Institution: University of Nottingham

Unit of Assessment: 5 - School of Life Sciences

Title of case study: REDACTED – FOR PUBLICATION
Commercialisation of Creatine and Carnitine for Sports Nutritional Supplements

1. Summary of the impact

An international patent emanating from research from Professor Paul Greenhaff's laboratory and owned by the University of Nottingham (UoN) was purchased by MuscleTech Inc. in 2001 (along with provision of £750k research funding), and used to underpin their highly successful creatine based sports supplement, CellTech. The patent has since been used in [text removed from publication] products creating sales worth $[text removed from publication] million (US) since 2010. A further international patent from the same laboratory based on research on carnitine as a sports supplement has to date been accepted in Australia and Canada and used by the Olympic Team GB in 2012. Negotiations between the UoN and a global company regarding the licencing of this technology are at an advanced stage.

2. Underpinning research

The Greenhaff laboratory, amongst others, had shown phosphocreatine depletion was linked to muscle fatigue during maximal intensity exercise. In humans 95% of the body's creatine store is in skeletal muscle and it plays an important role in energy transduction. Work arising from Greenhaff's laboratory showed that carbohydrate ingestion augmented accumulation of creatine in human skeletal muscle[1]. Thus, the amount of work that could be performed during repeated exercise could be increased, having important implications on maximal exercise performance. Additionally, Greenhaff's laboratory was able to offer a means for athletes to maximise the benefits arising from creatine ingestion by increasing creatine retention[2]. As a direct result of publication of this work, the Greenhaff laboratory's research formed the basis of a world-wide patent filing by the UoN, which was published in 1996 (International Publication Number WO1996018313). This patent centred on augmenting muscle creatine and phosphocreatine accumulation in human skeletal muscle by dietary means. In keeping with this, the same group demonstrated that increasing the muscle total creatine store improved maximal exercise performance in humans[3]. Fatigue during exercise was associated with the inability of skeletal muscle to maintain a high rate of aerobic ATP production from creatine. The group were able to attribute improved performance to increased ATP resynthesis during exercise as a consequence of increased creatine availability in skeletal muscle fibers. In 2001, Greenhaff was awarded the Scientific Achievement Award by the Society for Guanidino Compounds in Biology and Medicine for his pioneering work on muscle creatine metabolism.

As a consequence of achievement in the field of sports nutrition IP development (a novel approach even now), the UoN supported further IP filing in this area. In 2001, Paul Greenhaff successfully approached Lonza Ltd (the largest manufacturer of food grade L-Carnitine in the world) to fund a PhD Studentship. This subsequently created a novel means to increase human muscle carnitine transport and accumulation consequently altering human muscle metabolism (PhD recipient Dr Francis Stephens, now Lecturer, School of Biomedical Sciences, UoN). The group demonstrated that sodium dependent muscle carnitine transport was increased via an insulin dependent mechanism, resulting in muscle carnitine accumulation and changes in muscle fat and carbohydrate metabolism in humans[4]. This research formed the basis of a UoN patent filing (International Publication Number WO 2004/082674), which has been accepted in Australia and Canada. The research group successfully gained PhD funding in 2007 from the Ministry of Defence on the basis of this research (PhD recipient Dr Benjamin Wall, now Post-doctoral Researcher, University of Maastricht), and in 2011 published research demonstrating the efficacy of the technology in reducing muscle carbohydrate use during low intensity exercise (consistent with increased muscle lipid utilisation) and blunting muscle anaerobic ATP production during high intensity exercise in healthy volunteers[5]. These observations were directly in line with the dual

metabolic role of carnitine in muscle metabolism, which the group proposed was exercise-intensity-dependent. Importantly, these metabolic changes observed during exercise resulted in positive effects on perception of effort and work output using a validated exercise performance test. More recently research efforts have generated mechanistic insight concerning the impact of muscle carnitine elevation on body composition, fat oxidation and muscle genomic adaptation in humans. Importantly, a 20% increase in muscle carnitine content blunted the increase in body fat mass associated with excess carbohydrate ingestion, and was allied with an increase in fat oxidation and expression of gene networks involved in insulin signalling, peroxisome proliferator activated receptor (PPAR) signalling, and fatty acid metabolism[6].

