the taste and texture. In PBM, the perfect time and power density will lead to the maximal biological stimulation at the lowest economical cost – which is key when adding a new fundamental technology to general lighting! However, dosimetry in PBM is complex, and the factors mentioned above are only two of many which need to be included to arrive at the ideal PBM dosimetry.

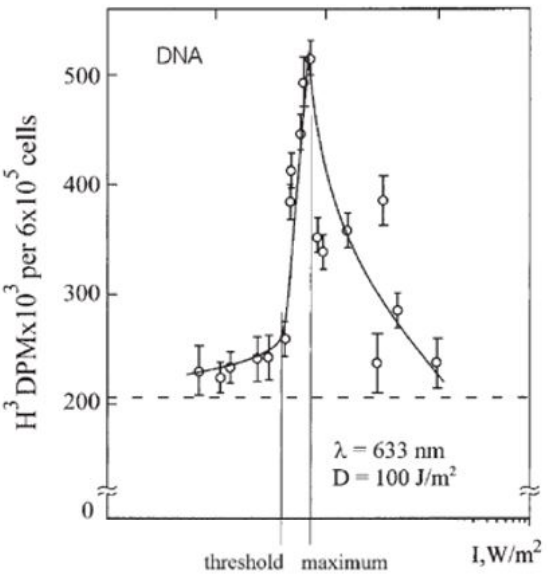

Figure 5: Dependence of stimulation of DNA synthesis rate on power density.

The fundamental equation of the required power density to cause systemic PBM

As already mentioned above, to compare power densities reached by daylight in the relevant skin layers with the power densities which are found to have the highest dose response in “in vitro” studies, is the key to define one of the most important parameters for PBM dosimetry in general lighting.

In the graphic overview (6) is shown how the effective power density supplied by sunlight can be derived from scientific insights, and how these can be compared with other scientific insights about PBM dosimetry *in vitro* and the optical properties of the skin, to come to a general understanding.

One can start at the right side of the graph, factoring in the intensities of sunlight during the day at certain wavelengths into the equation, together with the suggested action spectra and theories about the main and secondary mechanisms in PBM, to calculate the average, effective power density range during the day. This is the power density supplied to the skin under natural conditions, and it seems appropriate to speculate that such natural power densities may be most effective.

In fact, when starting in our theoretical calculation example at the target zones for inducing systemic PBM effects, assuming power densities in the relevant skin layers which have shown in *in vitro* studies the highest efficacy (at human cell samples irradiated in a lab environment), factoring in the losses over all skin layers and the reflection of the skin, then the calculation results in a similar power density range in the relevant wavelengths like supplied by sunlight!

This fundamental equation supports the hypothesis of the skin being a functional, light absorbing organ to cause systemic effects, but also enables us to implement this scientific insight in general lighting applications, like shown in the following example further below.

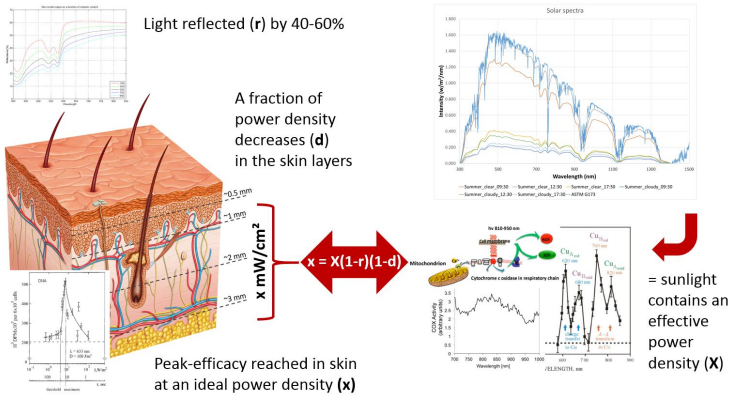

Figure 6: The effective power density supplied by sunlight can be derived from scientific insights to come to a general understanding of PBM dosimetry. This fundamental equation supports the hypothesis of the skin being a functional, light absorbing organ to cause systemic effects, but also enables us to implement this scientific insight in general lighting applications!

