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SUNLESS TANNING: SPRAY TANS TO MOLECULAR SCIENCE

Lorna Jackson talks to Prof. Desmond Tobin about small molecule research now driving the race to the fake tan marketplace.

Tanning, especially that induced by ultra-violet radiation (UVR) exposure, is a controversial topic. Many people have something of a 'love-hate' relationship with it – knowing the potential dangers, but wanting it nonetheless.

Having a 'sun-kissed' glow is considered a desirable attribute, adding a 'healthy' aspect to an individual; making it a sought-after skin accompaniment. Not wanting to look 'pale' and 'pasty' is all the driving force that most of us need to acquire a tan, whether naturally or unnaturally.

Have a UVR-induced tan can never really be called a 'healthy tan' – the reaction that your skin demonstrates when exposed to UVR is that of a fighter protecting itself, putting up a shield, but some of the targeted blows will still get past and inflict minor wounds in the form of long-term DNA damage, made worse by cumulative exposure or multiple 'battles'.

Most of us are aware of the inherent dangers from pursuing the sun, or sunbeds, for that all-over body bronzing – worst case we could end up with a serious melanoma or skin cancer, but there are plenty of other undesirable consequences including wrinkles and lax skin or pigmented age spots, alongside the dreaded 'leather-look' that all comes from sun-tanning. 80 to 90% of skin ageing on our faces is due to cumulative exposure to UVR, with intrinsic ageing playing only a minor role in this decline.

We know that we should wear high sun protection factor (SPF) sunscreen – "*doesn't that defeat the object though*", many wanting a tan will say – or that we should avoid the sun completely or cover-up (especially at the hottest times of the day), to be fully protected from UVR exposure. Artificial tanning beds are becoming more of a no-no in the public conscience. Regulators around the globe have implemented prohibitions on the availability of indoor sunbeds to those under 18 years of age, to kerb UVR exposure in the young, yet policing and monitoring remains an issue. The stark reality that we should all be aware of is that studies have shown that there are more skin cancer cases due to indoor tanning with sunbeds than there are lung cancer cases due to smoking.[1] Medical professionals are only now starting to see an explosion in incidents of melanoma in women entering their middle age who have had considerable exposure to UVR through tanning beds in their youth.

With this in mind – the desire for a tanned look, but the fear of health implications from a UVR-induced tan – has pushed many people to seek alternative ways to provide the 'tanned' colour change seen by natural melanin production, neo-melanogensis, in their skin upon sun exposure. The market growth in the self-tanning product manufacturing industry has seen projected revenues rise from $609.3m in 2012 to $1.017bn in 2017.[2]

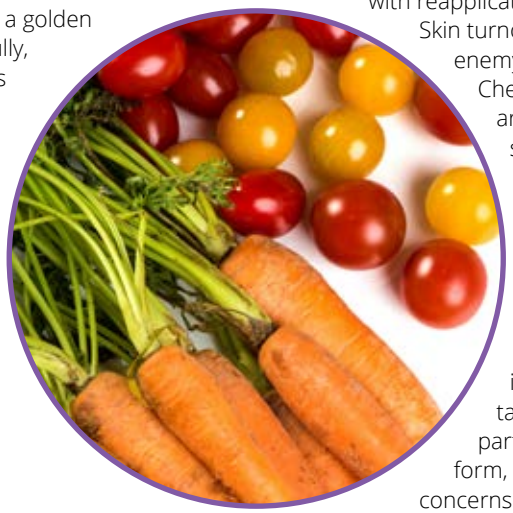
Some look at ways to '*eat yourself to a tan*', others look to stain the skin to create an artificial or fake tan effect through spray-on chemicals or natural stainers, and finally there are ways to stimulate the pigment cells to produce the desired melanin – so called melanogenesis stimulators. But now scientists are more interested in looking at new sun-less tanning options including topical peptide-derived and small-molecule solutions. The race to market is now on between researchers from the USA and the United Kingdom to bring a whole new option to the self-tanning marketplace.

Two such scientists, Professor Desmond J. Tobin and Dr. Suman Kumar Singh from the Centre for Skin Sciences at the University of Bradford are at the frontline of the UK's ambitions to achieve this goal, through the development of a topical peptide-derived solution. Speaking to Prof. Tobin, he explained the current marketplace and the exciting innovation he's now able to share.

