Institution: University of Ulster

Unit of Assessment: 3B Allied Health Professions, Dentistry, Nursing and Pharmacy – Biomedical Sciences

Title of case study: Riboflavin, *MTHFR* genotype and blood pressure

1. Summary of the impact (indicative maximum 100 words)

Novel work undertaken at this centre has demonstrated that vitamin B2 (riboflavin) can significantly decrease BP, specifically in people with a common genetic variant affecting the folate-metabolising enzyme MTHFR. The extent of BP-lowering demonstrated is as good as that expected from BP-lowering drugs and much better than that found with common dietary approaches and furthermore, the effect is independent of concurrent BP-lowering drugs. These findings offer a simple, cost-effective targeted treatment for the management of BP in this genetically at-risk group. The global prevalence of this genetic variant is 10% but can be as high as 32% in other countries such as Mexico and Northern China.

2. Underpinning research (indicative maximum 500 words)

The work is underpinned by a rolling research programme on riboflavin involving a series of sequential studies that have so far led to the publication of 6 original papers and several review articles.

Our land-mark research study (Horigan et al 2010) was an RCT aimed at examining the effect of intervention with riboflavin (a cofactor for methylenetetrahydrofolate reductase (MTHFR) on blood pressure in patients homozygous (TT genotype) for the common 677C -> T polymorphism in MTHFR. We investigated 197 premature cardiovascular disease patients, pre-screened for the *MTHFR* 677C->T polymorphism, from a much larger cohort to select those with the TT genotype (*n*=60) and those with heterozygous (CT; *n*=85) or wild-type (CC; *n*=75) genotypes. Of these, 181 completed an intervention in which participants were randomised within each genotype group to receive 1.6 mg per day riboflavin or placebo for 16 weeks. At baseline we observed that target blood pressure (< 140/90 mmHg) had been achieved in only 37% of patients with the TT genotype compared with 59% with the CT and 64% with the CC genotype ($P < 0.001$). Riboflavin intervention reduced mean blood pressure specifically in those with the TT genotype (from 144/87 to 131/80 mmHg; $P < 0.05$ systolic; $P < 0.05$ diastolic), with no response observed in the other genotype groups. This lowering was observed despite the fact that over 80% of all patients were taking one or more antihypertensive drugs at recruitment.

In a follow-up study carried out 4 years later, those with the TT genotype remained hypertensive despite marked changes in antihypertensive therapy but, once again, BP responded significantly to riboflavin administered at the dietary level of 1.6mg/d for 16 weeks. We have recently confirmed that these findings are not confined to high-risk CVD patients but apply to hypertensive patients generally and results suggest that the lowering achieved appears to be independent of number and type of antihypertensive drugs co-administered.

Riboflavin thus offers a novel, targeted approach to lowering blood pressure specifically in hypertensive individuals with this common polymorphism. These findings have important implications for a personalised approach for the management of hypertension given the high prevalence of this common variant worldwide.

Key Researchers at Ulster:

PhD students at Ulster: Geraldine Horigan (2003-2006); Carol Wilson (2007-2010); Rosie Reilly (2010-2013).

Current key staff: Mary Ward (Professor); Helene McNulty (Professor);JJ Strain (Professor).

External Collaborators:

Health Service Northern Ireland: John Purvis (Consultant Physician in Cardiology Western Health and Social Care Trust); Tom Trouton (Consultant Physician in Cardiology Northern Health and Social Care Trust).

Academic collaborators at Trinity College Dublin (1992-2012): John M Scott (Professor)

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

The work has been published in the top nutrition and hypertension journals:

Wilson, C. P., McNulty, H., Ward, M., Strain, J. J., Trouton, T. G., Hoeft, B. A., Weber, P., Roos, F.

