Institution:
UNIVERSITY OF LIVERPOOL

Unit of Assessment:
UOA6 - Agriculture, Veterinary and Food Science

Title of case study:
Improving the Diagnosis, Treatment and Monitoring of Canine and Feline Osteoarthritis

1. Summary of the impact

Canine osteoarthritis affects up to 20% of adult dogs and is of worldwide welfare importance. Research by the University of Liverpool (UoL) (with collaborators) has led to profound changes in the ways in which veterinarians manage canine and feline osteoarthritis. Molecular insights have led to new prescription diets that enable veterinarians to improve the health and wellbeing of companion animals and have provided economic impact through sales of these prescription diets. In addition, a new clinical metrology instrument ('*Liverpool Osteoarthritis in Dogs' or* "LOAD") for assessment of canine osteoarthritis by veterinarians and owners has changed veterinary practice through improved diagnosis, monitoring and management of dogs with osteoarthritis. LOAD has been licensed on a global basis to a pharmaceutical company (Novartis Animal Health).

2. Underpinning research

It was estimated that in the UK and USA, canine osteoarthritis affects up to ~16 million dogs at any one time, often from a young age and thus is a major canine welfare problem.

Work on the effects of omega-3 fatty acids on canine cartilage was performed by Innes (2001-present) and Vaughan-Thomas (2002-2008; deceased) at Liverpool in collaboration with colleagues at Cardiff University. These studies identified the importance of aggrecanases in spontaneous osteoarthritis in dogs [1]. Following a competitive process for initial funding, a series of subsequent funding rounds were secured from Hill's Nutrition Inc for a programme of work to investigate the potential of dietary omega-3 essential fatty acids (EFAs) to reduce the activity of aggrecanases (ADAMTS-4 and ADAMTS-5) in canine cartilage. Using an *in vitro* canine cartilage degradation model, the group (which included two jointly supervised PDRAs) demonstrated that eicosapentaenoic acid (EPA) significantly reduced the catabolic release of glycosaminoglycan (GAG) from canine cartilage which had been stimulated with catabolic cytokines interleukin-1β and oncostatin M. These cytokines stimulate chondrocytes to synthesize catabolic enzymes, such as aggrecanases, which degrade the extracellular matrix of cartilage (a critical component of which is GAG). Western blotting of culture media for products of GAG cleavage indicated that the reduction in GAG release was as a result of a reduction in aggrecanase-generated catabolites in the cartilage explants treated with EPA. Furthermore, gene expression analysis of cartilage explants indicated that EFAs induced a reduction in expression of the ADAMTS-5 gene. Other EFAs, docosahexaenoic acid (DHA) and alpha-linolenic acid (ALA), were shown not to have this beneficial effect. Thus, the research clearly indicated that the presence of EPA in the canine diet should reduce the progression or severity of osteoarthritis.

These data were used in the initial US patent application [2]. The patent applications protect the product Hill's Prescription Diet Canine j/d (www.hillspet.co.uk).

Subsequent work at Liverpool (Innes, Vaughan-Thomas) and Cardiff developed a feline cartilage degradation model [4] and similar findings for EFAs supported the formulation of Hill's Prescription Diet Feline j/d.

In parallel, Innes led research on the development of user-friendly, client-administered clinical metrology instruments (CMIs) since diagnosis, staging and assessing response to treatment in canine osteoarthritis are challenging aspects of this disease for practising veterinarians. Specifically, Innes has developed the '*Liverpool Osteoarthritis in Dogs'* ('LOAD') CMI [5,6] through a systematic psychometric validation process to provide data to underpin the use of such instruments in canine veterinary practice [5,6]. Such a validation process required testing for fact, content, construct and criterion validity as well as reliability and responsiveness. Although there are five other CMIs for chronic pain/lameness/arthritis in dogs in the peer-reviewed literature, LOAD has been tested through the most extensive validation process and thus can be considered the

current market leader due to its uniquely established 3 factor validation.

