Institution: University of Leeds

Unit of Assessment: UoA4

Title of case study: Case Study 1: Robust methodologies for appetite studies - supporting development and marketing of functional foods and anti-obesity products

1. Summary of the impact

Since 1993 researchers from the University of Leeds (UoL) have devised robust and standardised experimental methodologies to study human appetite and food consumption objectively. Companies in the food and pharmaceutical sectors have used these procedures to develop functional foods and anti-obesity drugs. The validated methodologies also allowed global clinical research organisation Covance to establish its Human Appetite Laboratory to provide product evaluation for US and EU pharmaceutical companies. Food regulators have also recommended the Leeds approach for producing evidence to support appetite control claims for functional foodstuffs.

2. Underpinning research

In the late 1980's Professor **Blundell** (Reader, 1982-95; Professor, Chair of Psychobiology, 1995-present, UoL) developed a conceptual model to explain how different food groups have psychological and physiological effects on the body that influence feelings of 'fullness' (satiation) and the period of time since eating, known as satiety, during which hunger is suppressed. This model, known as the satiety cascade, helps to explain why some foods weaken satiation and lead to overconsumption. It also demonstrates how drugs and functional foods can be used to improve appetite control, and how to measure these effects.

Since 1993, **Blundell** has headed research at the UoL to elucidate more detail about the cascade and the mechanisms that control human eating. He and his team have also carried out studies to identify novel foods and food additives, which may strengthen satiety and hence help to control appetite. The research by **Blundell** and his colleagues has been funded primarily through grants awarded by the Agriculture and Food Research Council (AFRC) **[i-iii],** the Biotechnology and Biological Sciences Research Council (BBSRC) **[iv-viii],** the European Commission **[ix]** and the National Institute of Health **[x]**, with a view to understanding the fundamental science of satiety and appetite control as well as to support the food and pharmaceutical industries **[xi]** in their development of functional foods and anti-obesity products.

New mechanisms of action in the satiety cascade

In 1993, an initial study carried out by UoL researchers **C.Lawton (**Research Fellow, UoL, 1991-94; Lecturer, UoL, 2010-present) and Burley (Research Fellow, UoL, 1988-96; Lecturer, UoL, 2000-present) under the supervision of **Blundell,** was one of the first experiments to provide evidence of the complex mechanisms driving the satiety cascade. The research indicated that dietary fat had weak effects on satiation and satiety in obese subjects **[1]** (155 cites), revealing the potential for a spiralling deterioration in the health of obese people as they have to consume relatively more fat before they feel full. Further studies by **Blundell** and Macdiarmid (PhD Student, 1992-94; Research Fellow, 1994-96, UoL) concluded that dietary fat is a risk factor for overconsumption and affects eating patterns **[2]** (122 cites).

New methodologies and measures of appetite – development and validation

The methodologies behind these two studies were remarkable, not just for their discovery of the role of dietary fat in regulating appetite; they also demonstrated that researchers could study food consumption and appetite objectively and quantitatively. Following these early experiments, **Blundell** and his team further extended the methodologies and developed standardised procedures for measuring human food intake and for objectively identifying the effects of different foods on satiation and satiety.

In 1997 **Blundell** and colleagues from the Biopsychology group at the UoL, along with Joanes from the Department of Statistics (UoL) developed a new concept in appetite measurement: the satiety quotient (SQ) **[3]**. This new parameter stemmed from a number of experiments in which subjects were presented with food or meals of varying composition; the researchers measured each subject's motivation to eat immediately prior to, and periodically after they ate the food. This quotient relates intake to the rate of return of motivation to eat in the period following the meal and

is a function of the energy consumed- a new relationship, which is not apparent on separate examination of the amount consumed or ratings of motivation to eat.

