Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-06 Developing a Better Understanding of Omega-3 Fats, Inflammation and Disease

1. Summary of the impact

University of Southampton research into the anti-inflammatory effects of omega-3 fatty acids and the mechanisms by which they act has delivered benefits for the treatment of cardiovascular disease, improving clinical practice, lowering mortality rates and reducing healthcare costs. The findings of a novel mechanism of action by which omega-3 reduces cardiovascular events and mortality have contributed to UK government guidelines on nutrition, have been cited in European atherosclerosis guidelines, and have been patented and licensed in several countries, resulting in new research income. They have also received significant media exposure and formed the basis of a number of educational events for health professionals.

2. Underpinning research

It is well established that omega-3 fatty acids reduce the risk of cardiovascular morbidity and mortality. However, the mechanism by which they act is less well understood. The favoured mechanism is via an anti-arrhythmic action, despite equivocal evidence about whether omega-3 fatty acids actually prevent cardiac arrhythmias.

Philip Calder, Professor of Nutritional Immunology, has led University of Southampton research on fatty acids, immunity and inflammation since 1995. Focusing on the anti-inflammatory effects of omega-3 fatty acids and the fact that inflammation causes plaques that accumulate in the artery wall's lining to rupture, the team has explored the action of omega-3 fatty acids within advanced atherosclerotic plaques as a potential mechanism for reduced cardiovascular morbidity and mortality.

This was tested through a placebo-controlled, double-blind, randomised trial of omega-3 fatty acids in patients awaiting surgical removal of advanced plaques from their carotid arteries. Funded by the Food Standards Agency, the trial and subsequent laboratory work were conducted from 1998 to 2001. The PIs were Robert Grimble (Professor of Human Nutrition; 1972 to 1996), Philip Calder (Professor of Nutritional Immunology; 1995 to present) and Cliff Shearman (Professor of Vascular Surgery; 1999 to present) and Patrick Gallagher (Consultant Pathologist at Southampton University Hospitals Trust).

The study, published in *The Lancet* in 2003 **[3.1]**, demonstrated plaque stabilisation with omega-3 fatty acids, representing the discovery of a novel mechanism by which these nutrients reduce the risk of cardiovascular events. The anti-inflammatory effect of omega-3 fatty acids within plaques was shown to reduce the vulnerability of atherosclerotic plaques to rupture and thus lower the likelihood of a myocardial infarction or stroke occurring. Calder led a subsequent study, funded by Pronova Biocare (now Pronova Biopharma), the global leader in omega-3-derived pharmaceuticals, to further investigate anti-inflammatory action of omega-3 in plaques. This showed omega-3 fatty acids reduce the inflammatory burden within the advanced plaque, consistent with its increased stability **[3.2]**.

This body of research indicates omega-3 fatty acids offer a therapeutic strategy for reducing the risk of cardiovascular morbidity and mortality. The identified plaque stabilising effect can explain the reduced mortality with omega-3 fatty acids seen in post-myocardial infarction patients in the GISSI-Prevenzione study, widely recognised as landmark research in cardiology. Calder's research into the anti-inflammatory effects of omega-3 fatty acids and the mechanisms by which they act has also increased the robustness of the evidence that these nutrients can be useful as an adjunct therapy in treating inflammatory diseases, including vascular disease, Crohn's disease, rheumatoid arthritis and asthma **[3.3-3.5]**.

The Southampton team has also shown that individual responsiveness to the anti-inflammatory effects of omega-3 fatty acids is in part determined by genotype for inflammatory genes. This demonstrates the value in targeting dietary advice or therapy towards those most likely to benefit, contributing towards ongoing debates on the importance of personalised nutrition.

Calder's research has, in addition, contributed to the clinical acceptance of novel lipid emulsions for use in intravenous nutrition and has informed European guidelines on use of parenteral lipids in intensive care. His trial conducted with critically ill patients demonstrated decreased inflammation in those receiving intravenous omega-3 fatty acids and this was linked with a faster recovery seen as a shorter time in hospital **[3.6]**.

