Institution:
Cardiff University

Unit of Assessment:
UoA5_Casestudy5

Title of case study:
Cardiff research supports the commercial use of 'omega-3s' in pet foods and dietary supplements

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

Producers of dietary supplements have historically lacked scientific rigour when advertising the health benefits of their products. Researchers at Cardiff University have addressed this problem in relation to omega-3 polyunsaturated fatty acids (PUFAs). They identified a family of enzymes (aggrecanases) as key players in the onset of arthritis, knowledge subsequently used to identify a specific subset of omega-3-PUFAs with beneficial activity in a canine arthritis model. This led to novel patents and product development in both the pet food and human dietary supplement markets. These include the patented use of omega-3 PUFAs in Hills'® Prescription Diet® range and the development and marketing of Seven Seas' 'JointCare' products.

2. Underpinning research (indicative maximum 500 words)

Fats are an important component of the diet and certain polyunsaturated fatty acids (PUFAs) are essential. They are divided into the omega-3 and the omega-6 series, depending on the position of their double bonds.

For over 30 years it has been suggested that omega-3 PUFA intake may have a direct influence on health, however the evidence for this has largely been anecdotal in nature. Research at Cardiff University has begun to address this issue by showing that the omega-3 PUFAs give rise to signalling molecules which are poorly- or anti-inflammatory, whereas omega-6 PUFAs are metabolised to products that are pro-inflammatory. This discovery provides a scientific mechanism which may underpin the beneficial claims, suggests that specific components of omega-3 PUFAs impact upon cartilage metabolism in patients with osteoarthritis[3.1], and may confer a level of protection against or alleviate chronic inflammatory diseases such as arthritis.

Omega-3s against arthritis

There was already considerable anecdotal and some epidemiological and clinical intervention evidence to suggest that fish oils or other sources of 'omega-3s' helped to alleviate the symptoms of arthritis. However, prior to Cardiff's investigations, the molecular mechanisms for their efficacy were unknown.

An interdisciplinary study was begun at Cardiff University between the lipid biochemistry group of Professor John Harwood (appointed Professor at Cardiff 01/07/1984) and the connective tissue research laboratory of Professor Bruce Caterson (appointed Professor at Cardiff 03/04/1995) and Dr Clare Hughes (appointed 01/05/1995 & promoted to reader 01/08/2013). The first publication from this cross-disciplinary group identified a number of factors that are associated with inflammation or have a role in cartilage degradation. These include the expression of aggrecanases (which degrade the matrix proteoglycan aggrecan), the presence of enzymes such as cyclooxygenase-2, and the expression of several cytokines. This paper was an accelerated publication in J. Biol. Chem[3.2]

Degradation products of aggrecan are present in the synovial fluid of patients with Arthritis. Caterson and Hughes produced five mono-clonal Antibodies (mAbs) which recognise these products and have subsequently been used in a variety of assay systems as a read out measure for cartilage degradation. This has accelerated the screening procedures used for the preclinical assessment of arthritis-modifying drugs. Prior to the development of these antibodies, researchers were reliant on non-specific assays as a measure of cartilage degradation or the expense of time consuming sequence analysis[3.3].

Continuing research then revealed the relative efficacy of different omega-3-PUFAs[3.4] to reduce inflammation, associating beneficial activity specifically with eicosapentaenoic acid (EPA). These studies also revealed that the ability of these 'omega-3s' to reduce gene expression (including of the aggrecanases) is paralleled by a decrease in cyclooxygenase-2 protein and activity. The researchers concluded that this deregulation of cyclooxygenase-2 explained activity of these long

known oils[3.5].

