Institution: Lancaster University

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Identification of novel effects of long wavelength UV (UVA) leads to updated evaluation of health risks and improved approaches to protection

1. Summary of the impact (111 words)

New research at Lancaster on the biological effects of UVA radiation has generated three main impacts, first resulting in a leading sun cream manufacturer (Boots Ltd. PLC) to re-evaluate its product development process to account for UVA exposure. Second, the research was one of the key drivers of a recent re-assessment of the validity of the UV index by a working group acting for the World Health Organization (WHO) and the International Commission on Non-Ionizing Radiation Protection (ICNIRP). Finally, the research has been used in public education related to sun protection and the use of tanning beds through both direct engagement with the media and work with North West Cancer Research.

2. Underpinning research (538 words)

Exposure to environmental UV radiation can cause a number of short- and long-term negative effects on human skin, including erythema (burning), ageing and skin cancer. Over 110,000 people in the UK were diagnosed with skin cancer in 2010, with the incidence of malignant melanoma having more than doubled in the past 20 years. Early work on UV carcinogenesis focused primarily on the effects of shorter wavelength UV radiation (UVB: 280-315 nm) due to its ability to directly induce genotoxic DNA damage and also cause erythema. As a result longer wavelength UV radiation (UVA: 315-400 nm) was comparatively neglected in terms of its contribution to skin cancer. Research carried out at Lancaster University under the guidance of Professor Trevor McMillan (Reader then Professor of Cancer Biology 1995-present), and more recently joined by Dr Sarah Allinson (formerly a North West Cancer Research Fund research fellow (2004-2009) and now lecturer (2009-present)), has shown that the cellular response to UVA, which causes damage to cells via photosensitiser-mediated processes, is significantly different to the response to UVB. Moreover, the established biomarkers of UV exposure, for example p53 activation, appear to significantly underestimate the damage caused by UVA. These findings have played an important role in the development of a new and more comprehensive understanding of UV carcinogenesis that takes into account the full spectrum of terrestrial UV radiation.

One important finding is that UVA elicits an unusual intensity-dependence effect whereby longer doses at low intensity irradiation are more harmful to cells than shorter more intense irradiation for the same total dose. UVA is able to induce a “bystander effect” whereby irradiation of cultured human skin cells results in cytotoxic and genotoxic damage in adjacent un-irradiated cells. Recently we have been collaborating with Boots UK Ltd (see below) and are publishing data on biomarkers of UVA exposure that will allow such harmful effects of UVA to be better evaluated. Our findings have contributed to a re-evaluation of the contribution of UVA to the harmful effects of prolonged exposure to sunlight on human health.

The key findings from the group include:

2.1 UVA causes free radical production and **damage that can be prevented by antioxidants**, including plant polyphenols and vitamin E (Refs 3.1 & 3.2)

2.2 UVA leads to the production of both **DNA single strand and double strand breaks** (Refs 3.1 & 3.3)

2.3 UVA elicits an **unusual intensity-dependent effect** whereby longer exposures at low intensity irradiation are more harmful to cells than shorter more intense irradiation for the same total dose. In particular this means that low intensity exposure, such as that encountered on overcast days or in winter, is likely to be more harmful than expected. (Ref 3.2)

2.4 UVA, in contrast to UVB, induces a **bystander effect** whereby irradiation of cultured human skin cells results in cytotoxic and genotoxic damage in adjacent un-irradiated cells (Ref 3.4)

2.5 Exposure to UVA induces a long-lasting state of **genomic instability** that increases mutation frequency in subsequent generations of cells (Ref 3.5).

2.6 UVA **does not activate p53**-dependent damage surveillance (Ref 3.6)

Taken together, our work demonstrates that UVA is highly detrimental to humans and shows that there is a need to increase awareness of its harmful effects and protect against it.