3. References to the research

3.1 Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003;361:477-485. [310 cites]

3.2 Cawood AL, Ding R, Napper FL, Young RH, Williams JA, Ward MJ, Gudmundsen O, Vige R, Payne SP, Ye S, Shearman CP, Gallagher PJ, Grimble RF, Calder PC. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. *Atherosclerosis* 2010; 212:252-259.

3.3 Calder PC. n-3 fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clin Sci* 2004; 107:1-11. [216 cites]

3.4 Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 2010; 376:540-550.

3.5 Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: Nutrition or pharmacology? *British Journal of Clinical Pharmacology* 2013; 75:645-662.

3.6 Barbosa VM, Miles EA, Calhau C, Lafuente E, Calder PC. Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. *Critical Care* 2010; 14:R5.

Grants

1. Grimble, Calder & Shearman; The effect of dietary n-3 and n-6 poly-unsaturated fatty acid intake on atheromatous plaque lipid composition; Ministry of Agriculture, Fisheries & Food; 3 years + 1 year extension; 1997-2001; £272,163 + £47,762.
2. Calder; Omega-3 fatty acids and stability of advanced atherosclerotic plaques (OCEAN); Pronova Biocare; 2 years; 2003-2005; £300,000.

4. Details of the impact

Research conducted at Southampton into the anti-inflammatory effects of omega-3 fatty acids has had wide-ranging benefits. These relate to the treatment, mortality rate and economic costs of cardiovascular disease; to clinical practice in and guidelines on cardiovascular disease and parenteral nutrition; to economic benefits through the patenting of the plaque stabilisation by omega-3 fatty acids; and to public health.

The research resulted in the discovery that atherosclerotic plaque stabilisation is likely to reduce cardiovascular mortality rates. The reduction in mortality would be a few percent in the general population but, based upon the extent of plaque stabilisation observed, 10 to 20% of those who had already suffered a major event like myocardial infarction or stroke survived. This should be considered in the context that, according to the British Heart Foundation, one in three of all deaths in the UK in 2010 was the result of cardiovascular disease. This equates to 180,000 deaths,

including 80,000 from coronary heart disease and 49,000 from strokes. There are 120,000 myocardial infarctions and 150,000 strokes in the UK each year. With cardiovascular disease costing the UK healthcare system around £8.7bn in 2009 (72% from hospital costs) and the UK economy around £19bn, the economic savings of reducing cardiovascular mortality and morbidity are considerable.

The 2003 Lancet paper has been cited over 300 times and was named by the NIH Office of Dietary Supplements (USA) as one of the top 25 research papers published in 2003. The findings are discussed in the 2011 position paper of the European Society of Cardiology (ESC) Working Group on Atherosclerosis and Vascular Biology **[5.1]**, directed at clinicians and scientists; the ESC has responsibility for establishing practice guidelines for cardiologists across Europe.

The application of Calder's research on omega-3 fatty acids to the development of novel lipid emulsions for use in parenteral (intravenous) nutrition has contributed to clinical acceptance of novel lipid emulsions and influenced the 2009 European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines on the use of parenteral lipids in intensive care **[5.2]**. These guidelines, aimed at intensive care physicians across Europe, refer to Calder's work on the anti-inflammatory actions of omega-3 fatty acids and support their provision for improved patient recovery.

Calder directly contributes to the translation of scientific findings for clinical end-users by giving presentations in many educational and continuing professional development events for health professionals across Britain and Ireland. These events are attended by 20-100 delegates – including GPs, cardiologists, cardiac rehab nurses, pharmacists, surgeons, intensivists and dieticians – resulting in a cumulative audience of several thousands of health professionals, helping to educate them and to translate the research findings into clinical practice. Calder has written several educational/CPD articles for health professionals **[5.3]** and in 2012 was interviewed in the Dutch medical magazine Nederlands Tijdschrift voor Geneeskunde **[5.4]**.

The discovery of plaque stabilisation by omega-3 fatty acids was patented and licensed to Pronova Biocare, and subsequently granted in a number of European countries (in 2009 **[5.5]**) and in Australia**,** China (in 2010) and Canada (in 2013) providing an intellectual and marketing advantage to the holder and contributing to wealth creation in the private sector. This discovery and its patenting supported the Pronova product Omacor, known in North America as Lovaza, globally the largest prescription omega-3 pharmaceutical. Calder's work influenced the funding decisions of several organisations during the REF impact period. Pronova Biocare awarded Southampton £300,000 for follow-up research and Calder received substantial funding to continue his research programme on omega-3 fatty acids and inflammation including grants from Food Standards Agency (£450,000), European Commission (£702,000 and £405,000), and industry (Unilever £110,000; B Braun £11,000; Vifor Pharma £325,000).