Current methods of sunless tan

Food

There are ways to *'eat yourself to a tan'* through consumption of copious quantities of carotenoid-laden carrots and lycopene-filled tomatoes which produce a golden pigment. Usefully, this also carries UV protection qualities in the skin, but issues exist with over-dosing the body with beta-carotene, due to the vast amounts needed to be consumed to achieve a 'tan'.



Another option is Monk's Pepper, *Vitex Agnuscastus* to give it its Latin name, which is a Mediterranean shrub with black berries reputed to have been used by monks as an aphrodisiac, due to its light β-endorphin effects. Beta-endorphin is a hormone from the pro-opiomelanocortin family and has been marketed successfully as MelanoBronze in combination with acetyl tyrosine.[3] The product gives a type of stain to the skin which builds up gradually.

Fake Tan

Artificial tanning products or fake tans include creams and spray-on solutions which are aimed at staining or tinting the skin. The majority of these products contain DHA, a dihydroxyacetone, also known as glycerone. DHA has been a self-tanner since the 1960s, and products usually contain between 1 and 15% DHA depending on their cost. Glycerone can be derived from a natural source, from sugar cane or sugar beet, or it can be manufactured in the laboratory via the fermentation of glycerine.

Typically, it takes 24 – 48 hours to achieve the 'tanned' result; often put on overnight. Formulations of fake tanners have improved dramatically over the years - getting rid of the streakiness and the more dramatic colouring effect from early products.

As a rule, these lotion or cream delivered products will stain the hands during application, so special mitts are usually worn. Ideally, users should exfoliate before application to keep the tanned effect for longer, and must then avoid further exfoliation, because as soon as the skin desquamates, the stained surface layers will come off and the impact of the 'tan' is reduced, with reapplication required. Skin turnover is the main enemy of fake tanners. Cheaper products are also known to simply rub off or come off with sweating.

DHA is not without issues though, and the use of it within self-tanning products, particular in spray form, has raised concerns. Back in the 1970s, the American Food & Drug Administration (FDA) approved the use of DHA to be 'externally applied' within a topical skin cream. At the time, a spray-tan product had not been developed. The FDA is now however concerned about its use as a spray and has placed restrictions on its use, such that the use of DHA in 'tanning' booths as an all-over spray has not been approved by the FDA.[4] The issue is that when you aerosolise DHA, and it's then taken into the lungs, there is a potential risk for mutagenesis or carcinogenesis, although the exact risks are still unknown. To date the European Union, through the EC Scientific Committee on Consumer Safety asserts that DHA spray tanners do not pose a risk, yet industry insiders point to a bias in the data provided to the committee for review towards this conclusion.

It's also worth noting that, even though the skin may look darker with the use of these self-tanning products, and in contrast to the effect achieved from ingesting carotenoids, there is no intrinsic photoprotection provided by the fake tan.[5] There might be, one or two hours afterwards, when there is a little bit of very low grade protection, but thereafter it's completely gone, so consumers cannot assume that because their skin looks darker, that there's any increased protection from UVR, thus should continue to apply SPF.

This has led to an increasing amount of news and publicity about the potential dangers from DHA and spray-tanners. Some of the online scare stories must be taken with a pinch of salt, but other aspects of it are important to be aware of, not least the growing popularity of spraying DHA-based products, and the fact that we don't really know to what extent it's fully integrated into the skin.

Previous thinking was that it stayed on the surface of the skin, but increasingly there's evidence to suggest that it may go deeper, as well as some evidence that it may block the skin's native ability to make Vitamin D[6], because you synthesise that in stratum sinosum and stratum granulosum keratinocytes. That is significant, and worthy of further study, because it is vital for the body to have the ability to make Vitamin D and that should not be compromised.