3. References to the research

1. **Innes JF**, Little CB, Hughes CE, Caterson B. (2005) "Products resulting from cleavage of the interglobular domain of aggrecan in samples of synovial fluid collected from dogs with early- and late-stage osteoarthritis. American Journal of Veterinary Research 66: 1679-1685. Citations:10 Impact Factor: 1.348

2. Caterson B, Little CB, Harwood JA, **Innes JF**, Fritsch DA, Jewell DE, Schoenher WD, and Richardson DC (2003) US Patent no. 2010256236 a US provisional patent application 60/608,926 which was filed on 11th Aug 2003 and from which a number of national patent applications (via the International PCT system) were derived. Resulting applications were filed in Australia, Brazil, Canada, China, Europe, Japan and Russia, a number of divisional applications in the US (including US2010256236) and South Africa. In the US, the original application has now been superseded by four divisional applications as follows:

   10/912,864 filed on 08-06-2004 which is Pending claims the benefit of 60/608,926
   12/820,766 filed on 06-22-2010 which is Pending claims the benefit of 60/608,926
   11/057,718 filed on 02-14-2005 which is Pending claims the benefit of 60/608,926
   12/820,813 filed on 06-22-2010 which is Pending claims the benefit of 60/608,926

3. **Gabriel N**, **Innes JF**, Caterson B, and **Vaughan-Thomas A**. (2010). Development of an *in vitro* model of feline cartilage degradation. J. Feline Med. Surg. 12: 614-620. Citations: 3 Impact Factor: 1.080

4. **Hercock C**, **Pinchbeck G**, **Giejda A, Clegg PD**, **Innes JF** (2009) "Validation of a client-based clinical metrology instrument for the evaluation of canine elbow osteoarthritis" Journal of Small Animal Practice 50, 266–271 Citations: 15 Impact Factor: 1.177

5. **Walton MB**, Cowderoy E, Lascelles D, and **Innes JF**. (2013). Evaluation of Construct and Criterion Validity for the 'Liverpool Osteoarthritis in Dogs' (LOAD) Clinical Metrology Instrument and Comparison to Two Other Instruments. PLoS One 8, e58125. Citations: 1 Impact Factor: 3.730

Key Grants

2001 – 2002, **Hill's Nutrition Inc**, Topeka, Kansas, USA. "Omega-3 fatty acids and canine articular cartilage degradation" $165,000, Caterson (Cardiff), **Innes**, Harwood (Cardiff). Competitive award following a call to US and EU veterinary schools

2003 – 2005, **Hills Nutrition Inc**, Topeka, Kansas, USA "Omega-3 fatty acids and canine articular cartilage degradation" £205,000, Caterson (Cardiff), **Innes**, **Vaughan-Thomas**

2005 – 2007, **Hill's Nutrition Inc**, Topeka, Kansas, USA "Omega-3 fatty acids and feline articular cartilage degradation" £122,515, **Innes**, **Vaughan-Thomas**

2003 – 2006 **Pfizer Global Research**, Sandwich, UK "Outcome measures of canine OA" £199,844, **Innes JF**, **Vaughan-Thomas A**, **Carter SD**;

4. Details of the impact

Novel research at the University of Liverpool by Innes and colleagues has made significant contributions to improving the way canine osteoarthritis is diagnosed, monitored and managed, impacting not only on animal welfare, but on veterinary practice, and a major pet food distributor. A recent systematic review on nutraceuticals for management of osteoarthritis in dogs, cats and horses concluded that the evidence base for efficacy of nutraceuticals in osteoarthritis was poor

with the exception of omega-3 fatty acids in dogs which confirmed the significance of this UoL research [6]. The use of a dietary additive has been shown to reduce the dose of non-steroidal anti-inflammatory drugs (NSAIDs) required by dogs with osteoarthritis, reducing the likelihood of adverse events associated with long-term NSAID use. The diet can considerably increase mobility [9].

The impact of the research since 2008 is best demonstrated by sales data for Hill's Prescription Diet Canine j/d which has been sold by Hill's (subsidiary of Colgate) throughout the developed world since 2003. The economic impact has increased steadily during the REF period (see table below) through support from UoL researchers (lectures and published reviews in North America and Europe, and research papers demonstrating the efficacy of the product). This product, which is based on the UoL research, has been assessed by independent investigators in a randomized clinical trial of dogs with naturally-occurring osteoarthritis. This study showed a significant increase (mean 5.6%) in peak vertical force (as measured by a force platform) in the index limb in dogs receiving the j/d diet compared to dogs receiving a standard control diet (mean 0.4%), thereby confirming the clinical efficacy of Hill's Prescription Diet Canine j/d for treatment of spontaneous canine osteoarthritis [7].