F., Horigan, G., McAnena, L., Scott, J. M. (2013). Blood pressure in treated hypertensive individuals with the MTHFR 677TT genotype is responsive to intervention with riboflavin: findings of a targeted randomized trial. *Hypertension,* 61: 1302-1308.
DOI: 10.1161/HYPERTENSIONAHA.111.01047
SJR: 2.173 SNIP: 2.183 Impact Factor: 6.207

Wilson, C. P., Ward, M., McNulty, H., Strain, J. J., Trouton, T. G., Horigan, G., Purvis J., Scott, J. M. (2012). Riboflavin offers a targeted strategy for managing hypertension in patients with the MTHFR 677TT genotype: a 4-y follow up. *American Journal of Clinical Nutrition*, 95: 766-72.
DOI: 10.3945/ajcn.111.026245
Times Cited: 7 SJR: 2.816 SNIP: 2.404 Impact Factor: 6.669
Of note, this paper was also selected for a pubcast:
Video Pubcast, Scivee (in association with American Society of Nutrition) (March 2012): Riboflavin offers a targeted strategy for managing hypertension in patients with the MTHFR 677TT genotype: a 4-y follow-up
Available at: http://www.scivee.tv/node/39315 537 views (as of 08/09/2013)

Horigan, G., McNulty, H., Ward, M., Strain, J. J., Purvis, J., Scott, J. M. (2010). Riboflavin lowers blood pressure in cardiovascular disease patients homozygous for the 677C>T polymorphism in MTHFR. *Journal of Hypertension*, 28: 478-486.
DOI: 10.1097/HJH.0b013e328334c126
Times Cited: 13 SJR: 1.292 SNIP: 1.527 Impact Factor: 4.021.

Hoey, L., McNulty, H., Strain, J. J. (2009). Studies of biomarker responses to intervention with riboflavin: a systematic review. *American Journal of Clinical Nutrition*, 89: 1960s-1970s.
DOI: 10.3945/ajcn.2009.27230B
Times Cited: 20 SJR: 2.816 SNIP: 2.404 Impact Factor: 6.669

McNulty, H., Dowey, L. C., Strain, J. J., Dunne, A., Ward, M., Molloy, A. M., McAnena, L. B., Hughes, J. P., Hannon-Fletcher, M., Scott, J. M. (2006). Riboflavin lowers homocysteine in individuals homozygous for the *MTHFR* 677C→T polymorphism. *Circulation*, 113: 74-80.
DOI: 10.1161/CIRCULATIONAHA.105.580332
Times Cited: 83 SJR: 5.760 SNIP: 4.273 Impact factor: 14.739

McNulty, H., McKinley, M. C., Wilson, B., McPartlin, J., Strain, J. J., Weir, D. G., Scott, J. M. (2002). Impaired functioning of thermolabile methylenetetrahydrofolate reductase is dependent upon riboflavin status: implications for riboflavin requirements. *American Journal of Clinical Nutrition*, 76: 436-441.
Times Cited: 130 SJR: 2.816 SNIP: 2.404 Impact Factor: 6.669

Grant income obtained (2003-2014) to undertake the studies was from DEL NI, Department of Agriculture (ROI), DSM, NI Chest Heart and Stroke:
Ward, M., McNulty, H., Strain, J. J. Blood Pressure lowering effect of riboflavin in hypertensive adults with a genetic predisposition to elevated blood pressure. Funded by DSM Nutritional Products Ltd.; 2011-2014; £322k.

Strain, J. J., McNulty, H., Ward, M. National Nutritional Phenotype Database ('JINGO'). Funded by The Irish Department of Agriculture, Food & the Marine and Health Research Board through the Food Institutional Research Measure (FIRM) initiative; 2008-2013; £631k.

McNulty, H., Strain, J. J., Ward, M., Wallace, J.M.W. Irish Universities Nutrition Alliance Project: Building additional and sustainable research capacity in nutrition and bone health. Funded by the Northern Ireland Department for Employment & Learning (DEL) through Cross Border R&D Funding Programme: 'Strengthening the All-Island Research Base'; 2008-2011; £1.24m.

