Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 5 (Biological Sciences)		
Title of case study: Commercialisation of a novel microRNA replacement therapy for equine and human tendinopathies		
Period when the underpinning research was undertaken: 2010–present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
(1) Dr Neal L Millar **(2)** Dr Derek Gilchrist **(3)** Prof Iain B McInnes	**(1)** Clinical Senior Lecturer **(2)** Postdoctoral Research Associate; Principal Investigator; Honorary Senior Lecturer **(3)** Muirhead Chair of Medicine	**(1)** 2014–present **(2)** 2010–2013; 2014–2017; 2017–present **(3)** 1993–present
Period when the claimed impact occurred: 2015–present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Tendinopathies are a debilitating category of sports injury, affecting 10% of people and 15%–30% of working and performance horses. UofG researchers identified a first-in-class regenerative therapy (***miRNA29a***) that restores injured tendons to normal structure and function. In 2015, **Causeway Therapeutics Ltd (CTL)** was created as a UofG spin-out to commercialise *miRNA29a*. CTL has attracted approximately GBP13.0 million in investment to advance veterinary (**EquiMiR™**) and human (**TenoMiR™**) versions of *miRNA29a*, indications that currently lack a market competitor. In August 2019, EquiMiR™ entered an experimental dose-finding and efficacy trial (36 horses), with regulatory approval secured for a multicentre pivotal veterinary trial. A 6-month first-in-human phase 1b clinical trial of TenoMiR™ among 24 patients with tennis elbow commenced in September 2020.

2. Underpinning research

One in 10 people will experience tendinopathy in their lifetimes, a rate equivalent to approximately 1.4 million cases per year in Europe and the USA alone. Furthermore, in the UK, one in three musculoskeletal general practice consultations are due to tendon disease, costing the NHS GBP250 million annually. Tendinopathy also occurs in 15%–30% of working and performance horses (approximately 2.3 million in the UK and USA). A 2013 survey of 340 UK equine practices found that each practice conducted 150–200 treatments for tendinitis per year. Despite this large market, current treatment options are effective in just 50% of all cases, leaving human and equine patients with weakened tendons and in pain. Consequently, an unmet need exists for effective treatment of this condition.

Understanding the pathogenesis of tendinopathy

Tendinopathy often arises from overuse and damage to the tendon. Injured tendons heal by irreversible fibrotic repair (rather than regeneration of new tendon), during which healthy collagen type 1 is replaced through overproduction of structurally inferior collagen type 3 (Col3), together with increased blood vessel formation and hyperproliferation of tendon cells (tenocytes). UofG researchers identified a model of early-stage human tendinopathy and developed a well-characterised clinical cohort (**Dr Neal Millar**, **Prof Iain McInnes**; 2010) [3.1]. This work enabled mechanistic investigation of the key molecular events across the spectrum of human tendon disease and highlighted inflammatory molecules as potential translational targets (**Millar**, **McInnes**; 2016) [3.2]. Clinically, these inflammatory features manifest as weakened and inflamed tendon that is prone to reinjury.

Identification of a key disease mechanism

In 2015, **Millar**, **Dr Derek Gilchrist** and **McInnes** demonstrated that elevated levels of the cytokine interleukin 33 (IL-33) during early-stage tendinopathy cause increased Col3 production, which in turn leads to structural changes in the injured tendon [3.3]. This work also identified a microRNA (***miRNA29a***) that regulates both IL-33 and Col3 production in mouse and human tendon injuries; loss of *miRNA29a* as a result of injury directly correlates with tendon disease [3.3]. MicroRNAs are small double-stranded RNA molecules (22–24 nucleotides long) that guide the RNA-induced silencing complex to specific target mRNA

sequences and prevent their translation to protein. In healthy human tenocytes, *miRNA29a* directly suppresses mRNAs transcribed from the *COL3A1*, *VEGFA*, *AKT3* and *TGFB1* genes, which in turn prevents overproduction of Col3, neovascularisation, tenocyte hyperproliferation and adhesion. UofG researchers showed that when synthetic *miRNA29a* is introduced into mice with damaged tendons, 'injury free' levels of this molecule are restored, with concomitant reduction in Col3 production, enabling tendon repair and reduced vascularization, tenocyte hyperproliferation and fibrosis [3.3].

This observation provided the first mechanistic insight into the pivotal role of *miRNA29a* in the development of tendinopathy, offering a promising therapeutic option for tendon disease. Furthermore, the sequence of *miR29a* and its binding sites in the target mRNAs are perfectly conserved across mammalian species, suggesting that this molecule might be exploited to treat tendinopathy in both human and equine patients. In 2014, UofG filed for patents worldwide covering the use of *miRNA29a* for microRNA replacement therapy in tendon injury and spun-out a company (**CTL**) to commercialise this approach (outlined in section 4).

