Institution: University of Bradford

Unit of Assessment: A3

Title of case study: Scientific discoveries in skin pigmentation contribute to the development of best-selling skincare products of high commercial value.

1. Summary of the impact

Ground breaking and unique research carried out at the Centre for Skin Sciences at the University of Bradford has led to the realization of commercial opportunities in two very high-value consumer brands. Technologies developed in collaboration with multi-national personal-care and cosmetic companies for the treatment of skin hyper-pigmentation have been launched on the market and have reached thousands of consumers. The first product launched by Alliance-Boots (April 2012) is sold within the UK's premier skincare range (No. 7). Success in Britain led to its launch in the US, Finland and Thailand. A second product within the Diorsnow range has been launched by Parfum Dior – a branch of LVMH Moët Hennessy • Louis Vuitton S.A.

2. Underpinning research

The production of melanin is crucial for the protection of the skin and other tissues against harmful ultraviolet radiation (UVR), our main physiological cutaneous stressor. The aging profile of citizens in the developed world is leading to a global rise in consumers with skin and pigmentation anomalies and disorders, many resulting from years of unprotected sun exposure. A key step in the formation of skin and hair pigment is the transfer of the melanocyte-specific and lysosome-related organelle - the melanosome - from melanocytes that make them into keratinocytes that receive them; a unique occurrence in mammalian biology. While melanin transfer is a commonplace event, its underpinning mechanism remains enigmatic.

Research in this topic is led by Des Tobin (Lecturer 1996-2000, Senior Lecturer 2000-2002, Reader 2002-2003, Professor 2004-present). Over the last five years, Tobin, together with Dr Suman Kumar Singh (PDRA 2006-2010, Lecturer 2010-2012), Dr Stephen Sikkink (PDRA 2010-present) and Richard Baker (Research Technician 2008-present), developed assays to visualize the transfer of melanin between human skin cells *in vitro* (1). Thereafter they unravelled an important new mechanism of melanin transfer between skin and hair follicle cells (2). They observed that melanin transfer in human skin cells is mediated by filopodia - nanotubes that communicate at the cell surface - and thereby provided a model for homotypic and heterotypic lysosome-related organelle transfer. This study provided conclusive experimental evidence that cytoplasmic extensions called filopodia can act as melanin granule conduits.

A critical novel finding was the identification of a key motor protein called Myosin X as the 'driver' of melanosomes in this hitherto enigmatic transfer process. We also showed that this motor/filopodia system is operative under both constitutive and facultative (post-UVR) conditions, and so may be an important tractable step in the sunlight-associated response. We called this new finding the "*filopodial-phagocytosis model*"; it also lends itself to the study of intercellular movement of cytoplasmic materials via filopodia in other tissue systems. In the context of melanocyte-keratinocyte communication in human skin, this model allows us to examine how pigmentary disorders involving melanin transfer can be addressed. This is a step change in our understanding, as most of the current and previous technologies attempt to control hyperpigmentation by inhibiting tyrosinase expression/activity and have proven very disappointing.

Several industrial companies approached Tobin over the last 5-6 years (i.e. LVMH 2008/9, Boots

2010/12, and L'Oreal 2012/13) to partner in the further exploration of how pigmentary anomalies and clinical disorders may be treated by understanding the potential role of melanin transfer in these conditions. In particular Tobin's team was able to uniquely establish, as part of these industry sponsored projects, whether melanin transfer can be up/down-regulated by bio-actives. Research outcomes from the collaborations with LVMH (1-3) and Boots (4) have been published in world leading peer-reviewed international journals.

Other pigmentary anomalies examined by Tobin's team are age-related solar lentigo (or age-spots) that appears principally on skin of the face and hands with accumulated unprotected sun exposure and melasma - a collection of sharply demarcated, blotchy, brown spots on the face. The latter is of great consumer concern and an area that can benefit from cosmetic technology, due to the lack of consumer acceptable medical alternatives for treatment.

