Institution: University of South Wales

Unit of Assessment: C26

Title of case study: Free radicals and vascular ageing; move your muscles, move your mind!

1. Summary of the impact

The Vascular Health Group led by **Bailey** has achieved international impact by transforming our understanding of the source, mechanisms and consequences of free radical formation in the ageing human. The development of novel biomarkers of health and well-being has challenged conventional wisdom, informed public policy and debate and raised public awareness to the vascular benefits of physical activity. These advances have improved health and welfare outcomes of the elderly including those suffering from advanced atheroslcerotic disease. Applied research focused on the pro-oxidant stimulus hypoxia, has led to improvements in the management of high-altitude illness amongst both mountaineers and native communities.

2. Underpinning research

Free radicals have long been implicated in the ageing process though human evidence is lacking due to a traditional reliance on indirect non-specific biomarkers confined to the peripheral circulation. By employing novel analytical techniques including electron paramagnetic resonance spectroscopic spin-trapping with regional arterio-venous blood sampling, **Bailey** has provided unique insight into the source, mechanisms and consequences of free radical formation in the ageing human with a clinical focus on the vascular endothelium.

Initial studies with the University of California San Diego (**Richardson**) were the first to identify that exercising human skeletal muscle directly generates free radicals. These works were subsequently extended to demonstrate that resting and exercise-induced free radical formation was more pronounced in old compared to young skeletal muscle (i), providing the first human evidence in support of the Free Radical Theory of Ageing postulated more than half a century ago. Follow-up studies provided a mechanistic basis to explain why vascular endothelial function becomes impaired with ageing which was attributed to a free radical-mediated reduction in the vascular bioavailability of the vasodilator molecule nitric oxide. These studies also highlighted the vascular benefits of antioxidant prophylaxis which has implications for slowing down the ageing process.

The observation that exercise-induced free radical formation was associated with a reduction in mitochondrial oxygenation led to a focus on hypoxia involving collaborations with the Universities of Heidelberg (Bärtsch) and Copenhagen (Pedersen, Saltin, Möller and Secher) with funding from the Danish Research Council to support a post-doctoral researcher (**Evans**). The research provided the first human evidence that free radical formation increased during hypoxia, contrary to traditional opinion. The brain and lungs were later indentified as “regional generators” allowing the team to calculate for the first time, local rates of free radical turnover (ii, iii). The findings also provided unique insight into the pathophysiology of high-altitude illness, notably the neurological and pulmonary syndromes of acute mountain sickness, high-altitude cerebral and pulmonary oedema. Contrary to prevailing dogma, it was later suggested that in physiologically controlled albeit undefined amounts, free radical formation in hypoxia may prove an adaptive phenomenon that can accelerate acclimatisation and boost exercise performance, akin to human “oxygen-sensing”. (iv). A series of follow-up studies in native highlanders, individuals born and bred at high-altitude, introduced the novel concept of a “physiological free radical threshold” beyond which diseases characterised by premature vascular ageing such as chronic mountain sickness may occur (v).

The past five years has seen the team focus on the ageing brain concentrating efforts towards the development and implementation of novel haemodynamic measures of cerebrovascular function in collaboration with **Ainslie**. Recent findings have identified physical activity maintained over the human lifespan can reduce the brain’s “functional age” by over a decade providing a mechanistic basis to explain why exercise reduces the risk of stroke and dementia (vi). These techniques have also been applied in the sporting context, providing improved sensitivity for the detection of subtle brain injury following concussion, a unique sports-based model of accelerated brain ageing that increases susceptibility to dementia.

3. References to the research (indicative maximum of six references)

i. **Bailey, D.M.,** McEneny, J., Mathieu-Costello, O., Henry, R.R., James, P.E., McCord, J.M., Pietri, S., Young, I.S. and Richardson, R.S. (2010). Sedentary aging increases resting and exercise-induced intramuscular free radical formation
Journal of Applied Physiology 109: 449-456.

ii. **Bailey, D.M.,** Taudorf, S., Berg, R.M.G., Lundby, C., McEneny, J., Young, I.S., Evans, K.A., James, P.E., Shore, A., Hullin, D.A., McCord, J.M., Pedersen, B.K. and Møller, K. (2009). Increased cerebral output of free radicals during hypoxia: implications for acute mountain sickness?
American Journal of Physiology (Regulatory, Integrative and Comparative Physiology) 297: R1283-R1292.