Omega-3s in pets foods

Humans are not the only animals suffering from arthritis; some dog breeds, such as Alsatians, are particularly susceptible to this inflammatory condition. The Cardiff research, in collaboration with Hill's Pet Nutrition (a member of the Colgate-Palmolive corporation), led to the development of a patent for the inclusion of the omega-3-PUFA (EPA) in pet food formulations. The patent cites the underpinning research throughout (for example, see sections 25, 33, 35-38, 41, 49-52, 53 and 58.)[3.6]

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

3.1 Curtis, C.L., Rees, S., Evans R., Dent, C., **Caterson, B**. and **Harwood, J.L.** (2004) The effects of n-3 PUFAs on cartilage metabolism in patients with osteoarthritis: the results of a pilot clinical trial. Proc. 3rd Europ. Fed. Lipids Congress, Edinburgh, p.216

3.2 Curtis, C.L., **Hughes, C.E.**, Flannery, C.R., Little, C.B., **Harwood, J.L.** and **Caterson, B.** (2000). n-3 Fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. *J. Biol. Chem*. **275**, 721-724. http://dx.doi.org/10.1074/jbc.275.2.721

3.3 Powell, A.J., Little, C.B., **Hughes, C.E.** (2007). Low molecular weight isoforms of the aggrecanases are responsible for the cytokine-induced proteolysis of aggrecan in a porcine chondrocyte culture system. *Arthritis & Rheumatism* **56**: 3010-3019. http://dx.doi.org/10.1002/art.22818

3.4 Zainal, Z., Longman, A.J., Hurst, S., Duggan, K., **Caterson, B.**, **Hughes, C.E.** and **Harwood, J.L.** (2009). Relative efficacies of omega-3 polyunsaturated fatty acids in reducing expression of key proteins in a model system for studying osteoarthritis. *Osteoarthritis Cartilage* **17**, 896-905. http://dx.doi.org/10.1016/j.joca.2008.12.009

3.5 Hurst S., Rees S.G., **Randerson, P.F., Caterson, B.**, **Harwood, J.L.** (2009). Contrasting effects of n-3 and n-6 fatty acids on cyclooxygenase-2 in model systems for arthritis. *Lipids* **44**,889-896. http://dx.doi.org/10.1007/s11745-009-3347-x

3.6 US Patent US2010/0261793A1. Method for decreasing cartilage damage in dogs. Inventors: **Bruce Caterson**, Christopher Little, **John Harwood** et al. Original assignee: Hill's Pet Nutrition, Inc. Filed: Oct14, 2010.

All publications available on request from the HEI.

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

Cardiff's research on chronic inflammatory diseases has had a direct economic impact on major global manufacturers of health supplements and pet foods (total global markets worth $142bn[5.1] and $58bn[5.2], respectively in 2011) through:

- contributing to the development of new products containing omega-3, and
- providing a credible scientific basis for successful marketing campaigns for these products, based on their beneficial anti-inflammatory effects.

Further economic benefit has been gained through the commercialisation of neoepitope mAbs developed at Cardiff through direct sales and licensing agreements with major pharmaceutical companies.

Patent driven Sales of Pet Food.

Cardiff performed in vitro research in collaboration with Hill's Pet Nutrition, Inc, a subsidiary of the Colgate-Palmolive group (a Fortune 200 company). Specifically, the three principal omega-3 PUFAs found in fish oil were tested using the biochemical readouts developed at Cardiff (Section 2) in collaboration with researchers from Liverpool University who performed clinical trials (Vet School). The director of Professional and Veterinary Affairs at Hill's Pet nutrition stated;

"Their research revealed that eicosapentaenoic acid ("EPA") was the most potent at reducing the breakdown signature seen in cartilage degradation. These trials led directly to a successful patent

filing in 2010 (US2010/0261793A1, Method for Reducing Cartilage Damage in Dogs), in which both Harwood and Caterson were named[3.6]. The aforementioned research, and by extension the patent, provided a verifiable foundation for Hill's to develop effective EPA dosages for dog food to be tested and brought to market. It led directly to the company's development of new products containing specific ratios of EPA to the other constituent PUFA's. Pet food products arising from this research are now marketed and sold by Hill's worldwide under the name Prescription Diet® j/d food[5.3]. The Hill's Pet Nutrition currently accounts for $2.16billion (13%) of Colgate-Palmolive's global net sales of $17 billion[5.3, 5.4].

Product sales are driven by a marketing campaign which specifically cites the research findings, viz "Hills® Prescription Diet® j/d® helps your dog walk, run and jump more easily in just 21 days"[5.5].