Southampton's research in this area has impacted on public health by creating considerable media coverage, contributing to public appreciation and understanding of science and to UK and US dietary guidelines for the general population. Calder regularly gives interviews for television (Channel Five news, Meridian news), radio (BBC Radio 4 Food Programme, several regional BBC stations, Jack FM), newspapers (Diario Jaen, Daily Mail, The Times, The Sunday Times, Los Angeles Times **[5.6]**, Daily Echo), magazines (Mens Health, Good Housekeeping, Bottom Line Health, Consumer Reports on Health) and on many websites (e.g. BBC, Irish Independent) as well as in food industry magazines (e.g. Nutraingredients **[5.7]**). Calder is regarded as an authoritative voice and key opinion leader in the area of fats and health, often serving to bring clarification amid public confusion in the light of conflicting scientific and media reports. Most recently, Calder has given interviews and been quoted in relation to recent research about saturated and omega-6 fats (e.g. Boston Globe, BBC regional radio stations, Jack FM) and to the changing regulatory view on omega-3 fats and cardiovascular disease (New York Times, 2013 **[5.8]**).

Calder presented his research findings at four Food Standards Agency Chief Investigator Review Workshops, at which the scientific basis that underpins the current UK dietary recommendations about fat and fatty acid intake were established in 2010 **[5.9]**. Calder's research was also reviewed, along with accrued evidence about fish and omega-3 fatty acids and (principally cardiovascular) human health, when the Scientific Advisory Committee on Nutrition and the Committee on Toxicology considered the UK guidelines for intake of fish and n-3 fatty acids. Published in 2004, the report established a new UK recommendation for omega-3 fatty acid intake **[5.10]**, which remains in place. This recommendation contributes significantly to UK public health policy.

5. Sources to corroborate the impact

5.1 Yla-Herttuala et al. (2011) Stabilisation of atherosclerotic plaques. *Thrombosis and Haemostasis* 106, 1-19.

5.2 Singer et al. (2009) ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clinical Nutrition* 28, 387-400.

5.3 Calder (2013) Omega-3 fatty acids in health and disease: the science behind the headlines. *NHD Magazine* 83, 18-19.

5.4 *Nederlands Tijdschrift voor Geneeskunde*, issue of 31 March 2012 (Volume 156, Issue 13, pages 542-543)

5.5 Patenting of the discovery of plaque stabilisation by omega-3 fatty acids: European patent number EP1501493 B1.

http://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20091007&DB=EPODOC&locale=en_EP&CC=EP&NR=1501493B1&KC=B1&ND=4

Licensing of patent from the University of Southampton to Pronova Biocare: corroboration can be provided by Clinical Research Manager at Pronova BioPharma (contact info. in separate form).

5.6 Calder interviewed and widely quoted in two articles in the *Los Angeles Times* 26 April 2010
http://articles.latimes.com/2010/apr/26/health/la-he-omega-3s-20100426

http://articles.latimes.com/2010/apr/26/health/la-he-omega-3s-how-much-20100426

5.7 Calder interviewed and widely quoted in two articles in the food industry magazine *Nutra Ingredients* on 18 October 2012:
http://www.nutraingredients.com/content/view/print/691010

http://www.nutraingredients.com/content/view/print/690994

5.8 Calder quoted on the *New York Times* website 07 March 2013
http://well.blogs.nytimes.com/2013/03/07/eat-your-heart-out/?_r=0

5.9 Sanderson et al. (2010) UK Food Standards Agency Workshop Report: Diet and Immune Function. *British Journal of Nutrition* 103, 1684-1687.

5.10 Scientific Advisory Committee on Nutrition and the Committee on Toxicity (2004) Advice of fish consumption: benefits and risks. TSO, London. These recommendations remain in force.