**Institution:** Royal Holloway, University of London

**Unit of Assessment:** 5 Biological Sciences

**Title of case study:** Transforming therapeutic outcomes of fatal Duchenne Muscular Dystrophy with genetic medicines

**Period when the underpinning research was undertaken:** 2000-2020

**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: |
|---|---|---|
| Dr Linda Popplewell | Reader<br>Lecturer<br>Research Officer<br>Senior post-doctoral research scientist | 2020<br>2015 - 2020<br>2012-2015<br>2005-2012 |
| Prof George Dickson | Emeritus Professor<br>Chair of Molecular Cell Biology | 2019 - 2020<br>1994-2019 |

**Period when the claimed impact occurred:** 2013-2020

**Is this case study continued from a case study submitted in 2014?** Y

## 1. Summary of the impact

Royal Holloway University of London (RHUL) has pioneered transformative gene therapies for Duchenne muscular dystrophy, a progressive, incurable, fatal, rare muscle disease. These therapies have significantly enhanced patients' quality of life and prevent their further deterioration. The research has resulted in two commercially available drugs, VyonDys-53 (patented by RHUL and approved by the US Federal Drugs Agency in December 2019) and ExonDys-51 (collaboratively optimised by RHUL). The commercial benefit for Sarepta Therapeutics Incorporated, the company that markets both drugs, is total sales of $834,400,000 for ExonDys-51 (since its approval in 2016 until 2019) and a 32% increase in its share price immediately following approval of VyonDys-53 in December 2019. Together these two drugs have the potential to provide therapeutic benefit to nearly 25% of patients living with Duchenne muscular dystrophy worldwide.

## 2. Underpinning research

Each week in the UK, two families receive a devastating Duchenne muscular dystrophy (DMD) diagnosis; there are currently approximately 2,500 patients alive in the UK and 300,000 patients worldwide with the disease. DMD has very high societal and economic burdens on families and on the health and social care system in general. Treatment options have been restricted to addressing the disease phenotype, rather than the genetic defect itself. The research performed at RHUL from 2005 onwards by Professor George Dickson and Dr Linda Popplewell focuses on developing genetic therapies for the treatment of muscular dystrophies, in particular DMD. DMD, a fatal heritable X-linked condition caused by multiple defects in the gene encoding dystrophin, and affecting 1:3,500-5,000 new-born boys, is characterised by progressive muscle degeneration and weakness that ultimately leads to premature death from cardiac and respiratory failure (Figure 1).

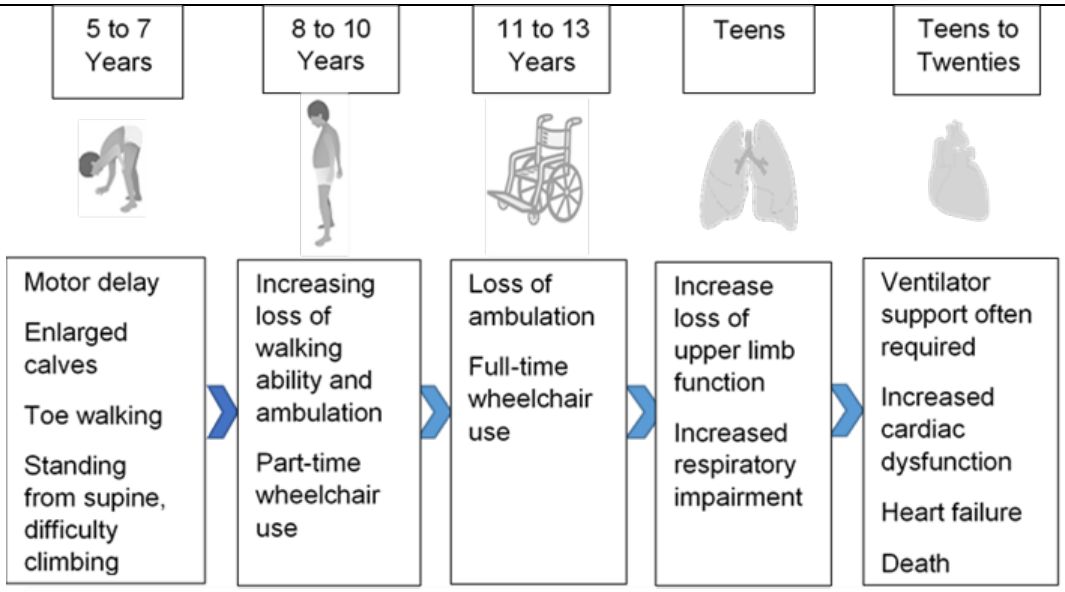


**Figure 1: Severe prognosis associated with DMD.**

The impact of the research programme is based on halting the progression of disease using antisense oligonucleotides (AOs) to induce exon skipping. Exon skipping re-opens the reading frame in the mutated *DMD* mRNA leading to expression of truncated yet functional dystrophin protein (Figure 2).

