Institution: Royal Veterinary College
Unit of Assessment: A 6 Agriculture, Veterinary and Food Science
Title of case study: A new treatment for equine and human tendon injuries

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

Fundamental and applied research at RVC has led to introduction of stem cell therapy supporting equine tendon regeneration, advancing equine clinical practice internationally. A resultant spin-out company has delivered revenue-generating veterinary clinical services internationally and is now developing new human treatments. The therapy offers improved health and welfare, particularly in racing, as treated horses are less likely to re-injure in comparison with those managed conventionally, and consequently less likely to be culled due to premature termination of their competitive careers. The acceptance by the Medicines and Healthcare products Regulatory Agency that the equine treatment data provide validation for a phase II human clinical trial without further preclinical studies represents a rare and significant outcome for veterinary research.

2. Underpinning research (indicative maximum 500 words)

Tendon biology has been a key research theme at RVC since the recruitment in 1996, from Bristol of Professors Alan Wilson (Lecturer in Physiology, then Senior Lecturer, progressing to Chair in Locomotion Biomechanics) and Allen Goodship, (Chair in Orthopaedic Sciences; Emeritus since 2011), to join the musculoskeletal biology group. Their earlier work proposed energy released from equine tendons in their spring-like action was partly responsible for their degeneration. The philosophy of Professor Lanyon's (Professor of Veterinary Anatomy from 1984; Principal from 1989) pioneering work on bone - to elucidate how a tissue's mechanical properties adapted to the strains imparted by normal locomotion and informed the importance of restoring a tissue's properties to achieve effective healing in any repair process – was therefore extended to tendon. Wilson's work led to measuring and then modelling function of musculoskeletal tissue in moving animals to understand more about how muscles and tendons work to achieve high athletic performance [1] and showing that exercise altered the crimp morphology at the tendon core [2]. This initial fundamental work inspired multi-disciplinary approaches and translational research in tendon biology.

Goodship's applied research showed that tendon injury was associated with changes in its extracellular matrix [3] predisposing it to partial rupture and post-injury weakness. He collaborated with Professor Roger Smith (following a Clinical Residency (1990) and PhD, Lecturer in Equine Surgery before becoming Professor of Equine Orthopaedics in 2003) and they generated a hypothesis that mature tendon lacks the ability to respond to strain and that tendonopathy probably occurs in horses and human athletes due to cumulative fatigue damage causing degeneration at the molecular level [4].

These fundamental and clinical observations led to the innovative idea that mesenchymal stem cells could help tendon injuries heal, by providing cells with potential to respond to strain as tendon would during growth and/or by altering the environment in the tendon sheath to effect tissue regeneration of biomechanically strong tendon rather than scar tissue formation leaving the tendon vulnerable to future injury. In 2002, RVC filed a UK priority patent application relating to treatment of equine tendon injury using autologous stem cells taken from the sternum and expanded in *in vitro* culture and span-out a company to commercialise the approach. A paper describing the clinical technique, which has changed clinical practice, was published in 2003 [5]. The company and subsequent competing businesses facilitated widespread uptake. Research subsequently showed the technique is safe and speeded recovery in comparison with historical controls [6]. A randomised controlled trial funded by HBLB on behalf of the racing industry has also demonstrated beneficial histological and biochemical effects of bone marrow implantation in horses with tendon injury supporting their original hypothesis [7], thus strengthening the evidence base for this novel clinical treatment.

Most recently, the research has been extended to the investigation of stem cell treatment for intrasynovial injury, including application to human rotator cuff injury.

Other Quality and Relevance Indicators

Smith R. Regenerating equine tendon using autologous mesenchymal stem cells. Horserace Betting Levy Board. £141,700. 2007-09

Smith R. The role of prostanoids in the development and progression of tendondegeneration and as therapeutic targets. BBSRC + Ceva CASE studentship £100,100. 2008-12

Smith R. Characterisation of human bone marrow-derived mesenchymal stem cells for the treatment of tendon injuries. TSB. £69,400. 2010-11.

Smith R. Engraftment and role of mesenchymal stem cells in extrinsic tendon healing - a feasibility study for intra-thecal clinical use. TSB. £68,200. 2010-11.

Smith R. Intrasynovial soft tissue healing - a novel translational goal for mesenchymal stem cell therapy. Medical Research Council. £564,800. 22012-15.