Using their new understanding of melanin transfer, Tobin's team explored potential biological response modifiers to stimulate or inhibit this process and discovered a unique role for BPM6 biology in melanin transfer and filed a patent (5). Further intellectual property is being generated via novel *in silico* screening to find small molecules to regulate pigmentation for potential therapeutic and cosmetic implications (e.g., sun-less tanning, reduction of hyperpigmentation including melasma and solar lentigo or age-spots).

3. References to the research

1. Singh SK, Nizard C, Kurfurst R, Bonte F, Schnebert S, Tobin DJ. (2008) The silver locus product (Silv/gp100/Pmel17) as a new tool for the analysis of melanosome transfer in human melanocyte-keratinocyte co-culture. *Experimental Dermatology* 17(5): 418-426. Impact factor =3.58. 6th of 59 journals in Dermatology category (ISI Thomson Reuters).

2. Singh SK, Kurfurst R, Nizard C, Schnebert S, Perrier E, Tobin DJ. (2010) Melanin transfer in human skin cells is mediated by filopodia--a model for homotypic and heterotypic lysosome-related organelle transfer. *FASEB Journal* 24(10): 3756-3769. Impact factor = 5.704. 7th of 85 journals in Biology category (ISI Thomson Reuters)

3. Singh SK, Abbas WA, Tobin DJ. (2012) Bone morphogenetic proteins differentially regulate pigmentation in human skin cells. *Journal of Cell Science* 125(18): 4306-4319. Impact factor = 5.88. 38th of 185 journals in Cell Biology Dermatology category (ISI Thomson Reuters)

4. Singh SK, Wibi J, Bell M. Tobin DJ. (2013) Effects of Sophora angustifolia and other Natural Plant Extracts on Melanogenesis and Melanin Transfer in Human Skin Cells. *Experimental Dermatology* 21(1): 67-69. Impact factor=3.58. 6th of 59 in Dermatology category (ISI Thomson Reuters).

5. *Compositions and methods for modulating skin pigmentation*, United States Patent Application 20110206625
   http://www.freepatentsonline.com/y2011/0206625.html

The following grants are also indicative of the quality of the research:

LVMH (France):
2006-2008. PI: DJ Tobin. *Investigations into the regulation of melanosome transfer from melanocytes to keratinocytes in human epidermis*, £140K.
2010-2012, PI: DJ Tobin. *Influence of UVR on Melanin Transfer in human skin*. £160K.
Alliance-Boots (UK):
2010-2013. PI: DJ Tobin. *Assessment of melanin transfer modifiers from natural plant extracts.* £60K.

4. Details of the impact

Hyperpigmentation may be caused by sun damage, inflammation, or other skin injuries including those related to dermatological disorders like acne vulgaris. People with darker skin tones are also more prone to hyperpigmentation, especially if they have excessive sun exposure. These conditions present significant cosmetic or psychological challenges to the affected person, and uneven skin tone and pigmentation is a key concern amongst consumers over the age of 40 (Mintel report http://www.mintel.com/). The most effective treatment of solar lentigo consists of invasive ablative therapies, while available topical drugs have challenging safety profiles e.g., hydroquinone. This impact case study describes two projects with industry that underpinned the creation of new skin care products to tackle hyperpigmentation in particular age-related solar lentigo.

The first project is in collaboration with Alliance-Boots GmbH, a multinational pharmacy-led health and beauty group. This company is rapidly developing its presence in skin care technology and the No7 skincare range is now the best-selling range of skin care cosmetics in Britain. The potential growth for Alliance-Boots in this sector was further expanded last year when the biggest US drugstore operator, Walgreens, acquired a 45% stake in the company (a). Alliance-Boots revenues in 2012/2013 were £22.4 billion (b).