New nutraceuticals

The Cardiff team also has an on-going collaboration with Seven Seas (now owned by Merck, a Fortune 100 company), which has included a successful preliminary clinical trial on the effects of omega-3 PUFA's on joint cartilage[5.6]. This collaboration has led, during the REF period, to the enhancement of existing products within the Seven Seas JointCare range (eg Jointcare Max, Supplex and Complete) for the alleviation of arthritis symptoms[5.7].

Seven Seas acknowledges the contribution of Cardiff, which 'provided scientific support for our existing omega-3 supplements and helped in the development of additional product variants…[and] helped strengthen the credible scientific basis for our marketing activities in relation to omega-3 PUFA based products. In turn, this helped consolidate our position in the global marketplace'[5.6]. The market value of dietary supplements in the UK was $1.1Billion in 2009 and Seven Seas accounted for 6.5% of the market[5.8]. Omega-3 PUFA-containing products are currently worth about €13 billion[5.9] globally.

Changing research practice

The five neoepitope mAbs developed by Caterson and Hughes have been commercialised by Cardiff University through licensing and direct sales to three of the top 10 pharmaceutical companies (Dupont, Hoechst, and Ely Lilly). They are also marketed through five major antibody-reagent sales and distribution companies (Abcam, Novus Biologicals, Millipore, MD Biosciences and ThermoFisher) which has generated royalties to Cardiff University of £85,000 since 2008, reflecting sales of approximately £450,000.

During the REF period the Cardiff team was involved in a Knowledge Transfer Partnership (KTP) with Obsidian Research Ltd. This company is a nutraceuticals formulation manufacturer, based in South Wales, which develops its own range of products for the global market. Since the KTP with Obsidian the company has adopted two scientific methods developed in Cardiff University to provide efficacy data for new formulations. These methods are:

- in vitro experiments using bovine cartilage explants to analyse the efficacy of active ingredients (developed by Caterson and Hughes);
- lipid analyses: for the quality control of lipid based products (developed by Harwood).

The KTP associate trained four Obsidian employees so that all new products could be validated using these improved methodologies[5.10].

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

5.1 Web source detailing Nutraceuticals market size 2011. http://www.foodengineeringmag.com/articles/89227-nutraceutical-markets-are-exceptionally-healthy

5.2 Web source detailing pet food market size 2011. http://www.petbusinessworld.co.uk/news/feed/global-pet-food-market-sees-4-2--growth

5.3 Statement from Director, Professional & Veterinary Affairs, Hill's Pet Nutrition. Corroborating the contribution of Cardiff's omega-3 research using the mAbs in the development and sales of specialist dog food formulations; Prescription Diet. (Statement available on request)

5.4 Colgate Palmolive Annual Report 2012 (Pages 9 and 20). Evidence of current market size and reach of the science diet range of products: http://www.colgate.com/us/en/annual-reports/2012/assets/pdf/Colgate_Annual_Report_Lowres.pdf

5.5 Hill's pet nutrition website corroborating claim of 21 day improvement in arthritic symptoms, based on Patented research: www.hillspet.com/healthy-mobility/nutrition.html

5.6 Statement from Senior Nutritionist, Seven Seas Ltd. Confirming the contribution of Cardiff to a clinical trial that subsequently supported marketing claims and the development of new product variants (Statement available on request)

5.7 Seven Seas Website, specifically claiming efficacy of omega-3 PUFA in their Joint care range of Products: http://www.seven-seas.com/jointcare/ingredients/omega-3-fish-oil

5.8 Canadian government source confirms Seven Seas market share in the UK (for 2009) of 6.5%. (tables on pages 3 and 20) http://www.ats-sea.agr.gc.ca/eur/pdf/5714-eng.pdf

5.9 Web source verifying Global nutraceuticals market size www.packagedfacts.com/Omega-global-product-6385341/

5.10 Statement from CEO, Obsidian Ltd. Confirming the adoption of methods for validating efficacy of nutraceutical products (Statement available on request)