The power density supplied by common light sources

As of today, literally no common artificial lighting since the commercialization of electric light has fulfilled the requirements to cause photobiomodulation in an effective and economical way.

Common general lighting can‘t enable useful power density for PBM under normal circumstances. This is true for all light sources, even for incandescent with its relatively high amount of optical power between 600-1100 nm.

The effective optical power for PBM in a standard 100 W incandescent bulb results in maximal 10 effective Watts (incandescent spectrum x generalized action spectrum PBM), resulting in an effective power density of arround 0,04 mW per cm^2 from a distance of 2 m. This is orders of magnitude weaker than the required intensity threshold to cause a noticeable effect via irradiating the skin!

Or, to phrase it in a more commonly applicable sentence: Today‘s general lighting simply lacks the required intensity at the relevant wavelengths to stimulate the PBM related photo-acceptors in human skin.

Application example “Troffer”

In this application we defined the amount of added optical watts per fixture in a theoretical room having fixtures installed of the same type, which is a popular troffer from company Trilux with the Name “Belvision C1 600 CDP LED3900nw 01”.

The assumed room has the size 5x4x3m. To achieve a standard illuminance of 500 lux on an assumed working surface 75 cm above the floor, we need 3 fixtures (rounded up from exactly 2,93), at a surface reflectivity of 70 (ceiling) / 50 (walls) / 20 (floor) % and a maintenance factor of 0,8.

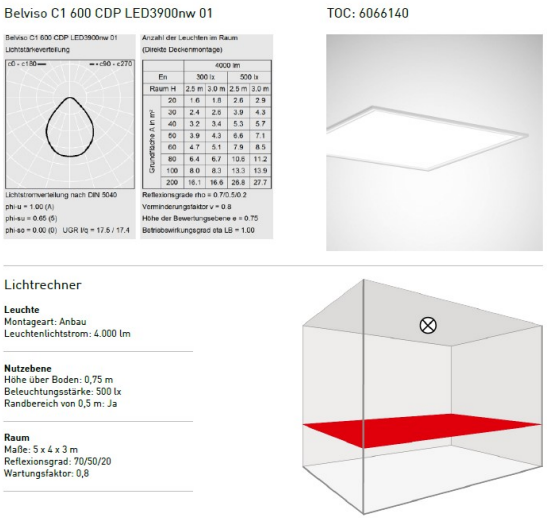

Figure 7: The theoretical room model we used for our calculations [31].

Each one of the troffers has an energy consumption of 27 W, totalling 81 W for all 3 fixtures. This results in about 4 W electronic energy consumption per m^2 working surface, or about 2 W optical per m^2 assuming an wall plug efficiency (WPE) of 50 %.

We defined the amount of added optical "PBM" watts assuming simmilar maintainance and reflection losses and simmilar radiation patterns for the integrated PBM technology (integrated wit the regular light for vision purpose). This was done following the fundamental dosimetry approach described above, to analyze how much percent of the total energy consumption per room must be allocated to the PBM technology to induce systemic PBM effects by irradiating the skin, on a daily basis in an office environment.

Position of application doses in the dose response curve

We assume that, since we target the skin to elicit systemic PBM effects, the dose response curve presented in the literature for local skin applications [30] is applicable for the stimulation strength of the systemic effects, too.

We carried out 5 different calculations with increasing doses, to compare the achieved strength of stimulating systemic and local PBM effects with the allocated percentage of electric power for PBM out of the total energy consumption for the fixtures in the assumed room:

Embodiment 2.4: 0,12 J per cm^2 per day; 0,7 W electrical power per fixture, 2 W additional electrical power per room.
Embodiment 2.0: 0,23 J per cm^2 per day; 1,3 W electrical power per fixture, 4 W additional electrical power per room.
Embodiment 2.1: 0,92 J per cm^2 per day; 5,3 W electrical power per fixture, 16 W additional electrical power per room.
Embodiment 2.2: 2,1 J per cm^2 per day; 12 W electrical power per fixture, 36 W additional electrical power per room.
Embodiment 2.3: 3,5 J per cm^2 per day; 20 W electrical power per fixture, 60 W additional electrical power per room.