To stain the skin using DHA, to cause a pigmented effect, the chemistry involved is known as a Maillard reaction. DHA darkens the skin by reacting with amino acids in the skin's surface. Studies have shown further understanding of this reaction, and raised concerns about the dangers of sun exposure for those with a DHA-induced 'tan', as well as the potential for accelerated cell ageing. The Maillard reaction causes the formation of irreversible advanced glycation end-products (AGEs), implicated in the ageing process; adding UVR exposure on top of this could accelerate the ageing process. In 2008, Jung et al performed tests and noted that DHA on the skin exposed to UVR can lead to a huge increase in the amount of reactive oxygen species at the skin

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level, compared to untreated skin. They suggested therefore that the exposure duration in the sun must be shortened when self-tanners are used.[7] However, the Skin Cancer Foundation and the American Academy of Dermatology maintain that self-tanning, with concomitant sunscreen use, is safer than tanning by ultraviolet radiation.[8]

For the first time, we are now starting to see self-tanning products being formulated with the addition of an SPF, as well as instant bronzers. Such products aim to give an immediate tanning effect via the bronzer, protect from UVR via the SPF, as well as producing a longer-lasting staining of the skin via the DHA. Yet most products on the market require separate application of SPF, and the consumer is not readily made aware of this fact. Self-tanning products not containing DHA also exist including botanically-derived and certified organic options.

Melanogenesis Stimulators

There is another class of tanning entities, based on alpha-melanocyte-stimulating hormones (α-MSH), called Melanotan I and Melanotan II.

Melanotan I, afamelanotide, has been approved in Europe for the treatment of phototoxicity in people with erythropoietic protoporphyria, to try and boost the pigment level in the skin for these people who are, in a sense, sun phobic. It is also being trialled in the treatment of vitiligo with the aim of dermal repigmentation.

Melanotan II, often just referred to as Melanotan, has caused something of a cult following with a subculture of people self-injecting or spraying it up their noses. It causes significant stimulation of pigmentation, but carries huge risks, and now has a widespread ban. The company that made it stopped all commercial development, but unlicensed and untested counterfeit products still exist, often sold over the Internet.

Sunless tanning innovation

The team at the Centre for Skin Sciences at the University of Bradford are at the forefront of alternative thinking to understand skin pigmentation at a molecular level. They strive to develop products that stimulate pigmentation via mechanisms that would be efficacious, safe, topically applied and increase natural melanin levels rather than staining; as well as potentially benefiting from the enhanced photoprotection this additional melanin may provide for the skin. Long-term, such a discovery would have implications for both the cosmetic tanning market, but also in the treatment of vitiligo, post-inflammatory hypopigmentation and other pigmentary concerns.

This has led them to research a pathway called BMP (Bone Morphogenetic Proteins) signalling. BMPs are a group of signalling molecules that belongs to the Transforming Growth Factor-β (TGF-β) superfamily of proteins. Initially discovered for their ability to induce bone formation, BMPs are now known to play crucial roles in all organ systems.[9] The team has made significant discoveries, which have now been patented and protected by their University. The Bradford researchers found an unusual effect of BMP6, in that it stimulated pigmentation and modulated the skin melanin level.[10]

The UK discovery has led them to seek a way to mimic the natural peptide involved in the BMP6 signalling pathway in order to develop a sunless tanning solution. So, they took it back to basics and this is what they learnt. Upon exposure to UVR, melanin is created in the lower part of the skin, the basal layer of the epidermis, by melanocytes. Melanocytes are characterised by their upside-down spider-like appearance with dendrites and filopodia (tiny nano-tubes) extending upwards like legs. Melanocytes and melanin synthesis is under the influence of the levels and activity of the tyrosinase protein.

The melanin produced in the melanocytes must be transferred through the dendrites and into the recipient keratinocytes via the connecting filopodia which form and elongate to drive the melanin (found to be in granule form) into the keratinocytes by phagocytic force. They discovered that the action of the filopodia is driven by a motor protein called Myosin-X.

The production and transfer of melanin reinforces the keratinocyte army with the shields that it needs to defend against the UVR attack ongoing on the skin. Ultimately melanin degrades and breaks down over several weeks, depending on the individual and a UVR-induced tan will fade over time as normal pigmentation levels return in the skin, mostly through natural skin exfoliation.

Not content with the discovery of Myosin-X, they started to look beyond to see how it is regulated and found the action of BMP6. Lab tests showed that the presence of BMP6 increases the number of dendrites and filopodia that are present in the skin. Adding BMP6 to cultures that contained both the melanocyte and the keratinocyte, they found that it significantly increased the amount of melanin transferred into the keratinocyte.