Equine proof-of-concept study

Scottish Enterprise proof-of-concept funding (GBP623,000; 2014–2017) enabled synthetic *miRNA29a* to be pharmacologically enhanced to improve its stability, activity and efficacy, while remaining non-immunogenic. This molecule does not require a delivery vehicle (e.g. liposome or nanoparticle) for targeted cellular uptake, a property that allowed the UofG team to test it in equine collagenase-induced tendonitis. This model of equine tendinopathy is the gold standard for veterinary investigations in horses, but also mimics the human disease.

A 16-week blinded randomised placebo-controlled trial among 17 horses demonstrated that a single dose of the enhanced *miRNA29a* led to a rapid and statistically significant improvement in tendon healing, determined ultrasonographically as a surrogate for functional healing (**Millar**, **McInnes**, **Gilchrist**; 2017) [3.4]. When compared with the control group, horses treated with *miRNA29a* showed reduced levels of *COL3A1* mRNA by week 2; reduced cross-sectional area of tendon lesions at weeks 6, 12 and 16; and improved cumulative histology scores at weeks 2 and 16 (cell density, vascularity, linear fibre, polarized collagen) [3.4]. In addition, less subcutaneous thickening and more normal tissue architecture was observed by ultrasonography at weeks 12 and 16 in the *miRNA29a* group versus the control group [3.4]. This work was conducted in collaboration with Dr Ashlee Watts (Texas A&M University, USA), who had developed the equine tendinopathy model. Publication of the study findings was accompanied by a commentary and journal cover feature. The commentary highlighted the potential of *miRNA29a* to 'fine tune' tendinopathy through modulation of the structural and compositional components of soft tissues, with improved quality of tissue repair and reduced chance of recurrence [3.4].

Consequently, the proof-of-concept study laid the groundwork for development of two trademarked versions of *miRNA29a*—EquiMiR™ and TenoMiR™—which are intended for use in equine and human patients, respectively (see section 4).

3. References to the research

1. **Millar NL**, Hueber AJ, Reilly JH, Xu Y, Fazzi UG, Murrell GA, **McInnes IB** (2010) Inflammation is present in early human tendinopathy. *Am J Sports Med*;38(10):2085–2091 (doi:10.1177/0363546510372613).
2. **Millar NL**, Akbar M, Campbell AL, Reilly JH, Kerr SC, McLean M, Frleta-Gilchrist M, Fazzi UG, Leach WJ, Rooney BP, Crowe LA, Murrell GA, **McInnes IB** (2016) IL-17A mediates inflammatory and tissue remodelling events in early human tendinopathy. *Sci Rep*;6:27149 (doi:10.1038/srep27149).
3. **Millar NL**, **Gilchrist DS**, Akbar M, Reilly JH, Kerr SC, Campbell AL, Murrell GA, Liew FY, Kurowska-Stolarska M, **McInnes IB** (2015) MicroRNA29a regulates IL-33-mediated tissue remodelling in tendon disease. *Nat Commun*;6:6774 (doi:10.1038/ncomms7774).
4. Watts AE, **Millar NL**, Platt J, Kitson SM, Akbar M, Rech R, Griffin J, Pool R, Hughes T, **McInnes IB**, **Gilchrist DS** (2017) MicroRNA29a treatment improves early tendon injury.

Mol Ther;25(10):2415–2426. (doi:10.1016/j.ymthe.2017.07.015). Accompanying commentary: doi:10.1016/j.ymthe.2017.09.004.

Grants:

- **Millar** (PI): Arthritis Research UK (ARUK) Project Grant (GBP232,000) Understanding how damage is caused in tendon disease (January 2017–September 2020).
- **Gilchrist**, **Millar** (Co-PIs): Wellcome Trust Institutional Strategic Support Fund Innovation Catalyst Grant (GBP27,000) microRNA29a in tendon disease (April 2106–April 2107).
- **Gilchrist**, **Millar** (Co-PIs): Scottish Enterprise Proof-of-Concept Grant (GBP623,000) Tendon therapeutic (TenoMiR) Proof of Concept (August 2014–March 2017).
- **Millar** (PI): Scottish Senior Clinical Research Fellowship (GBP467,000) The role of microRNA 29 in tendon disease (January 2014–December 2017).
- **Millar** (PI): Wellcome Trust Early Postdoctoral Training Fellowship for Clinician Scientists (GBP263,020) The role of microRNA in tendon disease (January 2013–August 2017).
- **Millar** (PI): Academy of Medical Sciences Starter Grants for Clinical Lecturers (GBP27,000) The role of mast cells in the pathogenesis of tendon disease (January 2013–January 2015).
- **Millar** (PI): Royal College of Surgeons Edinburgh and Cutner Joint Research Fellowship in Orthopaedics (GBP45,000) The role of interleukin 33 in tendon disease (August 2010–August 2011).
- **Millar** (PI): ARUK Orthopaedic Clinical Research Fellowship (GBP145,000) The role of interleukin 33 in tendon disease (October 2009–October 2011).