Sales of Hill's prescription diet Canine j/d are only through veterinary practices. As such, the product provides an income stream for both Hill's Pet Nutrition, being their second best selling product) and the veterinary profession in the developed world. Net global sales (data supplied by Hill's) 2008-2012 illustrate increasing economic impact, in the assessment period, from.

		2008	**2009**	**2010**	**2011**	**2012**
Canine		$	$	$	$	$
j/d	**Net Sales**	30,850,419	43,515,310	46,574,065	54,617,154	57,109,090

In a fragmented industry such as small animal veterinary practice, it is challenging to obtain corroboration from veterinary practitioners regarding sales of Canine j/d. However, the largest charitable provider of veterinary services in UK, the PDSA, has confirmed that in 2012, 3% of their pet food orders were for Hill's Prescription Diet Canine j/d [8]. As of 2013, Hill's Prescription Diet Canine j/d had been distributed to over 20 countries, the top five markets being United States, France, Canada, United Kingdom, and Denmark.

The Liverpool research has translated, during the REF period, to a similar impact in cats with osteoarthritis, again through provision of a diet (Hill's Prescription Diet Feline j/d) specifically designed to ameliorate this condition. The manufacturers claim a 61% improvement in cats with moderate or severe osteoarthritis [13].

In summary, the identification by the UoL of the potential of EPA as canine dietary additive has improved welfare for dogs internationally, reduced distress for owners, enabled veterinarians to extend their services, and generated business for a pet food company.

To further improve the diagnosis of canine osteoarthritis and to provide a standardised quantitative monitoring of the degree of osteoarthritis, the LOAD instrument has been licensed on a global basis from q4 2012 to Novartis Animal Health as a psychometrically-validated tool for veterinarians and dog-owners to use in the identification, diagnosis, staging and monitoring of canine osteoarthritis. This is the first validated CMI to be rolled out to the veterinary profession, the only one that is (i) licensed to a pharmaceutical company, (ii) in electronic format and (iii) available in five languages. It has resulted in increased awareness of this approach to improving canine welfare. The instrument is available in electronic and paper-based formats. Recently, the instrument has also been used in a clinical trial (sponsored by Pfizer Animal Health) to compare two treatments for canine osteoarthritis [10] and thereby demonstrated the field equivalency of a new, long-acting non-steroidal anti-inflammatory drug (NSAID) when compared to the UK market-leading daily NSAID. LOAD is also used, in modified form, by the British Veterinary Orthopaedic Association's Canine Hip Registry (www.caninehipreplacement.org) [11; established in Liverpool in 2011] and has demonstrated the efficacy of surgical management of hip osteoarthritis in reducing

LOAD scores of treated patients (mean score reduced from 18/52 to 5/52) [12].

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

6. Vandeweerd JM, Coisnon C, Clegg P, Cambier C, Pierson A, Hontoir F, Saegerman C, Gustin P, and Buczinski S. (2012). Systematic Review of Efficacy of Nutraceuticals to Alleviate Clinical Signs of Osteoarthritis. Journal of Veterinary Internal Medicine 26, 448-456.

7. Roush, JK, Cross, AR, Renberg, WC, et al. 2010. Evaluation of the effects of dietary supplementation with fish oil omega-3 fatty acids on weight bearing in dogs with osteoarthritis. J. Am. Vet. Med. Assoc. 236: 67-73.

8. Contact: PDSA

9. Video of dog after Hills j/d diet. http://www.youtube.com/watch?v=DJud6uVI3k4

10. Walton MB, Cowderoy E, Lascelles BDX, Innes JF (2013) “Efficacy of mavacoxib (Trocoxil™) compared with meloxicam (Metacam™) in the treatment of dogs with osteoarthritis” BSAVA Congress, Birmingham, April 2013

11. Forster KE, Wills A, Torrington AM, Moores AP, Thomson D, Arthurs G, Brown G, Denny HR, Scott HW, MacQueen I, Dunne J, Onyett J, Walker JD, Prior J, Owen MR, Burton N, Whitelock R, Girling S, Morrison S, Gilbert S, Langley-Hobbs SJ, Gemmill TJ, Innes JF (2012) “Complications and Owner Assessment of Canine Total Hip Replacement: A Multicenter Internet Based Survey” Vet. Surg. 41: 545–550

12. Cook JL (2013) “Canine Orthopedic Outcome Measures Program: Where are we now?” Veterinary Surgery *in press*

13. Contact: Hill’s Pet Nutrition. The manufacturers claim of a 61% improvement in mobility can be verified by this individual.