3. References to the research

Publications (University of Nottingham authors in bold, key author underlined)

1. **Green AL**, Hultman E, **Macdonald IA, Sewell DA, Greenhaff PL**. (1996) Carbohydrate Ingestion Augments Skeletal Muscle Creatine Accumulation During Creatine Supplementation in Humans. American Journal of Physiology-Endocrinology and Metabolism. 271(5); E821-E826 http://ajpendo.physiology.org/content/ajpendo/271/5/E821.full.pdf

2. **Green AL, Simpson EJ, Littlewood JJ, MacDonald IA, Greenhaff PL**. (1996) Carbohydrate Ingestion Augments Creatine Retention During Creatine Feeding in Humans. Acta Physiologica Scandinavica. 158(2): 195-202. DOI:10.1046/j.1365-201X.1996.528300000.x

3. **Casey A, ConstantinTeodosiu D, Howell S,** Hultman E, **Greenhaff PL**. (1996) Creatine Ingestion Favorably Affects Performance and Muscle Metabolism During Maximal Exercise in Humans. American Journal of Physiology-Endocrinology and Metabolism. 271(1): E31-E37 http://ajpendo.physiology.org/content/ajpendo/271/1/E31.full.pdf

4. **Stephens FB, Constantin-Teodosiu D, Laithwaite D, Simpson EJ, Greenhaff PL**. (2006) Insulin Stimulates L-Carnitine Accumulation in Human Skeletal Muscle. Faseb Journal. 20(2): 377-379. DOI: 10.1096/fj.05-4985fje

5. **Wall BT, Stephens FB, Constantin-Teodosiu D, Marimuthu K, Macdonald IA, Greenhaff PL**. (2011) Chronic Oral Ingestion of L-Carnitine and Carbohydrate Increases Muscle Carnitine Content and Alters Muscle Fuel Metabolism During Exercise in Humans. Journal of Physiology-London. 589(4): 963-973. DOI: 10.1113/jphysiol.2010.201343

6. **Stephens FB, Wall BT, Marimuthu K, Shannon CE, Constantin-Teodosiu D, Macdonald IA, Greenhaff PL** (2013) Skeletal muscle carnitine loading increases energy expenditure, modulates fuel metabolism gene networks, and prevents body fat accumulation in humans. Journal of Physiology-London. [e-pub ahead of print] DOI: 10.1113/jphysiol.2013.255364

Patents:

Greenhaff PL; Green AL; Macdonald IA; Hultman E. Increasing creatine and glycogen concentration in muscle. WO1996018313. Published 20.06.1996.

Greenhaff PL; Constantin TD. Carnitine Retention. WO2004082674. Published 30.09.2004.

Grant Funding:
Dunhill Medical Trust: Improving human skeletal muscle insulin sensitivity in healthy ageing; 2012 – 2014; **£202,160** (with Dr F Stephens PI).

ET-Healthcare & Biosciences iNet: Can carnitine supplementation modulate fat oxidation and weight loss during energy restriction and exercise training in obesity? 2013-2015; **£54,257** (with Dr F Stephens PI).

MRC-Arthritis Research UK (ARUK): Centre for Musculoskeletal Ageing Research: 2013-2017; **£635,381** (Greenhaff PL as PI, joint with University of Birmingham, £2.45 million overall)