4. Details of the impact

A novel approach to tendinopathy: microRNA replacement therapy

The standard treatment for tendinopathy is physiotherapy for people and 6–9 months' box rest for horses. Nonsteroidal anti-inflammatory drugs can be used but these agents are only palliative and do not target the underlying disease mechanism. Furthermore, the widespread uptake of biological therapies, such as platelet-rich plasma and autologous stem-cell injections, is limited by their ineffectiveness, restricted scalability and lack of understanding about their mode of action.

Replacement therapy with *miRNA29a* overcomes these hurdles. First, unlike other therapies, it directly targets the disease pathway and restores damaged tendon. Second, it can be chemically synthesised through an automated process and has a predicted shelf life of at least 2 years, thereby reducing manufacturing costs. Third, it can be delivered directly to the target tendon using ultrasonographic-guided injection, decreasing both systemic exposure and the dosage required for treatment.

UofG research on biological mechanisms underlying tendinopathy [3.1–3.3] and the proof-of-concept study of *miRNA29a* as a novel therapy [3.4] established **commercial pathways** for both equine and human indications. These pathways have progressed through:
(1) creation of a UofG spin-out company (CTL);
(2) securing funds from investors;
(3) obtaining patents for the *miRNA29a* replacement technology;
(4) forming a co-delivery partnership for development of EquiMiR™;
(5) securing UK, EU and US ethical and regulatory approvals for equine and human trials; and
(6) commencing trials for both EquiMiR™ (USA) and TenoMiR™ (UK).

CTL established to commercialise miRNA29a

CTL was co-founded by **Millar** and **Gilchrist** in 2015, with **McInnes** as the Lead Medical Advisor, to commercialise the *miRNA29a* replacement therapy for both equine and human indications [5.A].

During 2017–2020, CTL has attracted approximately GBP13 million in investment [5.B], with a current company valuation of GBP15 million. Initial seed investment of GBP1 million from Mediqventures and the Scottish Investment Bank provided a development runway to 2020 [5.B], enabling CTL to employ four full-time staff and develop EquiMiR™ and TenoMiR™ as its lead products. On announcing this funding, the Head of the Scottish Investment Bank stated: "*Scottish Enterprise, through the Scottish Investment Bank, is delighted to be co-investing with*

Mediqventures to help the company fully commercialise its technology. We have supported Causeway Therapeutics through our High Growth Ventures Programme to help with company formation, research and now investment to help it grow to the next stage. We look forward to working alongside Causeway to help it achieve its potential, both in Scotland and internationally" [5.B]. In 2020, CTL announced that a new round of venture capital investment opportunity would commence during January–March 2021 to raise GBP15 million in funding for the next phase of the company's development [5.B].

CTL holds the intellectual property for *miRNA29a* replacement therapy, with **Millar** and **Gilchrist** named as the inventors on patents describing this technology as a novel method to improve tendon healing [5.C]. Patents have been granted in Europe (December 2017), the USA (April 2018), Canada (August 2018), Hong Kong (September 2018) and Russia (July 2019) [5.C]. Applications are pending in Australia, New Zealand, Saudi Arabia, United Arab Emirates, Japan and China.

Veterinary trials of EquiMiR™ as a treatment for tendinopathy

The equine indication for *miRNA29a* has a potential market of GBP120 million in the UK and over USD600 million in Europe and the USA [5.A]. EquiMiR™ is expected to dominate the treatment of equine lameness as no other pharmacotherapies currently exist within this disease area and none has been developed since the collagen-crosslinking inhibitor Bapten, which was removed from the market in 1998. Therefore, commercialisation of the UofG *miRNA29a* replacement therapy will benefit equine health and welfare, particularly in racing, as horses treated with EquiMiR™ are less prone to reinjury than are horses managed conventionally. Racehorses receiving EquiMiR™ are also less likely to be culled following premature termination of their competitive careers, providing substantial value to owners and trainers. Finally, use of EquiMiR™ would avoid lengthy periods of box rest for injured animals, thereby limiting lost days of training and racing.

In September 2014, EquiMiR™ received Minor-Use-Minor-Species recognition from the European Medicines Agency, which appreciably reduces the amount of data required to obtain a Marketing Authorisation from this regulatory body [5.D]. EquiMiR™ also received a fee waiver from the US Food and Drug Administration (FDA) under the Barrier-to-Innovation provision of the Animal Drug User Fee Act (July 2016) [5.E]. This waiver accelerates the development and regulatory process of EquiMiR™ towards marketing authorisation in the USA. These two regulatory approvals considerably decrease the cost of drug development and production, which will ultimately reduce the final price for end users of EquiMiR™.