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

1. Wilson, AM, McGuigan, MP, Su, A, van den Bogert, AJ. 2001 Horses damp the spring in their step. Nature; 414: 895-899 DOI: 10.1038/414895a

2. Patterson-Kane, JC, Wilson, AM, Firth, EC, Parry, DAD, Goodship, AE. 1998 Exercise-related alterations in crimp morphology in the central regions of superficial digital flexor tendons from young Thoroughbreds: a controlled study. Equine Veterinary Journal; 30: 61-64 DOI: 10.1111/j.2042-3306.1998.tb04089.x

3. Birch, HL, Bailey, AJ, Goodship, AE. 1998 Macroscopic 'degeneration' of equine superficial digital flexor tendon is accompanied by a change in extracellular matrix composition. Equine Veterinary Journal; 30: 534-539 DOI: 10.1111/j.2042-3306.1998.tb04530.x

4. Smith, RKW, Birch, HL, Goodman, S, Heinegard, D, Goodship, AE. 2002 The influence of ageing and exercise on tendon growth and degeneration - hypotheses for the initiation and prevention of strain-induced tendinopathies. Comparative Biochemistry and Physiology A-Molecular & Integrative Physiology; 133: 1039-1050 DOI: 10.1016/S1095-6433(02)00148-4

5. Smith, RKW, Korda, M, Blunn, GW, Goodship, AE. 2003 Isolation and implantation of autologous equine mesenchymal stem cells from bone marrow into the superficial digital flexor tendon as a potential novel treatment. Equine Veterinary Journal; 35: 99-102 DOI: 10.2746/042516403775467388

6. Godwin, EE, Young, NJ, Dudhia, J, Beamish, IC, Smith RK. 2011 Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Veterinary Journal; 44: 25-32 DOI: 10.1111/j.2042-3306.2011.00363.x.

7. Smith, RKW, Werling, NJ, Dakin, SG, Alam R, Goodship, AE, Dudhia, J. 2013 Beneficial effects of autologous bone marrow-derived mesenchymal stem cells in naturally occurring tendinopathy. PLoS ONE Sep 25;8(9):e75697. DOI: 10.1371/journal.pone.0075697

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

When VetCell Bioscience Ltd was established in 2002, as a spin-out from RVC, it was the first company in the world to offer a veterinary stem cell based treatment. RVC granted an exclusive licence to VetCell to the patented technology identifying Professors Roger Smith and Allen Goodship (with others) as inventors [a]. The company was purchased in 2010 by Quy Biosciences Ltd, and in 2013 became a subsidiary of Westhouse Medical Ltd, [text removed for publication] [b]. The patent is now granted or pending in UK, USA, Canada, Europe, (Austria, Belgium, Switzerland, Germany, Spain, France, Ireland, Italy, Netherlands and Sweden), Australia and New Zealand. Professor Smith has been a director (1/08 – 1/11) and advisor (1/11 – 12/12) to the company though much of the impact assessment period.

VetCell works with a large number of independent veterinary surgeons (including those of RVC) who provide the clinical components of the therapy (collection of stem cells and injection to the injured tendon of the expanded culture). The company, authorised by the Veterinary Medicines

Directorate, undertakes expansion of the cells using a commercial contract laboratory. Substantial international expansion of the business during 2008 was enabled through the UK Trade and Investment Passport to Export programme (initiated in 2007), which recognised VetCell for Outstanding Achievement through the Programme and in its Special Award for BioEntrepreneurial Company of the Year 2007 [c]. VetCell's services are now offered in the UK, USA, Canada, Germany, France, Spain, Netherlands, Belgium, Denmark, Sweden and Norway, with 1,235 horses treated between 2008 and 2012.

Tendon injuries are a particular problem in performance horses, especially National Hunt racehorses, with approximately 25% incurring some tendon damage during training. In 2012, there were nearly 5,000 horses in training for National Hunt racing in Great Britain and Ireland, which accounts for approximately 50% of jump racing worldwide. Flat racers – more than 9,000 in the UK in 2012, are also at significant risk. Stem cell treatment has advanced equine clinical practice, for this problem, becoming an accepted methodology internationally. A senior Newmarket veterinarian comments: "*A particular value is the decreased risk of re-injury – which is consistent with good repair of damage, rather than formation of scar tissue – enabling successful return to pre-injury exercise levels. The equine veterinary profession has followed the introduction of this novel treatment modality with great interest; many adopting it as a significant improvement on more traditional treatments*." [d]. Research reference 6 was the most downloaded paper (2,153 times) from the Equine Veterinary Journal website in 2012 [e], indicating the interest in the value of the technique from specialist veterinarians in this field.

Smith's published work and VetCell's success as an international market leader in veterinary regenerative medicine established the market opportunity for others, which has fostered a range of businesses using mesenchymal or adipose-derived stem cell treatments (e.g. V-Care Biomedical and 2F-stemcells (Germany), Equstem, Vet-Stem and Medivet America (USA), Fat-Stem (Belgium), Eponacell (Czech Republic), Vet Biotechnology and Regeneus (Australia)), many of which reference Smith's publications on their websites.[text removed for publication].

