-Dr Michael R Hamblin's opinion on the laser therapy for hair loss practised by Advanced Hair Studio.

Michael Hamblin is a Principal Investigator at the Wellman Center for Photomedicine at Massachusetts General Hospital, an Associate Professor of Dermatology at Harvard Medical School and a member of the Affiliated Faculty of Harvard-MIT Division of Health Science and Technology. He was trained as a synthetic organic chemist and received his PhD from Trent University in England. He joined Wellman Labs in 1994. He worked initially in targeted photodynamic therapy (PDT) and prepared and studied conjugates between photosensitizers and antibodies or targeted proteins and polymers of varying charge.

His research interests are now broadly in the area of phototherapy for multiple diseases. One focus is the study of new photosensitizers for infections, cancer, and heart disease. A specialty of the Hamblin lab is the development of new animal models for testing PDT approaches. The study of how PDT can activate the host immune system to attack advanced cancer is a new direction in the Hamblin lab. A second focus is low-level light therapy (LLLT) for wound healing, arthritis, traumatic brain injury and hair regrowth.

Dr. Hamblin has published over 185 peer-reviewed articles, over 150 conference proceedings, book chapters and international abstracts, and he holds eight patents. He has edited the most recent and comprehensive textbook on PDT entitled "Advances in Photodynamic Therapy: Basic, Translational and Clinical". He also co-edited a book entitled "Photodynamic Inactivation of Microbial Pathogens: Medical and Environmental Applications" and an authoritative and comprehensive textbook entitled "Handbook of Photomedicine" with 70 chapters and 800 pages is reaching completion. He has developed an interest in elucidating the basic molecular and cellular mechanisms of LLLT, and for the past eight years has chaired an annual conference at SPIE entitled "Mechanisms for Low Level Light Therapy" and has co-edited the 8 Proceedings of SPIE volumes associated with these conferences. He is Associate Editor of 7 International Journals including Photochemistry and Photobiology, PLoS ONE, Photodiagnosis and Photodynamic Therapy and Journal of Nanomedicine and Nanotechnology. He is on the editorial boards of a further 15 journals and has peer-reviewed for a total of 165 journals. He has served on numerous study sections and grant-reviewing panels and is on the scientific advisory boards of several companies.·

Declarations

I have read and complied with CPR Part 35.

I have read Ms Banno's Witness Statement including reference to 4 adjudications by the ASA (paragraphs 17-21) which show laser therapy in a negative light.

Low Level Laser (Light) Therapy for Hair Regrowth

It is interesting to recall that low level laser therapy (LLLT) was accidentally discovered by Endre Mester·in 1967 [1] when attempting to cure mice with cancer [2] using the newly discovered ruby laser

(1960) [3]. Although he did not cure cancer, he did induce regrowth of mouse hair in the shaved areas that were specifically irradiated with laser spots. This serendipitous discovery spurred Mester on to make many further discoveries in the area of laser therapy used for wound healing and relief of pain and inflammation [4,5].

The next publications regarding laser therapy induced hair regrowth came about because of the rise in popularity of laser hair removal. It was noticed that in some cases that, increase in hair density, color or coarseness or a combination of these occurs at or around sites treated for hair removal with lasers [6,7,8,9]. This phenomenon was called 'Paradoxical Hypertrichosis' and the incidence varies from 0,6% to 10% [6]. A group of researchers also observed transformation of small vellus hairs into larger terminal hairs upon low fluence diode laser treatment and named this phenomenon 'terminalization' of vellus hair follicles [10,11].

Yamazaki and colleagues observed in that following irradiation of the backs of Sprague Dawley rats with SuperLizer (a light with a high output (1.8 W) of infrared radiation (600-1600 nm), there was increased hair growth. This was attributed to an upregulation of hepatocyte growth factor (HGF) and HGF activator expression [12]. In order to test the effect of linear polarized infrared irradiation in clinical treatment of alopecia areata, a study was conducted with 15 patients (6 men, 9 women) using Super Lizer ™ [13]. The scalp was irradiated for 3 min. once every week or for every 2 weeks and additionally carpronium chloride 5% was applied twice daily to all the lesions [13]. Furthermore, oral antihistamines, cepharanthin and glycyrrhizin (extracts of Chinese medicine herbs) were prescribed [13]. As a result of this study, in 47% of the patients, hair growth occurred 1,6 months earlier in irradiated areas than in non-irradiated areas [13].