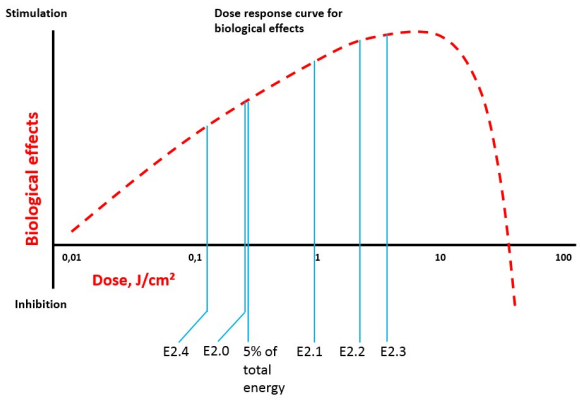

Figure 8: We have demonstrated that we may cause up to 66 % of the maximal achievable biological effect by adding less than 5 % energy consumption to a common lighting system.

Taking into account the dose effect curve of figure 8, a daily dose in the range of 0.1 to 1 J per cm^2 is the economical optimum. For reference purpose we added the line which shows the dose when we allocate 5 % of the total energy consumption of

the fixture to its PBM function and 95 percent to its regular illumination function.

We recently built and tested our first prototype on basis of the above mentioned calculations, which we used for double blind perception tests with a test pannel with subjects from our own organization. The test subjects could not visually identify if the PBM technology was switched on together with the general lighting device, or not. This shows that the technology can be built using the versatility of today‘s available LEDs and drivers, and that our technology can be implemented as an add-on to existing general lighting solutions.

Future outlook

Seaborough continues to invest in this field to obtain further evidence for the validity of the central hypothesis described in this conference contribution. Furthermore, we invite interested parties to join our ongoing efforts to develop the LED devices and lamps and fixtures for this new and very exciting dimension of human centric lighting and promising emerging value add to general lighting. Finally, we support the Good Light Group, an initiative launched during LpS 2019 by Jan Denneman, which promotes healthy and nutritional light, in which PBM fits seamlessly.

Author’s CV

Jürgen Honold, Dipl.Des.(FH)

Jürgen feeds as Technical Fellow Seaboroughs advanced lighting research and development, and founded in 2016 Seaborough Life Science, a Seaborough subsidiary with the focus on light and health. With an entrepreneurial focus and interdisciplinary approach he detects and starts research in several fields of interest, such as luminescent materials and advanced designs and systems. As renowned developer of lighting concepts, electronics researcher, and award winning designer, Jürgen has lived for the vision of bringing LED light to life since 1999, adding numerous inventions to his name since.

Martijn Dekker, Dr.

After a PhD in theoretical physics, Martijn has joined Philips in 1993 and contributed to several different fields such as electron optics, micromagnetism, optical recording, lithography and personal care products. In 2007 he joined as CTO Lemnis Lighting, a pioneering company for retrofit LED lighting solutions. Between 2013 and 2017 he was MD of Carus, a fully automated German manufacturer of LED retrofit lamps. At present he is CEO and CTO of Seaborough, a Dutch R&D company that specializes in breakthrough technology developments in electronics, materials and applications for LED.

Organisation

Seaborough

Seaborough invents, develops and commercializes groundbreaking innovations for the lighting industry. Based in Amsterdam, Seaborough employs an expert team of electrical and lighting engineers, industrial designers, physicists and chemical engineers, and works in close collaboration with external specialists, each of them prominent in their field. In addition, the company runs a number of long-term research and development projects in collaboration with world leading research institutes and universities.

Seaborough develops for its own account intellectual property rights (IP)-specifically in LED systems- that are commercialized through licensing, outright sale or contracts with strategic partners. Some of the concepts and IP are developed in-house through to finished products and commercialized through dedicated, group-owned, companies. Seaborough is majority-owned by Momentum Capital, a specialized private equity firm; is fully financed by shareholder funds, and completely free of bank debt.