Alliance-Boots (UK) engaged us to assess the efficacy of several of their lead botanical extracts. In additional to revealing the efficacy of some of these in terms of modulating melanin levels and transfer to keratinocytes *in vitro*, we were also able to suggest likely mechanisms of action. Our results *in vitro* informed the design of a clinical trial that confirmed our *in vitro* data (c). This technology is now included in their new anti-age spot serum, Lift & Luminate, Day & Night serum (rrp for 30ml is £25) within their No7 range. No7 is the premier anti-aging serum and skin care brand in the UK (Boots commercial data). The skin serum sector of the skin care market is growing fast, and this product has sold well in Britain since its April 2012 launch. It has since been launched in Thailand, the US, and Finland. This was a new product to the markets and within the first month of launch (from April 18th 2012 to end May 2012), 84 pieces of media coverage were generated with a total reach estimated to be over 22 million consumers (d). The Boots Skin Care Scientific Advisor commented that, "*The research we carried out with Professor Tobin and the University of Bradford enabled us to identify new safe cosmetic actives that could tackle age related hyper-pigmentation and provide strong peer reviewed science that reinforced No7's credibility in this area. This has helped us provide a step change in the performance of our No7 anti-ageing products*" (d). Tobin is a member of the Alliance-Boots International Skin Advisor Panel, where he helps inform the Alliance-Boot R&D strategy for new product development. The University of Bradford Centre for Skin Sciences has now entered into a Framework Contract agreement with Alliance-Boots to facilitate a continuing partnership over multiple individual projects.

The second of these projects, funded by LVMH Moët Hennessy • Louis Vuitton S.A. (or LVMH), a French-based multinational company considered to be the world's largest luxury goods conglomerate (revenues in 2012 of £28 billion; £3.6 billion in cosmetics) (e), assessed whether the expression of Myosin X (our discovered 'melanin transfer driver') can be inhibited *in vitro* and, if so, whether melanin transfer could be up/down-regulated by bio-active ingredients. Thereafter, several actives from the LVMH library were assessed and some proved successful in our *in vitro* assays and passed LVMH clinical assessment *in vivo*. This technology is included in their new high-end product 'Diorsnow' (f). The associated marketing materials make explicit reference to the Myosin X technology and (with permission) the collaboration with the University of Bradford (g). This is patented technology (h) with Bradford researchers credited with the discovery of the role Myosin X

plays in the transfer of pigment granules between skin cells. The University has a royalty agreement with LVMH on sales of this product. This technology is being marketed for solar lentigo and other hyper-pigmentations associated with aging. Patients with melasma commonly also use this type of product in the absence of effective medical treatments.

5. Sources to corroborate the impact (indicative maximum of 10 references)

a. http://investor.walgreens.com/results.cfm Joint synergy program with Alliance Boots delivers combined first-year net synergies of $154 million, exceeding the previously stated range of $125-$150 million

b. Alliance Boots Annual Report: http://annualreport2012-13.allianceboots.com/Assets/PDFs/overview.pdf

c. Khemis A, Bhadoran P, Sladen C, Marlow I, Bell M, Ortonne J-P. (2012) Reduction in the appearance of facial solar lentigines following use of either hydroquinone 4% or a cosmetic 'anti-ageing' regimen. *British Journal of Dermatology* 166(4): e39.

d. Skincare Scientific Advisor. Alliance Boots. Nottingham. http://www.boots.com/en/No7-Lift-Luminate-The-science_1262934/ (commentary on Bradford Team involvement).

e. http://www.lvmh.com/investor-relations/lvmh-at-a-glance/key-figures

f. Launch marketing materials for 'Diorsnow' from LVMH (on file), which clearly show the direct link between the discovery of the role of Myosin X in melanin transfer via University of Bradford research and the development of this product.

g. Patent describing the role of Myosin X in pigmentation and how selective actives can module pigmentation via effect on Myosin X. Filed by LVMH but with co-inventors at University of Bradford. *Methods useful in studying or modulating skin or hair pigmentation, plant extracts for use in compositions and cosmetic care method*. United States Patent: 8409633

h. Coordinator of Technology Platforms, BioScience Innovation Manager, LVMH Recherche