iii. **Bailey, D.M.,** Dehnert, C., Luks, A., Menold, E., Castell, C., Schendler, G., Faoro, V., Gutowski, M., Evans, K., Taudorf, S., James, P., McEneny, J., Young, I.S., Swenson, E., Mairbäurl, H., Bärtsch, P. and Berger, M.M. (2011). High-altitude pulmonary hypertension is associated with a free radical-mediated reduction in pulmonary nitric oxide bioavailability.
Journal of Physiology 588: 4837-4847

iv. **Bailey, D.M.,** Taudorf, S., Berg, R.M., Lundby, C., Pedersen, B.K., Rasmussen, P. and Møller, K. (2011). Cerebral formation of free radicals during hypoxia does not cause structural damage and is associated with a reduction in mitochondrial PO_2; evidence of O_2-sensing in humans?
Journal of Cerebral Blood Flow and Metabolism 31: 1020-1026.

v. **Bailey, D.M.,** Rimoldi, S.F., Rexhaj, E., Pratali, L., Salmòn, C.S., Vilena, M., McEneny, J., Young, I.S., Nicod, P., Allemann, Y., Scherrer, U. and Sartori, C. (2013). Oxidative-nitrosative stress and systemic vascular function in highlanders with and without exaggerated hypoxemia.
Chest 143: 444-451.

vi. **Bailey, D.M.,** Marley, C.J., Brugniaux, J.V., Hodson, D., New, K.J., Ogoh, S. and Ainslie, P.N. (2013). Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics.
Stroke 44: 3235-3238.

4. Details of the impact

Health and welfare impacts

Having identified increased free radical formation and impaired vascular structure/function subsequent to a selective depletion of the antioxidant vitamin C in patients with abdominal aortic aneurysms (AAA), the Vascular Health Group in collaboration with Prof MH Lewis (Visiting Professor, Consultant Vascular Surgeon and **Bailey**'s PhD student), are involved in the Wales AAA Screening Programme (http://www.aaascreening.wales.nhs.uk/home). The Group have widened the protocol to include novel free radical and vascular biomarkers including cardiopulmonary exercise testing to reduce the vascular complications and untimely deaths associated with AAA rupture and direct surgery. By improving screening sensitivity, these activities have had a beneficial impact on the patients' quality of life, their families and society in general. We anticipate that this will improve on the current 53% risk reduction in AAA-related deaths and mean cost effectiveness of £28k per patient per life-year gained.

Similar approaches have been applied to stroke patients scheduled for elective carotid endarterectomy, a surgical procedure that corrects carotid stenosis improving perfusion to the brain. **Bailey**'s Group have shown that the speed of surgical repair (*ie*. reducing the time that clamps are applied to the diseased artery) dictates the extent of free radical formation and corresponding neurocognitive decline that persists during the post-operative recovery phase, highlighting why "surgical speed" is so critical for patient outcome. Furthermore, it was generally accepted that this procedure improves cognitive function, due in part to increased cerebral perfusion. This was "misinformed" given that prior investigators consistently failed to take into account learning effects. As a consequence, patients are now being advised cognitive function will be impaired during the recovery period thereby reducing post-operative stress.

Given that arterial hypoxaemia is a common feature of vascular disease with the capacity to stimulate free radical formation, the group have also focused on chronic mountain sickness (CMS), a novel model of accelerated vascular ageing and decreased longevity. Recognised by the World Health Organisation, CMS affects 5-10% of an estimated 140 million natives living at altitude with treatment largely ineffective. They identified that CMS was associated with impaired systemic vascular structure/function due to a free radical-mediated reduction in the vascular bioavailability of nitric oxide. Similar to the surgical patients previously outlined, this was attributed to a selective depletion in the antioxidant vitamin C, providing clear justification for antioxidant prophylaxis as a viable clinical intervention. In collaboration with the Bolivian High Altitude Biology Institute (IBBA), pharmacological (*iv* ascorbate infusion) and dietary (fresh fruit and vegetables) approaches have since been deployed to increase the concentration of circulating antioxidants, interventions that are already having a positive impact on patient health and well-being (personal communication, Dr M Villena, IBBA).

Extending this work from the systemic to the cerebral circulation, novel cerebrovascular function tests have been deployed within the sporting context, notably in mountaineers to screen for "subtle" imperfections in brain blood flow regulation that can be detected even at sea-level and inform the risk of developing altitude-related illnesses during ascent to high-altitude. These tests have been communicated to commercial companies (*eg*. Altitude Centre, Icicle Expeditions) given that they have the potential to improve management of environmental risk with implications for indemnity and insurance. Similar tests have been applied for the detection of subtle brain injury following concussion, a novel model of accelerated brain ageing that increases susceptibility to dementia. A recent publication in professional boxers highlighted that the majority of brain injury occurs due to the mechanical trauma incurred by repetitive, sub-concussive head impacts associated with sparring "training" and not as traditionally believed, due to a single knockout blow during "competition". This message has been communicated globally through the USA warning combat specialists to limit their sparring. Similar warnings have been communicated to rugby union players (including the Welsh Rugby Union) and help inform "return-to-play" guidelines that currently lack any clinical or scientific gravitas with an arbitrary 3 week suspension.