Over 74% of racehorses treated by VetCell have successfully returned to racing, post treatment. Nearly 2,000 runs have been recorded post-treatment, with over 600 wins or placings, including the winner of the Welsh Grand National 2010 [f]. The statistically significant reduced re-injury rate of horses treated with stem cell therapy is also associated with welfare benefit: Re-injury in racing horses is likely to lead to consideration of culling. Hence the therapy can extend the (healthy) lifespan of the horse.

A further welfare benefit and impact through changed professional practice, has been gained through the switch to the new treatment: Although conventionally advised treatment for equine tendon injury has been a period of rest followed by a gradual return to full 'work', the controversial practice of thermocautery or 'firing' (the application of a red-hot firing iron, or occasionally liquid nitrogen to induce scar tissue,) is still used. A professional racehorse trainer [g], commented : "*The welfare impact of this [stem cell] therapy is to have certainly helped reduce the amount of firing that takes place and certainly it has helped the horses that have been able to return to full athletic function after treatment, by not having had to be considered for culling*."

Since 2008, VetCell has received more than £250,000 in European funding and from the Technology Strategy Board to develop its stem cell technologies for human application. RVC has been a sub-contractor or collaborator on each of the projects. Human phase II clinical trials for Achilles tendinopathy have ethical approval and acceptance from the UK Medicines and Healthcare products Regulatory Agency based on protocols and results from equine therapy [h]. The trials are proceeding with funding from the UK Stem Cell Foundation. A Consultant Orthopaedic Surgeon at the Royal National Orthopaedic Hospital commented: *"…the approval and funding for trialling a human application, based on a body of equine research and clinical experience is an outcome of notable significance*." [i]

Adaptation of autologous stem cell treatment to the intra-synovial environment, for human rotator cuff injury is also underway at RVC with funding from the Medical Research Council [j]. The Nuffield Professor of Orthopaedic Surgery at the University of Oxford has commented: "*Although the ramifications of this work on human health have yet to be realised, the equine results and their acceptance as a basis to advance to an intra-synovial human treatment represent a significant impact on human clinical medicine. Historically, clinical veterinary therapies – medical and surgical – have often been derived from the development of human treatments. Hence it is of particular note that Professor Smith's autologous mesenchymal stem cell therapy for equine injuries of the superficial digital flexor tendon has been pioneering in this field*." [k]

In addition to the impacts on professional practice and health, stem cell therapies have attracted much public interest, and consequently, this work has been taken up widely in the media. Smith's work has been widely cited in discussion and review articles relating to the opportunity and potential for, and ethics of, human treatment as well as the existing veterinary applications, and so contributing more generally to the public understanding of and interest in healthcare science [l, m,n].

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

a.http://worldwide.espacenet.com/publicationDetails/biblio?DB=worldwide.espacenet.com&II=0&ND=4&adjacent=true&locale=en_EP&FT=D&date=20130214&CC=WO&NR=2004022078A1&KC=A1 [accessed Sep/13]
b. http://westhousemedical.com/services/ [accessed Sep/13]
c. Vetcell Passport to Export video http://www.freshbusinessthinking.com/tv/player.php?Mode=Ondemand&PID=49 [accessed Sep/13]
d. Statement from Managing Partner of Rossdales Equine Hospital and Diagnostics Centre, Newmarket. Held by RVC.
e. Correspondence from Editor of Equine Veterinary Journal. Held by RVC.
f. http://www.vetclick.com/news/stem-cells-help-injured-racehorse-to-return-to-form-and-win-the-welsh-national-p976.php [accessed Sep/13]
g. Statement from professional racehorse trainer. Held by RVC.
h. MHRA correspondence available from RVC.
i. Statement from Consultant Orthopaedic Surgeon, Royal National Orthopaedic Hospital and UCL. Held by RVC.
j.MRC Grant for developing autologous stem cell therapy for human rotator cuff injury /intrasynovial healing grant awarded Nov 2011.
k. Statement from Nuffield Professor of Orthopaedic Surgery, University of Oxford. Held by RVC.
l. http://www.newscientist.com/article/mg21028163.700-stem-cell-therapy-wasnt-unfair-help-for-baseball-star.html?DCMP=OTC-rss&nsref=online-news [accessed May/13]
m. 2011 report discussing research planned for human Achilles tendon http://singularityhub.com/2011/03/10/uk-stem-cell-company-cures-race-horse-tendons-humans-next/ [accessed May/2013]
n. http://www.nature.com/news/stem-cells-boom-in-vet-clinics-1.12765?WT.ec_id=NATURE-20130411 [accessed Sep/13]