A study conducted by Wikramanayake et al. on the C3H/HeJ mouse model of alopecia areata used mice treated with the Advanced Hair Studio Laser Comb manufactured by HairMax® **(**emits 9 beams and attached combs help to part the hairs and improve delivery of laser light to scalp), 655 nm for 20 s daily three times per week for a total of 6 weeks [6]. At the end of the treatment, hair regrowth was observed in all the laser treated mice but no difference was observed in sham-treated group [6]. On histology, while increased number of anagen hair follicles was observed in laser-treated mice, sham-treated mice demonstrated hair follicles in the telogen phase [6].The increased number of hair follicles showed decreased inflammatory infiltrates [6]. Considering that inflammatory infiltrates are highly disruptive to the hair follicles and multiple cytokines such as IFN-γ, IL-1α and β, TNF- α, MHC and Fas-antigen and macrophage migration inhibitory factor are all involved in the cyclic hair growth and have been shown to play a role in the pathogenesis of AA, modulatory effects of LLLT on inflammation might have a significant role in treatment of AA [6].

Shukla et al. investigated the effect of helium-neon (He-Ne) laser (632 nm, at doses of 1 and 5 J/cm^2 at 24 hour intervals for 5 days) on the hair follicle growth cycle of testosterone-treated and un-treated Swiss albino mice skin [14]. The results showed that exposure to the He-Ne laser at a dose of 1 J/cm^2 led to significant increase in % of hair follicles at anagen phase compared to that of the control group which received no testosterone treatment nor He-Ne laser irradiation and exposure to the He-Ne laser at a dose of 5 J/cm^2 led to a significant decrease compared to control group, which might be expected considering the biphasic effect of LLLT [14,15]. Moreover, testosterone treatment led to the inhibition of hair growth with respect to the control group, which was characterized by a significant reduction in % catagen follicles [14]. However, in the testosterone-treated mice that received He-Ne laser at a dose of 1 J/cm^2, a significant increase in % of hair follicles, with respect to only testestorone treated mice has been observed. When the testosterone treated mice received He-Ne laser at 5 J/cm^2, relative % of hair follicles at telogen phase doubled [14]. Since hair growth promoting effect of He-Ne laser (1J/cm^2) was much higher for the testosterone-treated mice than the control, it can be suggested that cells growing at slower rate or under stress conditions respond better to the stimulatory effects of LLLT. Another important observation in this study that is worth mentioning is that; in He-Ne laser (1 J/cm^2) irradiated skin, some of the anagen follicles appeared from a higher depth and possessed a different orientation [14]. Such follicles are known to represent the late anagen stage in the hair growth cycle so the presence of these follicles may suggest that laser irradiation prolongs the anagen phase [16,17]. Furthermore, in testosterone-treated and He-Ne (1 J/cm^2) irradiated skin, hair follicles were seen to originate from the middle of the dermis, and these follicles represent early anagen phase [14]. These two observations taken together conclude that majority of catagen and telogen follicles re-enter into anagen phase as a result of low-level laser irradiation at 1 J/cm^2.

Using 655 nm red light and 780 nm infrared light once a day for ten minutes, 24 male patients with androgenetic alopecia (AGA) were evaluated by Kim and colleagues [18]. Evaluation was performed via global photography and phototrichograms [18]. Following 14 weeks of treatment, the density of hairs and anogen/telogen ratio on both the vertex and occiput was significantly increased, and 83% of the patients reported to be satisfied with the treatment [18].

Satino et al. tested the efficacy of LLLT on hair growth and tensile strength on 28 male and 7 female AGA patients [19]. Each patient was given a HairMax LaserComb® 655 nm, equivalent to the Advanced Hair Studio Laser Comb to use at home for 6 months for five to ten minutes every other day [19]. In terms of hair tensile strength, the results revealed greater improvement in the vertex area for males and temporal area for females, however both sexes benefited in all areas significantly [19]. In terms of hair count, both sexes and all areas had significant improvement but males and the vertex area had the best results [19]. The same device was tested by Leavitt et al. in a double-blind, sham device-controlled, multicenter, 26 week trial randomized study among 110 male AGA patients [20]. The subjects used the device three times per week for 15 minutes for a total of 26 weeks [20]. Significantly greater increase in mean terminal hair density compared to subjects in the sham device group has been reported [20]. Significant improvements in overall hair regrowth, slowing of hair loss, thicker feeling hair, better scalp health and hair shine were also demonstrated in terms of patients' subjective assessment at 26 weeks over baseline [20].

Acceptance of LLLT for hair growth by scientific community.

In my opinion the date when the scientific community accepted laser therapy as efficacious in hair regrowth was after the publication of the first LaserComb study in a US peer reviewed journal in 2009 [20]. Since this was the pivotal study consisting of a randomized, double-blind, sham device-controlled, multicentre trial that led to US FDA approval it cannot be ignored, disputed or disbelieved. It is a fundamental tenet of peer-review of the biomedical literature that a published report has to be accepted by the scientific community unless it can be shown by at least one (and preferably more than one) different study that the data was unrepeatable or else evidence of fabrication is brought forward. Since none of these events has occurred the validity of the study must still be accepted. Furthermore its validity has been bolstered by additional reports of clinical efficacy and further studies in animal models.