Creativity and practitioner impacts

The analytical advances outlined have led to research findings that have challenged conventional wisdom/established norms and changed the modes of thought and practice of research groups that have traditionally relied on indirect, non-specific biomarkers of free radical activity to inform the disease process. Internationally-renowned groups in the USA and Europe have adopted the direct technique of EPR spectroscopy with specialist input from **Bailey**.

Science communication impacts

Concerted attempts have been made to engage with the public to disseminate research findings that have clear practical implications for improving lifelong health and well-being in both the clinical and sporting context. The reach has been considerable raising awareness both locally and globally.

5. Sources to corroborate the impact

i. Citation by broadcaster/public debate in the media/parliamentary debate/improved welfare/satisfaction measures for beneficiaries

Patient testimonial(s) broadcast by the BBC attesting to the life-saving benefits of vascular screening involving members of the Vascular Health Group (May 2010).
http://news.bbc.co.uk/1/hi/wales/8676071.stm

ii. "End-user" engagement

Older People & Ageing Research & Develoment Network (OPAN) Translational Research Seminar/Workshop –, Novotel, Cardiff (May 2012)

The OPAN Stroke Research Group held a research development event on Monday 9th May in Cardiff with the theme of Translational Research. The aim of the day was to bring together stroke and ageing researchers and clinicians and service users from across Wales to link "bench" to "bedside", to identify priorities for clinical research with input from stroke patients and develop potential collaborations.

iii. Committee positions helping inform public policy and debate
Cardiovascular Physiology Lead (2010-present) to the Cardiovascular Research Group Cymru (CVRG-C),a Registered Research Group funded by the National Institute for Social Care and Health Research. The aim of the CVRG-C is to improve NHS healthcare by facilitating and supporting high quality cardiovascular research in both the commercial and academic sectors, encouraging collaborations between academics, cardiovascular clinicians, cardiovascular service users and research funders.
http://www.wales.nhs.uk/sites3/page.cfm?orgid=949&pid=52205

iv-vi. Dissemination activities
Reaching out to local government:
Science and the Assembly: Sports and Science conference (May 2012).
http://storify.com/Protohedgehog/science-and-the-assembly-cardiff-2012-theme-sports

Reaching out to the lay public:
Cheltenham Science Festival (June 2013).
http://www.cheltenhamfestivals.com/science/whats-on/2013/will-humans-evolve-in-the-future/

Reaching out to school children:
I'm a Scientist Get Me Out of Here! Human Limits Zone (c/o The Physiological Society, August 2013).
http://humanj13.imascientist.org.uk/profile/damianbailey/

vii. Practitioner debate
Formal invitation (October 2012) from the lead clinician and founder of FightMedicine.net to contribute monthly columns to an American website reaching out to an international audience of combat specialists. Based on an original article published by Bailey [**Bailey, D.M.,** *et al*. (2013). Impaired cerebral hemodynamic function in professional boxers. ***Clinical Science*** 124: 177-189], the forum provides educational material and practical advice highlighting the long-term health implications of sports concussion focusing on chronic traumatic brain injury.

viii-x. Broadcast citations
Wales Online (April 2012).
"Researchers to play high-altitude rugby matches to test male vs female brain theory. A group of researchers will play a high-altitude game of rugby sevens at the culmination of a unique project to discover whether the female brain is better than the male".
http://www.walesonline.co.uk/news/health/researchers-play-high-altitude-rugby-matches-2047833

and April 2010.
"Fifteen former Wales captains and coach Warren Gatland will attempt to reach the summit of Kilimanjaro in September to raise money for lung cancer research. Health Editor Madeleine Brindley, who will be part of the Brains SA Captains Climb, examines the impact the high-altitude trek will have on the team".
http://www.walesonline.co.uk/news/health-news/2010/04/05/kilimanjaro-can-be-a-killer-91466-26175103/

BBC News (July 2009).
"Medical students from Glamorgan University prepare for a trek to test the levels of human endurance at high altitude".
http://news.bbc.co.uk/1/hi/wales/7506400.stm