3. References to the research

3.1 Tobi SE, Gilbert M, Paul N, McMillan TJ (2002). The green tea polyphenol, epigallocatechin-3-gallate, protects against the oxidative cellular and genotoxic damage of UVA radiation. Int J Cancer 102: 439-44 (doi: 10.1002/ijc.10730)

3.2 Shorrocks J, Paul ND, McMillan TJ (2008). The dose rate of UVA treatment influences the cellular response of HaCaT keratinocytes. J Invest Dermatol 128:685-93 (doi: 10.1038/sj.jid.5701037)

3.3 Fell LJ, Paul ND, McMillan TJ (2002). Role for non-homologous end-joining in the repair of UVA-induced DNA damage. Int J Radiat Biol 78: 1023-7 (doi:10.1080/09553000210000016558)

3.4 Whiteside JR, McMillan TJ (2009). A bystander effect is induced in human cells treated with UVA radiation but not UVB radiation. Radiat Res 171: 204-11 (doi: 10.1667/RR1508.1 submitted in REF2)

3.5 Phillipson RP, Tobi SE, Morris JA, McMillan TJ (2002). UV-A induces persistent genomic instability in human keratinocytes through an oxidative stress mechanism. Free Radic Biol Med 32: 474-80 (doi: 10.1016/S0891-5849(01)00829-2)

3.6 McFeat GD, Allinson SL, McMillan TJ (2013) Characterisation of the p53-Mediated Cellular Responses Evoked in Primary Mouse Cells Following Exposure to Ultraviolet Radiation. PLoS ONE 8(9): e75800 (doi: 10.1371/journal.pone.0075800 submitted in REF2)

Grants awarded

3.7 Cellular effects of UV. (PI McMillan) Dowager Countess Eleanor Peel Trust, 2003-2007, £60,000

3.8 Dose rate effects of UV light. (PI McMillan) The Colt Foundation, 2005-2008, £46,500

3.9 The role of recombination repair in genomic instability induced by radiation and oxidative stress (PI Benson and McMillan) Department of Health 2002-2005 £180,000

3.8 DNA damage sensing and repair processes underlying the changes in cellular effects of UVA when delivered at different dose rates (PI Allinson & McMillan) North West Cancer Research Fund, 2007-2009, £77,938

3.9. Mechanisms underlying the cellular response to ultraviolet light and heavy metals (PI Allinson & McMillan), Dowager Countess Eleanor Peel Trust, 2007-2010, £122,621

3.10 Cellular responses to UVA (pilot study) (PI Allinson & McMillan), Boots PLC 2010 £40,100

3.11 Development of a novel bioassay for UVA-induced skin damage (PI Allinson & McMillan)

Boots PLC and BBSRC DTG co-funded PhD studentship, 2012-2016 £103,320

Evidence of the quality of the research

Our work on UVA has been supported by a mix of industrial and charitable funding (including grants awarded in open competition) totalling some £630,000 since 2003 [3.7-3.11 above]. The papers cited above [refs 3.1-3.6] were all peer-reviewed and continue to be widely cited within the field (e.g. [3.1] and [3.6] have each been cited more than 65 times), informing continuing efforts to understand and evaluate the impact of ultraviolet radiation on human health. For example, several of our papers [including refs 3.4 and 3.5] were cited in the authoritative IARC *Monograph on Solar and Ultraviolet Radiation* (IARC (2012) IARC Monogr Eval Carcinog Risks Hum 100D: 35-101), contributing to IARC's re-evaluation of the evidence on the carcinogenicity of UVA.

4. Details of the impact (819 words)

The effects of UVA have been long under-estimated. However, due to its significant penetration through the atmosphere, added to the increased use of sunbeds where UVA is the primary component, it is a highly significant constituent of the non-ionising radiation to which the human population is exposed. Moreover, its high penetrance of the epidermal and even dermal layers of the skin mean that UVA has significant potential for causing harm. The body of work done at Lancaster [3.1-3.6] brought to the fore these deleterious biological effects and it is now clear that UVA is an important carcinogen. We have taken three approaches to maximise the impact of this research to increase awareness and modify behaviour of the public, industry and policy makers.

Impact 1

Boots UK Limited are one of the UK's biggest producers and retailers of sun creams and have a particular interest in developing skincare products that offer improved UVA protection. The harmful effects of exposure to solar UV can be mitigated by the application of sun creams, the effectiveness of these being expressed in terms of a sun protection factor (SPF) related to the UV dose required for erythema. However, despite the well-established negative effects of UVA, many sun creams do not provide significant protection against this type of radiation. Moreover, since exposure to UVA does not cause erythema the current industry standard tests for evaluating sun cream effectiveness are likely to over-estimate the protection offered against the harmful effects of UV.