Seaborough Life Science

Seaborough Life Science (SLS) is a Seaborough subsidiary with the focus on light and health. Founded in 2016, SLS invents and develops technologies to improve peoples well-being and health. Next to running a material research with the aim to enable novel therapies to treat certain skin diseases, SLS‘s most recent activities are in the field of photobiomodulation, a science of certain biochemical interactions of light with living tissue.

References

[1] Hamblin, M. R. (2018). Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. Photochemistry and Photobiology, 94(2), 199–212. doi:10.1111/php.12864

[2] Durieux, J., Wolff, S., & Dillin, A. (2011). The Cell-Non-Autonomous Nature of Electron Transport Chain-Mediated Longevity. Cell, 144(1), 79–91. doi:10.1016/j.cell.2010.12.016

[3] Kim, B., Brandli, A., Mitrofanis, J., Stone, J., Purushothuman, S., & Johnstone, D. M. (2017). Remote tissue conditioning — An emerging approach for inducing body-wide protection against diseases of ageing. Ageing Research Reviews, 37, 69–78. doi:10.1016/j.arr.2017.05.005

[4] Johnstone, D. M., Moro, C., Stone, J., Benabid, A.-L., & Mitrofanis, J. (2016). Turning On Lights to Stop Neurodegeneration: The Potential of Near Infrared Light Therapy in Alzheimer's and Parkinson's Disease. Frontiers in Neuroscience, 9. doi:10.3389/fnins.2015.00500

[5] Daniel M Johnstone, John Mitrofanis, Jonathan Stone (2015). Targeting the body to protect the brain: inducing neuroprotection with remotely-applied near infrared light. Neural Regeneration research, V10;Issue3. Doi:10.4103/1673-5374.153673

[6] L. Gaspar, (2009). Professor Endre Mester, the father of photobiomodulation,J. Laser Dentistry. 17, 146–148.

[7] Mester, A., & Mester, A. (2017). The History of Photobiomodulation: Endre Mester (1903–1984). Photomedicine and Laser Surgery, 35(8), 393–394. doi:10.1089/pho.2017.4332

[8] TUNÉR, J., & HODE, L. (1998). It's All in the Parameters: A Critical Analysis of Some Well-Known Negative Studies on Low-Level Laser Therapy. Journal of Clinical Laser Medicine & Surgery, 16(5), 245–248. doi:10.1089/clm.1998.16.245

[9] Huang, Y.Y., Sharma, S.K., Carroll, J., Hamblin, M.R., 2011. Biphasic dose response in low level light therapy – an update. Dose Response 9, 602–618. doi: 10.2203/dose-response.11-009.Hamblin

[10] Jenkins, P. A., & Carroll, J. D. (2011). How to Report Low-Level Laser Therapy (LLLT)/Photomedicine Dose and Beam Parameters in Clinical and Laboratory Studies. Photomedicine and Laser Surgery, 29(12), 785–787. doi:10.1089/pho.2011.9895

[11] Tsai, S.-R., & Hamblin, M. R. (2017). Biological effects and medical applications of infrared radiation. Journal of Photochemistry and Photobiology B: Biology, 170, 197–207. doi:10.1016/j.jphotobiol.2017.04.014

[12] Daniel Barolet, François Christiaens, Michael R. Hamblin (2016).Infrared and skin: Friend or foe. Journal of Photochemistry & Photobiology, B: Biology 155 (2016) 78–85. doi: 10.1016/j.jphotobiol.2015.12.014

[13] Marín-Conde, F., Castellanos-Cosano, L., Pachón-Ibañez, J., Serrera-Figallo, M. A., Gutiérrez-Pérez, J. L., & Torres-Lagares, D. (2018). Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radio-chemotherapy: prospective randomized controlled trial. International Journal of Oral and Maxillofacial Surgery. doi:10.1016/j.ijom.2018.12.006

[14] Chung, H., Dai, T., Sharma, S.K., Huang, Y.Y., Carroll, J.D., Hamblin, M.R., 2012. The nuts and bolts of low-level laser (light) therapy. Ann. Biomed. Eng. 40,516–533. doi: 10.1007/s10439-011-0454-7