Through the UofG research collaboration with Texas A&M University [3.4], CTL was introduced to [redacted], a mid-sized UK-based international veterinary pharmaceutical manufacturer with appreciable access to the equine market. In August 2017, CTL signed [redacted] as a co-delivery partner to share EquiMiR™ product development and be responsible for retail and distribution. [Redacted] has contributed GBP8 million to development costs to support safety studies, equine trials and regulatory approval, which includes GBP3 million in milestone payments to CTL. This partnership provides [redacted] with access to CTL's cutting-edge research and development capability, and so will position it as the field leader in treating equine lameness.

In 2019, EquiMiR™ underwent a 6-month experimental dose-finding and efficacy trial at Texas A&M University using the equine collagenase-induced tendonitis model. Substantial improvements in structural parameters were demonstrated by ultrasonography among 36 horses treated with high doses of EquiMiR™ (findings not yet publicly available). An FDA-approved pivotal veterinary trial is scheduled to commence at several US sites in 2021 (originally due to start in 2020 but stalled owing to COVID-19).

Clinical trials of TenoMiR™ as a treatment for tendinopathy

The market for treating tendinopathy in humans is valued at USD5 billion worldwide [5.A]. Potential indications for TenoMiR™ include lateral epicondylitis (tennis elbow), which is

predicted to be worth USD903 million in the USA, EU and Japan by 2020 [5.A]. As a first-in-class therapy, there is currently no competitor for TenoMiR™ in this clinical arena.

Recognising the success of CTL in developing EquiMiR™ [3.4], Mediqventures and the Scottish Investment Bank invested an additional GBP1 million in 2018 [5.B]. This funding—together with grants from Innovate UK of GBP1.4 million (2018) and GBP1.3 million (2019) [5.B]—accelerated the development of TenoMiR™ for human indications, particularly the preclinical packages required for filing an Investigational New Drug application. In 2020, CTL received a GBP230,986 Innovate UK COVID-19 Continuity Grant that enabled clinical work on TenoMiR™ to proceed during the pandemic [5.B].

Data from the equine studies of the *miRNA29a* replacement therapy supported regulatory filings by CTL to conduct first-in-human clinical trials of this approach. An NHS Research Ethics application was approved in September 2019, with TenoMiR™ designated as an Investigational New Drug by the UK Medicines and Healthcare Products Regulatory Agency in August 2020 [5.F]. In September 2020, a phase 1b clinical trial of TenoMiR™ commenced in Manchester among 24 patients with tennis elbow (8 patients enrolled as of November 2020) [5.F]. With a positive read-out from this trial expected to occur before May 2021, CTL will actively seek larger pharmaceutical partners either to sell or co-develop TenoMiR™. In addition, CTL has extended its preclinical development pipeline to other novel miRNA replacement therapies targeting conditions such as osteoarthritis and intravertebral disc disease (OsteoMiR™); skin ageing (DermaMiR™); and wound healing (*miRNA-148b*) [5.F].

5. Sources to corroborate the impact [available in PDF except where indicated]

A. **About CTL**: (1) Business plan, including data on the potential market share for equine and human indications of *miRNA29a*; (2) Registration at Companies House; (3) Promotional video by Gilchrist [YouTube].

B. **Investment in CTL**: (1) Company news (2015–2020); (2) Scottish Investment Bank case study (September 2018); (3) Call for investors (2020); (4) Innovate UK grants 104286 (2018), 105289 (2019) and 72092 (2020).

C. **Examples of CTL patents**: EP3094727B1 (EU, December 2017) and US9932582B2 (USA, April 2018). Millar and Gilchrist named as the inventors.

D. **European Medicines Agency**: (1) Correspondence confirming Minor-Use-Minor-Species recognition for EquiMiR™ (11 September 2014; Ref PN160); (2) Minutes of the Committee for Medicinal Products for Veterinary Use (CVMP) meeting of 9–11 September 2014 (see p.3).

E. **FDA**: (1) Correspondence confirming fee waiver for EquiMiR™ under the Barrier-to-Innovation provision of the US Animal Drug User Fee Act (July 2016); (2) Confirmation of filing for Investigational New Animal Drug status for EquiMiR™ (September 2016).

F. **Clinical development of TenoMiR™**: (1) CTL pipeline for human tendinopathy (TenoMiR™ listed as CWT-001) and other indications (CWT-002, CWT-003 and CWT-004); (2) Announcement of the phase 1b clinical trial (September 2020).