On the basis of our research [3.2], Boots recognised the importance of year-round protection against UVA even in climates such as that of the UK. Consequently they introduced UVA protection into their highly acclaimed and popular *Protect and Perfect* range of cosmetic products. This has not only increased public awareness of the problems caused by UVA (e.g. featuring in magazines such as http://www.womanandhome.com/hair-and-beauty/498540/no-7-protect-perfect-intense-day-cream-5-protection-spf-15), it has been a highly beneficial product for Boots. The Skin Care Scientific Advisor at Boots has stated that "*The research at Lancaster University into the effects of UVA irradiation on skin cell ageing genes was critical in supporting the impact of daily UVA exposure on the skin. This led to the launch of the first day cream with five star UVA protection. Subsequently all day creams within No 7 now include five star UVA protection"* [5.1]. We have an active research collaboration with Boots, through which we have identified several new biomarkers for UVA damage. This work was reported worldwide [5.2, 5.3] and we are currently developing a bioassay in partnership with Boots.

Impact 2

The profile of the research led to Dr Allinson being invited by the ICNIRP and WHO to join a working group on re-evaluation of the UV Index, providing the only input on the cellular and

subcellular damaging effects of UVA.

The UV Index is used globally to encourage sun protection behaviour in at-risk populations and its re-evaluation was prompted in part by the mounting evidence of the importance of UVA in solar carcinogenesis. Our research [3.1-3.6] formed the basis to consider the underlying health effects of UVA by the working group. The conclusions and recommendations of the panel, co-authored by Dr Allinson, were that the UV Index captures the risk of UVA sufficiently that it can continue to be used as a valuable tool in public health, and the consequent increased confidence of the Index will mean that more lives will be saved. The recommendations were published in *Health Physics* and underpin the communication of UV risk to millions worldwide [5.4].

Impact 3

The findings on UVA in this case study have been disseminated to the public via both newspaper articles and radio programmes e.g. BBC Radio Merseyside, 1/6/11. One particularly successful route has been our partnership with North West Cancer Research, a regional charity that supports primary research into the causes and treatment of cancer. Prof McMillan and Dr Allinson are the only researchers working on UV to have been funded by the charity. Both have spoken at NWCR fundraising and awareness events in the local community and at Lancaster University. On the basis of our research and with our support the charity launched a 'Scrap Sunbeds' campaign [BBC Radio Merseyside 31/01/11; ref 5.5], which successfully led to the removal or lack of installation of sunbeds from twenty-five gyms and health clubs in the North West including our own new University Sport Centre. The Chief Executive Officer of the charity acknowledged our input to the campaign as follows: "*To support our claims we worked closely with our funded researchers at Lancaster University who provided us with statistics and evidence to support the Campaign. Professor Trevor McMillan also gave an interview on the subject to BBC Radio Merseyside"* and *"Lancaster University's ongoing support of our work is incredibly valuable and acts as great motivation for our fundraisers. The Campaign was a great success and we are very grateful for the support of the team"* [5.6].

5. Sources to corroborate the impact

5.1 Statement from Alliance Boots, Skin Care Scientific Advisor

5.2 Poulter S (2010) 'Sunshine can give you wrinkles 'even through a window'' *Daily Mail* 7 September [online] Available at: http://www.dailymail.co.uk/health/article-1309678/Sunshine-wrinkles-window.html

5.3 Anonymous (2010) 'Sunshine can give you wrinkles' *The Hindu* 7 September [online] http://www.thehindu.com/sci-tech/health/rx/sunshine-can-give-you-wrinkles/article619460.ece

5.4 Allinson S, Asmuss M, Baldermann C, Bentzen J, Buller D, Gerber N, Green AC, Greinert R, Kimlin M, Kunrath J, Matthes R, Pölzl-Viol C, Rehfuess E, Rossmann C, Schüz N, Sinclair C, Deventer EV, Webb A, Weiss W, Ziegelberger G (2012) Validity and use of the UV Index: Report from the UVI Working Group, Schloss Hohenkammer, Germany, 5-7 December 2011 *Health Phys.* **103:** 301-306

5.5 North West Cancer Research Fund (2010) Annual Report [available online] http://issuu.com/nwcrf/docs/nwcrf_anrep0809?e=1826604/5161618

5.6 Statement from North West Cancer Research, Chief Executive Officer