Ward, M. Innovation Leaders. Funded by R&D Office; 2009-2010; £11.5k
Ward, M., McNulty, H., Purvis, J., Strain, J. J. The homocysteine-lowering effect of riboflavin in

CVD patients with different MTHFR C677T genotypes. Funded by Northern Ireland Chest Heart and Stroke Association; 2004-2006; £36k.

McNulty, H., Ward, M., Pentieva, K., Strain, J. J. Influence of gender, age .and genotype on the known sub-optimal status of folate, vitamin B-12, vitamin B-6 and riboflavin. Funded by Food Standards Agency; 2003-2006; £432k.

4. Details of the impact (indicative maximum 750 words)

The findings described in this case study of a new gene-nutrient interaction involving riboflavin, a folate-metabolising gene and blood pressure are innovative and novel. Although of recent origin, the work has begun to make sizeable impacts because of its benefits for both the prevention and treatment of blood pressure in genetically predisposed individuals.

These novel findings have not only led to important publications but also the filing of a series of patent applications which have since granted in Europe, China, Mexico and Eurasia with applications pending in the US and Japan **[1]**, both of which have important implications for personalised nutrition. Our initial papers in this area (notably *McNulty et al 2002*) have had impacts in health and welfare and informed dietary guidelines; at grass-roots level, our works have contributed important evidence to the Scientific Advisory Committee on Nutrition's (SACN) 2006 report **[3]** and, further afield, the findings of *McNulty et al 2002* informed the Australian National Health and Medical Research Council's Nutrient Reference Values, 2006). **[4]**.

Public awareness of the health benefits of riboflavin is constantly being raised on a global scale. Our publications (notably *Wilson et al 2012*) have attracted considerable media coverage, from BBC News to German and New Zealand radio stations **[5]**. Our most recent publication (*Wilson et al 2013*) has already been captured on social networking site Twitter **[6]**. Various websites, all of which promote new developments in micronutrient research and are aimed at consumers, healthcare professionals and policymakers, have reported the team's research and include NUTRIFACTS, nutraingredients and talkingnutrition.dsm **[7]**.

Public engagement activity has gone beyond 'business as usual' and key investigators have been invited to deliver findings at prestigious international events, hosted by major players in industry and healthcare (e.g. DSM Nutritional Products, Nestlé, IADSA, World Hypertension League). The focal point of such events is to promote treatments of non-communicable diseases globally and translate them into policy.

Considering the major-risk posed by high blood pressure, evidence indicates that disease prevention is being enhanced by our work. The UK's Blood Pressure Association ran a report, in a 2012 edition of Positive Pressure Magazine **[8]**, encouraging patients to take their vitamins; this report was informed by the findings of *Wilson et al 2012* and has already stimulated interest amongst patient-groups.

Innovation within the food industry is proving most significant; for example, findings from *Horigan et al 2010* were integrated into a 2010 Food for Thought article (a Netherlands-based magazine aimed at food industry decision-makers) **[9]** and an invited article featured in a 2011 edition of AgroFood Industry HiTech **[10]**. It should be noted that the patent licensing is currently under discussion with Nestlé, the world's leading food company **[2]**. Financial support (£322K to date) from DSM Nutritional Products Ltd., the world's leading ingredient company, is facilitating the exploration of mechanisms and further work to support the patent. DSM's ongoing commitment to our novel discovery is evidenced by a number of outputs over the last 2 years which include regular press and web updates **[11]**.