The Leeds group also took existing visual analogue scales for measuring subjective sensations such as hunger and fullness and adapted them to create the Electronic Appetite Rating System (EARS), used for handheld electronic data capture devices which allowed subjects to record their experiences and appetite reliably and conveniently. The validity of this experimental approach was evaluated in collaboration with several independent research groups. The University of Copenhagen led an evaluation of the visual analogue scales in a project that involved replication studies to compare the electronic vs. paper scales in Leeds, Aberdeen and Copenhagen **[4]** (151 cites).

Several other laboratory procedures first developed by the Leeds team were also evaluated through collaborations with other appetite research groups. These studies found the Leeds methodologies for measuring human food intake and their effects on satiation and satiety were reliable, valid and robust **[5, 6]** (76 and 463 cites, respectively). In parallel to these validation studies, and in order to disseminate the developed methodologies more widely, **Blundell**, **Hetherington** (Professor, UoL, 2009-present) and **Finlayson** (Associate Professor, UoL, 2007-present) co-authored a comprehensive review of appetite research methodologies in collaboration with colleagues, published as a chapter on 'Measuring Food Intake, Hunger, and Satiation in the Laboratory' in the 'Handbook of Assessment Methods for Eating Behaviors and weight related problems' (Alison, D.B., & Baskin, L.S. (Eds.) (2009). *Handbook of Assessment Methods for Eating Behaviors and weight related problems* (pp. 283-325). Newbury Park, CA: Sage Publications).

3. References to the research

[1] Lawton*, C.L., Burley*, V.J., Wales*, J.K., & **Blundell*, J.E.** (1993). Dietary fat and appetite control in obese subjects: weak effects on satiation and satiety. *International Journal of Obesity, 17,* 409-416. pmid: 8395476
This research demonstrates the importance of the distinction between satiation and satiety in the assessment of nutrients on appetite control.

[2] Blundell*, J.E., & Macdiarmid*, J.I. (1997). Fat as a risk factor for overconsumption: satiation, satiety, and patterns of eating. *Journal of American Dietetic Association, 97,* S63-S69. doi: 10.1016/S0002-8223(97)00733-5
This paper shows how satiation and satiety, as features of the eating pattern, embody risks for overconsumption and weight gain.

[3] Green*, S.M., Delargy*, H.J., Joanes*, D., & **Blundell*, J.E.** (1997). A Satiety Quotient: A Formulation to Assess the Satiating Effect of Food. *Appetite, 29*(3), 291-304. doi: 10.1006/appe.1997.0096
This paper describes a procedure for quantifying the capacity of a food to modulate the strength of satiety.

[4] Stubbs, R.J., Hughes, D.A., Johnstone, A.M., … Stratton, R.J., Delargy*, H.J., King*, N.A., & **Blundell*, J.E.** (2000). The use of visual analogue scales to assess motivation to eat in human subjects: a review of their reliability and validity with an evaluation of new hand-held computerized systems for temporal tracking of appetite ratings. *British Journal of Nutrition, 84,* 405-415. doi: 10.1017/S0007114500001719
This paper demonstrates how electronic data capture of motivational ratings allows easier personal quantification of the effects of food on satiety.

[5] Blundell*, J.E., de Graaf, C., Hulshof, T., Jebb, S., Livingstone, B., Lluch, A., … & Westerterp, M. (2010). Appetite Control: methodological aspects of the evaluation of foods. *Obesity Reviews, 11,* 251–270. doi: 10.1111/j.1467-789X.2010.00714.x
This paper describes, along with other techniques, the status of the Leeds objective procedures for quantifying the effects of foods on satiation and satiety.

[6] Flint, A., Raben, A., **Blundell*, J.E.**, & Astrup, A. (2000). Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single meal studies. *International Journal of Obesity, 24,* 38-48. doi: 10.1038/sj.ijo.0801083
This paper confirms the scientific capacity of the Leeds measures for assessing the impact of foods on satiety under controlled laboratory conditions.

Key funding and grants

[i] AFRC FG24/544. (1994-1997). Investigation of the Effect of Dietary fat on the Satiation Power of Food and Food Selection in Man. **Blundell*, J.E.** £79,950.