[15] Rojas, J.C., Gonzalez-Lima, F., 2011. Low-level light therapy of the eye and brain.Eye Brain 3, 49–67. doi: 10.2147/EB.S21391

[16] Low level laser therapy (LLLT) / photobiomodulation (PBM) / red/NIR phototherapy studies - a comprehensive database by V.Heiskanen

[17] Zhevago, N. A., & Samoilova, K. A. (2006). Pro- and Anti-inflammatory Cytokine Content in Human Peripheral Blood after Its Transcutaneous (in Vivo) and Direct (in Vitro) Irradiation with Polychromatic Visible and Infrared Light. Photomedicine and Laser Surgery, 24(2), 129–139. doi:10.1089/pho.2006.24.129

[18] Wang, R., Dong, Y., Lu, Y., Zhang, W., Brann, D. W., & Zhang, Q. (2018). Photobiomodulation for Global Cerebral Ischemia: Targeting Mitochondrial Dynamics and Functions. Molecular Neurobiology. doi:10.1007/s12035-018-1191-9

[19] López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The Hallmarks of Aging. Cell, 153(6), 1194–1217. doi:10.1016/j.cell.2013.05.039

[20] Wenz, T. (2011). Mitochondria and PGC-1α in Aging and Age-Associated Diseases. Journal of Aging Research, 2011, 1–12. doi:10.4061/2011/810619

[21] Whitaker, R. M., Corum, D., Beeson, C. C., & Schnellmann, R. G. (2016). Mitochondrial Biogenesis as a Pharmacological Target: A New Approach to Acute and Chronic Diseases. Annual Review of Pharmacology and Toxicology, 56(1), 229–249. doi:10.1146/annurev-pharmtox-010715-103155

[22] Pieczenik, S. R., & Neustadt, J. (2007). Mitochondrial dysfunction and molecular pathways of disease. Experimental and Molecular Pathology, 83(1), 84–92. doi:10.1016/j.yexmp.2006.09.008

[23] Camps, J., & García-Heredia, A. (2014). Introduction: Oxidation and Inflammation, A Molecular Link Between Non-communicable Diseases. Oxidative Stress and Inflammation in Non-Communicable Diseases - Molecular Mechanisms and Perspectives in Therapeutics, 1–4. doi:10.1007/978-3-319-07320-0-1

[24] Bartos, A., Grondin, Y., Bortoni, M. E., Ghelfi, E., Sepulveda, R., Carroll, J., & Rogers, R. A. (2016). Pre-conditioning with near infrared photobiomodulation reduces inflammatory cytokines and markers of oxidative stress in cochlear hair cells. Journal of Biophotonics, 9(11-12), 1125–1135. doi:10.1002/jbio.201500209

[25] R Hamblin, M. (2017). Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophysics, 4(3), 337–361. doi:10.3934/biophy.2017.3.337

[26] Mvula, B., Moore, T. J., & Abrahamse, H. (2009). Effect of low-level laser irradiation and epidermal growth factor on adult human adipose-derived stem cells. Lasers in Medical Science, 25(1), 33–39. doi:10.1007/s10103-008-0636-1

[27] Moshkovska, T. (2005). It is time to test low level laser therapy in Great Britain. Postgraduate Medical Journal, 81(957), 436–441. doi:10.1136/pgmj.2004.027755

[28] J. Ty Hopkins; Todd A. McLoda; Jeff G. Seegmiller; G. David Baxter (2004). Low-Level Laser Therapy Facilitates Superficial Wound Healing in Humans: A Triple-Blind, Sham-Controlled Study. Journal of Athletic Training 2004;39(3):223–229

[29] T.I. KARU, Ph.D., and S.F. KOLYAKOV, M.S. Exact Action Spectra for Cellular Responses Relevant to Phototherapy. Photomedicine and Laser Surgery. Volume 23, Number 4, 2005

[30] Ari Whitten (2018) The Ultimate Guide To Red Light Therapy: How to Use Red and Near-Infrared Light

Therapy for Anti-Aging, Fat Loss, Muscle Gain, Performance, and Brain Optimization
[31] https://www.trilux.com/products/id/Belviso-C1-600-CDP-LED3900nw-ET-01