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

1) Patent family entitled "Use of riboflavin in the treatment of blood pressure in people with the MTHFR 677C→T polymorphism" (U104) and claiming priority from UK application (GB0703514.0) filed on 23rd February, 2007 has granted in Europe (EP2139488) with validation in force in Ireland, Switzerland, Spain, Italy, France, Netherlands, Germany, and the UK; China (ZL200880013520.9),

Mexico (MX/a/2009/009020) and Eurasia (2009 011 45) with applications pending in the US, Japan and Canada. Inventors include: Ward M, McNulty H, Scott JM, Horigan G, Strain JJ, Purvis J. All rights have been assigned to University of Ulster.
2) A License to Evaluate Agreement with Option was executed with Nestec Limited (Business division for Nestle) in December 2011 and extended in July 2013. Under the terms of this License, Innovation Ulster Limited has granted Nestec an Exclusive Option to obtain a commercial license for further development of U104 in the field of nutrition products and/or components in the territories of Mexico, Japan, China, the US and European countries of Spain, France and Switzerland. Licensing revenue generated to date as a result of this Agreement total £25,000.
3) Scientific Advisory Committee on Nutrition (2006) Folate and Disease Prevention. TSO, London. Available at: http://www.sacn.gov.uk/pdfs/folate_and_disease_prevention_report.pdf [Accessed August 2012].
4) Australian National Health and Medical Research Council (2006). Nutrient Reference Values for Australia and New Zealand.
Available at: http://www.nhmrc.gov.au/guidelines/publications/n35-n36-n37 [Accessed August 2012].
5) Media Coverage:
BBC News Online (11 May 2012) UU Vitamin research combats stroke risk.
Available at: http://www.bbc.co.uk/news/uk-northern-ireland-18025721
C-TRIC (11 May 2012) Vitamin link to curbing blood pressure announced at TMED Conference.
http://www.c-tric.com/2012/vitamin-link-to-curbing-blood-pressure-announced-at-tmed4-conference
A radio interview on potential for personalised nutrition with a German radio station ((Deutschlandfunk-28.9.2012) following a scientific presentation at the joint meeting of the German, Austrian and Swiss Nutrition Societies http://www.dradio.de/dlf/sendungen/forschak/1879373/
New Zealand Listener (27 July 2012) Riboflavin to the Rescue
http://www.listener.co.nz/lifestyle/nutrition/riboflavin-to-the-rescue/
6) Blog from Science Director Eurogenetica Ltd:
Grimaldi, K. (24 April 2013) Riboflavin for hypertension in MTHFR 677TT genotype - effective when medication is not/ Twitter. Available from: https://twitter.com/eurogene [Accessed: April 2013].
7) Website reports:
NUTRI-FACTS (3 February 2012) Vitamin B2 may benefit people with increased risk of hypertension
http://www.nutri-facts.org/News.10+M5bffbc1cdf2.0.html
Nutraingredients (15 May 2012) Personal Nutrition: Vitamin B may offer blood pressure benefits to 1 in 10 people
http://www.nutraingredients.com/content/view/print/636565
TalkingNutrition.dsm.com (25 January 2012) Are you part of the 10 percent who needs more riboflavin for healthy blood pressure?
http://talkingnutrition.dsm.com/en_US/public/pages/blog/20120125_rib.jsp;jsessionid=007B17F34B402E765A5A87205330CCB2
8) Positive Pressure Magazine (2012) Blood pressure news – take your vitamins. Blood Pressure Association 31. p4.
9) Food for Thought Magazine (May 2010) Nutrigenomics and personalised nutrition
Available at: http://www.nfia.com/fft/201005/article6.php
10) Ward, M. and McNulty, H. (2011). Vitamin B2 (riboflavin) might have a clinically important impact on lowering hypertension. *AgroFood Industry HiTech* 2011 22(1), 58-59.
11) DSM-related publicity:
DSM Nutritional Products (29 May 2012). DSM announces new research revealing how a B vitamin can help lower blood pressure. Kaiseraugst.
http://www.dsm.com/en_US/html/dnp/news_items/2012_05_29_new_research_B_vitamin.htm
Sight and Life Magazine (2010). Congress Report (2nd World Congress of Public Health and Nutrition). 83-84.