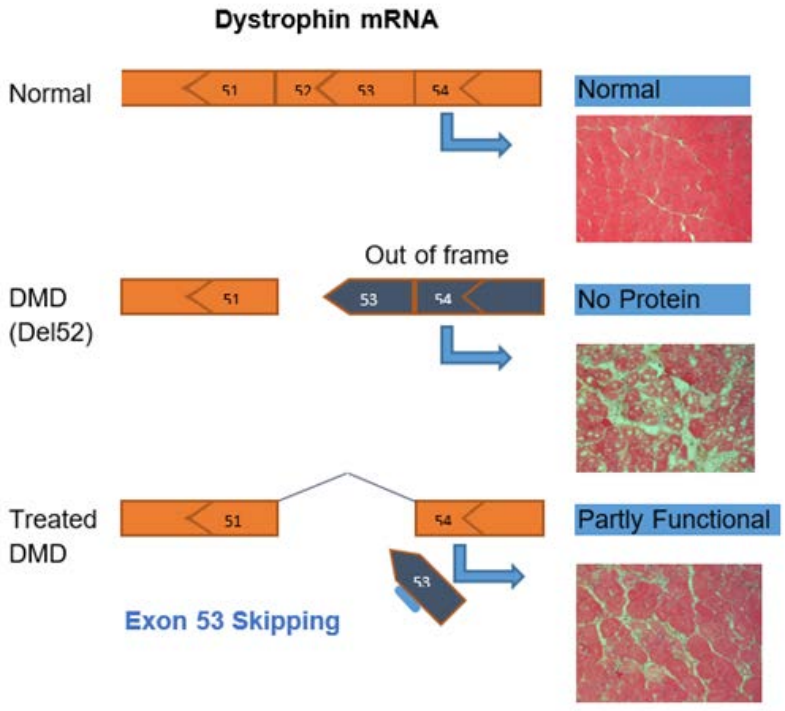


**Figure 2: AOs restore dystrophin protein expression through process of exon skipping.**

RHUL was the first to demonstrate that AOs could induce therapeutic exon skipping and restore dystrophin protein expression in a DMD animal model. Exon skipping is a personalised medicine; different mutations require the skipping of different exons. RHUL has optimised AOs for the human disease **(R1),** focusing on those exons whose skipping would have the highest patient applicability; four patents have been granted [US patents numbers 8,084,601, 8,324,371, 8,461,325, and 8,552,172] and licensed to two pharmaceutical companies. RHUL was also involved in the collaborative optimisation of an AO to skip exon 51 **(R2).**

Following clinical trials in the US and UK in which RHUL was a named partner **(R3, R4),** this AO, marketed as ExonDys-51, received FDA approval on 16th September 2016 on the basis of stabilisation of the disease phenotype. Another multi-centre EU-funded placebo-controlled trial followed, in which RHUL was as a named partner **(R5),** one of our patented AOs, trial name Golodirsen, is now being marketed as VyonDys-53 by Sarepta Therapeutics Inc. Accelerated FDA approval was achieved for this AO on 19th December 2019 on the basis of significant exon skipping ($p<0.001$) in all patients treated for 48 weeks or longer (n=25), and a significant increase ($p<0.001$) in dystrophin protein expression from 0.10% of normal baseline to 1.02%. This level of dystrophin protein expression is sufficient to significantly reduce muscle pathology by 2.2% in treated patients**.** Trials are continuing to further assess clinical benefit, The higher dystrophin protein level seen with VyonDys-53 relative to that seen with ExonDys-51 suggests enhanced positive therapeutic outcomes will be seen.

Another type of gene therapy developed by RHUL researchers, based on using viral vectors to deliver a working copy of the dystrophin gene **(R6)** that has applicability to all patients, received Orphan Drug Designation in 2014 and is the subject of an ongoing multi-centre clinical trial sponsored by Genethon.

**3. References to the research**

Names in **Bold** are **staff** (including former staff) of **Royal Holloway University of London**. All references are peer-reviewed **Open Access** publications and are cited in the text above as [number].

**(R1). Popplewell LJ**, Adkin C, Arechavala-Gomeza V, Aartsma-Rus A, de Winter CL, Wilton SD, Morgan JE, Muntoni F, **Graham IR**, **Dickson G**. (2010). Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human *DMD* gene: implications for future clinical trials. Neuromus Disord 20: 102-10. doi: 10.1016/j.nmd.2009.10.013.

**(R2.** Arechavala-Gomeza V, **Graham IR, Popplewell LJ**, Adams AM, Aartsma-Rus A, Kinali M, Morgan JE, van Deutekom JC, Wilton SD, **Dickson G**, Muntoni F. (2007). Comparative analysis of antisense oligonucleotide sequences for targeted skipping of exon 51 during dystrophin pre-mRNA splicing in human muscle. Hum Gene Therapy 18: 798-810. DOI: 10.1089/hum.2006.061.

**(R3).** Kinali M, Arechavala-Gomeza V, Feng L, Cirak S, Hunt D, Adkin C, Guglieri M, Ashton E, Abbs S, Nihoyannopoulos P, Garralda ME, Rutherford M, McCulley C, **Popplewell L**, **Graham IR**, **Dickson G**, Wood MJ, Wells DJ, Wilton SD, Kole R, Straub V, Bushby K, Sewry C, