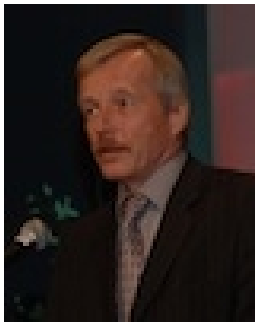
FormulaCare

FormulaCare Free Webinar hosted by the Leading Industry Authority on Skin Whitening Professor Dr. Karl Lintner



Many of you will know Dr Karl Lintner from his days with Sederma but now Karl is working as a consultant to the Industry via his company Kalidees karl.lintner@kalidees.com

Karl says that from α (Alpha amino acids) to π (Peptides) and to ω (Omega hydroxy ceramides), modern cosmetic formulas (skin care, hair care, body care…) need **concepts** based on science, understanding of skin and hair physiology, innovative mechanisms of action and marketing appeal.

His 20 years of wide ranging experience in the field allow him to propose his services to assist companies in the above tasks by bringing "Beauty Ideas to the Beauty Counter", from Mass Market to Luxury Brand, from Anti-age to Whitening, from Me-too to Exclusive High-Tech.

Karl is also an Associate Professor at Versailles St. Quentin University in France and has very kindly given his time to give free training to the formulators in Asia via FormulaCare webinars.

His presentation Age spots: causes and cosmetic treatments was well attended and below is the summary of his presentation.

These webinars are free to anyone who wishes to register and are held approximately every 6 weeks with a different topic. www.formulacare.com to register and check to see what webinar you would like to attend.

Age spots – Causes and Treatments

Prof. Dr. Karl LINTNER

Age spots, also called *Lentigo senile*, are small, localized, sharply circumscribed sites of hyperpigmentation of the skin. Contrary to freckles, which are due to an UV-induced increased, but reversible production of melanin, lentigines are caused by local hyperplasia (cell proliferation) at the basal layer of the epidermis. Melasma, another symptom of hyperpigmentation and of esthetic concern to Asian population, is characterized by diffuse patches of brownish colour, often induced by hormonal imbalance ("pregnancy masks") and sometimes reversible.
In order to understand the causes of age spots, a few words about the physiology of skin pigmentation: melanocytes are embedded at the base of the epidermis, close to the epidermal/dermal junction. From a single melanocyte, dendrites (finger like extensions) reach out to the surrounding keratinocytes (about 35-40 of those are in contact with one melanocyte, this entity being called the Melanin Unit). In the melanocyte, small organelles called Melanosomes are formed continuously and migrate to the extremities of the dendrites. These melanosomes are the true "factories" of melanin production: they contain a large number of copies of the enzyme Tyrosinase, which is a key molecule in the synthetic pathway of melanin. Tyrosinase needs the amino acid Tyrosine as the initial substrate for melanin synthesis, which proceeds from Tyrosine to Dopa, to Dopaquinone, to Leucodopachrome, to 5,6 indolequinone and via polymerization steps to melanin. The melanosomes are then transferred to the surrounding keratinocytes in a process that resembles phagocytosis.

Fig 1 (slide 1)

Several of these transformative steps are catalyzed by Tyrosinase, and are based on the oxidizing power of this enzyme. The process is however more complex than can be described here, a number of side-tracks and alternative paths can be activated, such that tyrosinase inhibition alone is rarely successful in treating hyperpigmentation.
Tyrosinase is not the only story; we need to look upstream events, linked to UV irradiation: solar rays (UV-B) stimulate keratinocytes to produce POMC (proopiomelanocortine) which is then metabolized to α–MSH, the melanin stimulating hormone. It attaches to the MC1R receptor of melanocytes, activates adenylcyclase, leading to increased amount of cAMP. Via PKA, CREB and MITF transcription factors, increased production of tyrosinase is initiated, in the end leading to more melanin.

Fig 2 (slide 2)
However, it is not only UV radiation that can cause hyperpigmentation; inflammatory processes (caused by medication, injections and other stresses) as well as hormonal imbalance (estrogens) are well known to induce free radical production, increase in pigmented macrophages and increased melanin production.
The appearance of age spots requires one more explanation: why is the hyperpigmentation symptom not homogenous, but localized? Recent studies by the LVMH company have begun to elucidate the reasons. The epidermal/dermal junction (EDJ) is not a flat sheet but a very convoluted curvy structure, where so called rete ridges extend more or less deeply into the dermal tissue. It is in these rete ridges that pigmentation accumulates, especially when the EDJ is disrupted and disorganized, e.g. as a consequence of inflammation, traumatic stress, metabolic perturbations. Consequently, increased amounts of interleukin 1α, GM-CSF and Endothelin-1 are released by keratinocytes, which molecules are all signals for increased melanin production. Investigations by Shiseido have revealed another culprit: heparanase, an enzyme that degrades heparin sulfate at the epidermal basement membrane causes epidermal

hyperplasia, increase in blood vessel generation and increased melanin synthesis. This is further confirmation for the observation that disruptive processes at the basal membrane are – at least partially – responsible for excessive pigmentation at the local level. The researchers also saw that inhibiting the heparanase enzyme decreased melanogenesis.

This brings us to the question of possible cosmetic treatments and counteractions.
From the above paragraphs it becomes evident that a number of attack points exist:

- inhibition of the tyrosinase enzyme and/or of its activation within the melanocyte
- enhancement of the enzyme's degradation and disappearance
- downregulation of MC1R activity and inhibition of MITF transcription
- interference with melanosome maturation and transfer
- inhibition of heparanase
- increase in desquamation and chemical peeling to remove older pigmented cells

Classical melanogenesis inhibitors have been described over many years: hydroquinone (HQ) was used for a long time for "skin whitening", until its risks to human health became too obvious to overlook, it is now banned in most countries.
Arbutin, the glycosylated form of HQ is reputed to be less toxic; it binds to tyrosinase and inhibits its activity. Kojic acid acts mostly by specific sequestering of the copper ions needed for tyrosinase activity; this substance also raised toxicological concerns.
Widely used are ascorbic acid (vitamin C)and its derivatives for their considerable anti-oxidant activity (we have seen that melanin synthesis requires several oxidation steps with which any anti-oxidant might interfere). The mechanisms by which retinoids act on melanin synthesis appear to be many, but at the same time confusingly so.
As *lentigo* – although localized – is still caused by excessive melanogenesis based on the same mechanisms as elsewhere in the skin, there is little chance of finding specific products to treat these age spots. What works on melanin synthesis in general will work on age spots, maybe even more. This is also claimed for a novel analogue of arbutin, called Deoxyarbutin, recently patented and licensed to an American company.
A literature survey of recent attempts to find new melanogenesis inhibitors turns up various exotic substances, such as Platycodin D, acting on the cAMP/MITF pathway and reducing inflammation; DMHF, a natural furanone that acts on CREB, MITF and Tyrosinase transcripton; Diosgenin (yam extract) interfering with the PI3K pathway and MITF; quercetin (from oak bark) that reduces TRP1 and TRP2 expression, and diminishes cAMP production; and Zeolite A4, an aluminum silicate which appears to have multiple activities including copper chelation, calcium transport inhibition and MITF reduction.
Better documented and studied approaches involve a derivative of the natural boldine substance (diacetylboldine) which inhibits α,β adrenergic receptors, Calcium transport and PKC activation of tyrosinase, leading to measurable skin lightening, including phototype V and VI skins and age spots on Caucasian skin.
A specific hop extract rich in xantohumol was shown to interfere with the all important keratinocyte-melanocyte communication (via GM-CSF) and the β-catenin pathway in melanocytes. Genomic analysis allowed the mechanisms to be well understood, while clinical data showed the pertinence of the concept.
Niacinamide and Oridonine (a *Rabdosia rubescens* extract) are active by inhibiting melanosome transfer and melanin uptake by keratinocytes; some anti-inflammatory plant extracts of recent development (tomato extracted phytoenes, *Narzissus tazetta* bulb extract, sea lily extract, *Rheum rhaponticum* extract) might also be mentioned.

In conclusion it is important to understand that melanin synthesis is a highly complex process that is still only partly understood and which involves too many parallel pathways for a single active ingredient to be significantly effective. A multi-pronged approach to skin lightening is therefore recommended. Care must be taken to evaluate ideas and substances not only on mouse melanoma B16 cells, but also on normal human melanocytes, on 3D skin models of various provenance and skin types and finally in well conducted clinical trials.