Having created a useful assay test to see what would stimulate melanin production - and the transfer of it between the melanocyte that makes it to the keratinocyte that receives it - they started to look at the interaction between the BMP6 molecule and receptors on the surface of the melanocyte to see if they could design very, very short peptides which would be able to penetrate the skin. Then, they would be able to test those small peptides, given that peptide technology is well developed in skin care, to see if they would also stimulate pigment production in assays, and ultimately in humans. Embarking on the process they started in melanoma cells, moving to normal human melanocytes, then melanocyte:keratinocyte cultures, and then onto a 3-dimensional skin equivalent called Melanoderm from a company called MatTek that has melanocytes and keratinocytes, which form a near normal pigmented epidermis which grows open to the air.

They applied the peptides into the culture medium, onto the Melanoderm surface, to see if they would stimulate pigmentation. Some of the peptides tried were able to make more melanin, in contrast to the control, but two of those tested showed significant up regulation of normal brown/black melanin in the human skin equivalents. The next step is human ex-vivo skin testing to establish if they can also get into intact human skin and if successful, clinical testing will follow. While the skin equivalent (Melanoderm) has a stratum corneum, it may have a slightly more permeable stratum corneum than in a typical human, so they need to make sure that the peptides will transfer evenly and effectively into the skin.

What else is out there?

It's fair to say that a large group of the scientific community is looking at the influence of single molecules on melanogenesis; but typically, it's the Americans that are shouting the loudest! Prof. Tobin and his team have kept quiet, and away from publishing papers and mainstream media attention until they establish precisely what they are going to do with the peptide technology that they have been working on for almost 10 years.

You could argue they have been pipped to some of the glory when a team headed by Prof. David E. Fisher, MD from the renowned Harvard Medical School Labs at Massachusetts General Hospital in Boston hit the headlines in June 2017 by claiming to have the first small molecule to be shown to drive up normal melanogenesis in a UVR-independent manner. First, by dint of publishing about it perhaps, but certainly not the only one as Prof. Tobin will testify.

Their published paper[11] suggests the development of a small drug molecule, not a cosmetic, that is skin permeable, called a SIK inhibitor or Salt-Inducible Kinase inhibitor. The authors explain that the presence of dark melanin (eumelanin) within human epidermis represents one of the strongest predictors of low skin cancer risk. Topical rescue of eumelanin synthesis, previously achieved in 'redhaired' (Mc1r) melanocortin-receptor-1-deficient mice, demonstrated significant protection against UV damage. However, application of a topical strategy for human skin pigmentation has not been achieved, largely due to the greater barrier function of human epidermis. Salt-inducible kinase (SIK) has been demonstrated to regulate microphthalmia-associated transcription factor (MITF), the master regulator of pigment gene expression, through its effects on CREB-regulated transcription co-activator (CRTC) and cAMP-responsive-element-binding protein (CREB) activity.

They are now able to demonstrate the development of small-molecule SIK inhibitors that were optimised for human skin penetration, resulting in MITF upregulation and induction of melanogenesis. When topically applied, pigment production was induced in Mc1r-deficient mice and normal ex-vivo human skin (taken from breast reduction surgeries). They conclude that these findings demonstrate a realistic pathway toward UV-independent topical modulation of human skin pigmentation, potentially impacting UV protection and skin cancer risk.

Despite not performing tests on live human skin yet, they were able to demonstrate pigment stimulation, and an increase in melanin levels, after approximately eight days of application, independently of UV irradiation. Notably, they sometimes had to re-rub it in to try and increase the transfer through the upper layers of the skin. The topical application of this small molecule has yet to be examined in humans and would require careful consideration with respect to safety. It is not clear if this drug could be used for cosmetic purposes, like sun-less tanning, at least not until substantial safety testing would be conducted.

Conclusion

This is a most exciting time for research and development activities into strategies to meet the clear cosmetic market demand for skin tanning. We urgently need alternatives to unprotected UVR-derived tanning, either under natural sunlight or under artificial bulbs (i.e., in tanning salons). Both represent significant public health concerns, as both increase skin cancer risks. Sun avoidance behaviour however, can lead to de/insufficiency in Vitamin D levels – detrimental to optimal health and cancer protection. The introduction of natural skin pigmentation stimulators, provided topically and safely to skin, would provide multiple benefits in one go; cosmetic self-tanning, exploitation of melanin's intrinsic sun-screen, and correcting sun avoidance behaviour to facilitate more optimal Vitamin D synthesis in skin.

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