[ii] AFRC F00248. (1996-1999). An Investigation of High fat Consumers: Personal, Social and Physiological Characteristics. **Blundell*, J.E.,** & Cade*, J**.** £134, 510.

[iii] AFRC D02501. (1997-2000). The Effect of Exercise and Diet Composition on the Pattern of Appetite and Energy balance in Man. **Blundell*, J.E.,** & Stubbs, R.J. £184,753.

[iv] BBSRC BBS/B/05079. (2004-2007). Individual Variability and Characterisation of Compensatory Responses to exercise Interventions. **Blundell*, J.E**., & King*, N. £293,045.

[v] BBSRC (DRINC) BB/G005524/1. (2009 -2012). Drivers of eating behaviour during chronic overconsumption. **Blundell*, J.E.,** & **Finlayson*, G.** £675,694

[vi] BBSRC BB/G530141/1. (2009-2013). Hedonic responsivity in individuals susceptible and resistant to weight gain. PhD studentship linked to **[v]**. **Blundell*, J.E., & Finlayson*, G.** £178,827.

[vii] BBSRC BB/H004971/1. (2009-2012). Increased Propionate Production in The Colon Is Associated With Reduced Appetite, Body Weight And Improved Insulin Sensitivity. Frost, G., & **Blundell*, J.E.** £673,268.

[viii] BBSRC BB/I022325/1. (2011-2014). Emulsion structure: a novel mechanism of delivering fatty acids to regulate gut function and satiety. Wilde, P., & **Blundell*, J.E.** £830,893.

[ix] European Commission: Partner in Projects funded in Framework 5 (Response to High Fat Diet in Europe), Framework 6 (DIOGENES) and Framework 7. Ongoing: FP7-KBBE-2011-5. (2011-2015). SATIN. Satiety control through food structures made by novel processing. Co-PI: **Blundell*, J.E.** €5,992,880.

[x] NIH/NIDDK [R01 DK081714-01A2]. (2011-2016). Portion size effects on body weight: free living setting (with Univ Minnesota). French, S., & **Blundell*, J.E.** $2,688,410.

[xi] Received industrial support for satiety projects from National Starch & Chemical Ltd, Roche, Unilever, Danisco, Du-Pont, Sanofi-Aventis, Barilla, VINNOVA (Swedish Government Research Agency) and Covance CRC.

Note: All UoA4 researchers in **bold**; *research conducted by academics at the UoL.

4. Details of the impact

In its efforts to elucidate the detailed mechanisms of action behind the satiety cascade concept, **Blundell's** research group has developed laboratory procedures and methodologies which have since been adopted by industry and recommended by European and North American regulatory authorities as a standard approach to food consumption and human appetite studies. The methodologies have been used in studies to support the development of anti-obesity drugs and functional foods for appetite control.

Setting standards of evidence for food and health regulators

In 2012 the Food Directorate of Health Canada made extensive reference to the Leeds Methodology (pages 3, 5, 6,10,11,13,14) in its guidelines and recommendations on the scientific assessment of functional foods for satiety. These guidelines set out how companies must validate any claims they make regarding the effects of novel foods **[A]**. This Leeds research has also informed the European Food Safety Authority (EFSA) in setting standards for evaluating the food companies claims for foods to exert effects on appetite, through **Blundell's** position as a consultant to the EFSA NDA panel (2008 -10) **[B]**.

Product development – functional foods and anti-obesity products

Appetite suppression is a major focus for anti-obesity drugs developed by the pharmaceutical industry and for appetite-controlling functional foods developed by the food industry. The global pharmaceutical corporation Merck adopted Leeds' methodologies to evaluate two novel obesity drugs, the MC4 R agonist and CB1R inverse agonist. The trials showed that MC4R agonists lacked the potency required for further development, but the appetite action of CB1R was related

to brain activity **[C]**.