4. Details of the impact

Impact 1: Creatine commercialisation

Creatine is a naturally occurring guanidino compound confined principally (95%) to skeletal

muscle, where it plays a pivotal role in maintaining energy homeostasis. Pre 1990, worldwide sales of creatine monohydrate were low, when it was used as a food additive in mg quantities. In the 1990's a body of work from the UoN and Professor Eric Hultman's laboratory, Karolinska Institute, Sweden (a close collaborator of Greenhaff and Visiting Professor at the University of Nottingham) led to a surge in interest in creatine as a research topic and a nutritional supplement. As a direct result of this research, creatine supplements became a boom industry in the mid 1990's, e.g. "nothing has captured the hard-core sports nutrition enthusiast quite as well"[A]. In 2003, creatine sales were estimated to have totalled $193 million (U.S.) or ~10% of the $1.9 billion (US) sports supplement market[A]. The UoN patent (WO1996018313, Increasing creatine and glycogen concentration in muscle) was purchased by the North American company MuscleTech Inc.[B] in 2001 (along with provision of £750k research funding to the Greenhaff laboratory) and was used to underpin their highly successful carbohydrate and creatine supplement, CellTech. In 2006, MuscleTech was ranked the 6th largest sports nutrition company in North America with annual sales estimated at $40 million and a 30% year-on-year growth rate[A]. Creatine is a world-wide market leader in sports-nutrition and the company currently claims to be "America's #1 selling bodybuilding supplement brand based on cumulative wholesale dollar sales 2006-present"[A]. MuscleTech, now Iovate Health Sciences International Inc. has used the patent for [text removed from publication] products since 01/01/10 amounting to sales in excess of $[text removed from publication] million (U.S.)[C]. Translation of this science from the field of exercise biochemistry has, in addition to the commercial benefit, also resulted in numerous clinical trials into the efficacy of creatine supplementation in conditions where muscle and nervous tissue energy metabolism and function are compromised[D].

Impact 2: Carnitine commercialisation

More than 95% of the body store of carnitine is located within skeletal muscle, where it fulfils two essential metabolic roles. Firstly in mitochondrial fatty acid translocation, and secondly, as a buffer of acetyl group accumulation during intense exercise. Furthermore, it has been proposed that muscle free carnitine availability is rate limiting to both of these processes, particularly during exercise. Not surprisingly therefore, oral carnitine feeding has been targeted as a potential nutritional strategy to enhance exercise performance. Research and IP developed at the UoN produced a novel technology to increase muscle carnitine transport and accumulation (by 15-20%) in human skeletal muscle via an insulin dependent mechanism, which also impacted upon muscle fuel metabolism. All published attempts to increase muscle carnitine accumulation up to that point had failed. This research formed the basis of the UoN patent filing WO 2004082674. On the foundation of this research, further work unequivocally demonstrated muscle carnitine content could be elevated in human volunteers by dietary means, and had a significant impact on muscle fuel use during both low and high intensity exercise, resulting in performance benefits in humans[E]. NutraMet Ltd, a UoN spin out company, was formed in July 2011 with an exclusive licence to commercialise this latest novel carnitine related technology, which was used by Team GB athletes before the 2012 London Olympics[G]. As a result of the collective achievements of Greenhaff's laboratory in the area of human muscle carnitine transport and metabolism, a Heads of Terms and Exclusive Option agreements between the University of Nottingham and a global company regarding carnitine related intellectual property licensing have been signed[H].

5. Sources to corroborate the impact

A. Document to corroborate the size the size of the creatine supplement sports nutrition business.

B. Web link http://www.muscletech.com/products/celltech_hardcore/index.shtml#science_tab

C. Sales statement from [text removed from publication].

D. Adhihetty PJ, Beal MF. (2008) Creatine and its potential therapeutic value for targeting cellular energy impairment in neurodegenerative diseases. Neuromolecular Medicine. 10(4): 275–290. DOI:10.1007/s12017-008-8053-y

E. http://www.lonza.com/about-lonza/media-center/news/2011/new-study-carnipure-tartrate-increases-muscle-l-carnitine-content.aspx

F. http://www.nutramet.co.uk/

G. Letter from Head of Research and Innovation, UK Sport to corroborate the use of carnitine by Team GB

H. Letter from the Head of IP Management, Financial and Business Services, University of Nottingham to corroborate the advanced nature of discussions between the University of Nottingham and the interested company.

Corroborative documents and copies of webpages are held on file and are available on request.