Since 2009 there in fact have been at least two peer-reviewed reviews published on the use of LLLT for hair regrowth. One by Ghanaat [21] in the Southern Medical Journal in 2010 entitled "Types of hair loss and treatment options, including the novel low-level light therapy and its proposed mechanism." and another by Avram and Rogers [22] in 2009 in the Journal of Cosmetic Laser Therapy entitled "The use of low-level light for hair growth: part I.".

LLLT has been proposed as a treatment for many severe diseases such as stroke, traumatic brain injury, spinal cord repair, heart attacks, Alzheimer's disease, multiple sclerosis to name a few [15]. I believe that compared to these serious and life-threatening conditions, the use of LLLT for hair regrowth is perhaps the most believable and obvious application [15]. The question may be asked – why would it not work?

Hair follicles are superficial, the fundamental follicular structure is still intact in patients with thinning hair and there is a plausible mechanism of action (see below).

Mechanisms of action of LLLT for hair growth.

The molecular, cellular, and physiological mechanisms involved in the use of laser therapy in hair regrowth are becoming understood. The photons are absorbed in cytochrome c oxidase (CCO) which is unit 4 in the mitochondrial respiratory chain. CCO is a multi-sub-unit protein that contains two heme groups and two copper centers that provide distinct absorption bands in the red and near infra-red spectral regions. Nitric oxide (NO) that is bound to CCO may be released by photon absorption [23], and it is certain that CCO activity, oxygen consumption, mitochondrial membrane potential, and ATP formation are all increased [24]. Increased ATP leads to more cyclic AMP (cAMP) and the raised mitochondrial activity leads to a short burst of reactive oxygen species (ROS). cAMP, NO and ROS are all potent signaling molecules that can cause activation of transcription factors such as NF-kB [25]. NF-kB is responsible for causing expression of many genes related to proliferation, cell migration and cell adhesion molecules all of which are needed for hair regrowth [26]. Perhaps most relevant to hair regrowth is the fact that the hair follicle stem cells that reside in the bulge region [27] are extremely sensitive to laser therapy. It has recently been discovered that quiescent stem cells are hypoxic, have slow metabolism, only rudimentary mitochondria and rely on glycolysis rather than on oxidative phosphorylation [28]. When the photons are absorbed in their rudimentary mitochondria the stimulation sets of a whole chain of events resulting in the quiescent stem cells becoming activated, proliferating and differentiating [29]. Mitochondrogenesis (the proliferation of mitochondria) is set off and oxidative phosphorylation is upregulated [30]. These activated stem cells become the progenitor cells in the bulb of the hair follicle responsible for producing new hairs [31].

Other physiological mechanisms that may be operating are the increased blood flow [32] to the hair follicle caused by the NO release secondary to laser therapy [33]. Moreover there is evidence that NO itself may be involved in hair follicle function and hair growth [34]. Furthermore it is well-known that laser therapy is anti-inflammatory [35] and there is evidence (particularly in the case of alopecia areata and fibrosing alopecia) that inflammation is heavily involved in hair loss [36]. By analogy to the action of minoxidil on increasing hair growth it may also be hypothesized that LLLT might work by increasing VEGF expression [37] as does minoxidil [38] or by opening ATP-sensitive potassium channels as does minoxidil [39]. Laser phototherapy is assumed to stimulate hair follicles to re-enter anagen growth phase from telogen phase, increase rates of proliferation in active anagen hair follicles, prevent premature catagen development and prolong duration of anagen phase [6,20].

Laser parameters employed by Advanced Hair Studio (AHS).

There are several devices that have been employed to deliver LLLT to the scalp with the purpose of stimulating hair growth. They can be divided into three broad categories (i) laser comb type devices that deliver light to the scalp with some mechanical action needed to part the hair provided by the user; (ii) laser cap type devices that are worn on the head by the user and provide4 light to the whole scalp at one time; (iii) laser hood type devices; these are used at spas and clinics and are similar to a hair dryer with a hood that covers the head. The light that is used Is most frequently coherent laser light rather than non-coherent LED light and the wavelengths are mostly in the red range (630-670 nm) but some infrared is also used either alone or combined with red. Total power levels are in the range of 50 mW to 1.2 W and irradiances are in the region of a few mW/cm^2 to tens of mW/cm^2. Total fluences applied are in the region of 1 J/cm^2 to 20 J/cm^2. Since AHS use 635 or 655 nm and total powers in the region 5—180 mW and in one case they combine the red laser with NIR LED (940-nm). **I would therefore assert that the AHS parameters are well within the range of parameters that have been shown to be successful for hair regrowth, and that there is therefore no reason to doubt that the treatment would regrow hair in suitable subjects (i.e. thinning hair).**

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