The concepts of the satiety cascade and Leeds' approach to appetite control studies are embedded within the functional food R&D of large consumer food companies such as Danone and Kraft Foods. Companies have produced a booklet developed from satiety cascade methodology, which provides educational background on the value of controlling appetite as a public health strategy **[D]**. The satiety cascade forms the major principle underlying a pan-European project called SATIN. This project involves nine industrial partners (five SMEs) who have applied the satiety cascade and used Leeds' experimental methodologies for innovative functional food product development for appetite control (http://www.satin-satiety.eu/workpackage-4) **[E]**. The project has identified six candidate products that the partners are taking through to further development.

Commercial development and growth

In 2004 the Covance Clinical Research Centre, established its Human Appetite Laboratory (HAL) for the measurement of food behaviour and the use of instruments for the quantitative assessment of hunger and motivation to eat **[F]**. The working practices and procedures of this facility are based on the satiety assessment methodologies developed by the Leeds research team, specifically the work by **Blundell** in collaboration with Covance to adapt the methodologies into standard procedures for clinical evaluations of appetite control **[G]**. The HAL studies for US and EU companies represent Proof of Concept (POC) and First in Man (FIM) - the results of which determine whether the drug proceeds to Phases 2 and 3 **[G]**.

5. Sources to corroborate the impact

[A] Guidance Document. Scientific requirements for satiety health claims on food. (2012). Food Directorate, Health Products and Food Branch, Health Canada (pp. 3,5,6,10,11,13,14). Corroboration for the impact of **Blundell's** work on this document can be obtained from a Scientific Evaluator at Health Canada.

[B] Evidence of **Blundell's** participation as a consultant for the EFSA DNA (Diet Nutrition and Allergies) Panel 2008 onwards (26.5.2011).

[C] Corroboration on the application of Leeds methodologies by Merck for the evaluation of novel drugs (MC4 R agonist and CB1R Inverse agonist) for the treatment of obesity:

Krishna, R., ... **Blundell, J.E.,** Bray, G.A., Fujioka, K., Heymsfield, S.B., Wagner, J.A., & Herman, G.A. (2009). Potent and Selective Agonism of the Melanocortin Receptor 4 With MK-0493 Does Not Induce Weight Loss in Obese Human Subjects: Energy Intake Predicts Lack of Weight Loss Efficacy. *Clinical Pharmacology and Therapeutics, 86(6),* 659-666. doi: 10.1038/clpt.2009.167

Addy, C., ... **Blundell, J.E.** Hargreaves, R.J., Wagner, J., Gottesdiener, K., Amatruda, J.M., & Heymsfield, S.B. (2008). The Acyclic CB1R Inverse Agonist Taranabant Mediates Weight Loss by Increasing Energy Expenditure and Decreasing Caloric Intake. *Cell Metabolism, 7,* 68–78. doi: 10.1016/j.cmet.2007.11.012

[D] Kraft Foods Europe document (brochure, 2010) uses Satiety Cascade methodology. Further corroboration for the impact of **Blundell's** work on this document and its implications for scientific assessment of satiety potential of foods can be obtained from the Nutrition Research Manager at Kraft Foods.

[E] The Satiety Cascade is the formative principle in this pan-European project (2012-16) under the call KBBE.2011.2.3-04: Satiety Control through Food Structures made by Novel Processing: The SATIN (SATiety INnovation) Project (http://www.satin-satiety.eu). Impact on industrial enterprise (http://www.satin-satiety.eu/workpackage-4) can be obtained from the SATIN coordinating and dissemination partner.

[F] Methodology used in establishment of the HAL by Covance Clinical Research Centre for the assessment of anti-obesity drugs in clinical development. At least four compounds have been evaluated using the methodology.

[G] Corroboration for the impact of **Blundell's** research on work conducted at the HAL and impact on commercial development and growth can be obtained from the Scientific Director of Covance.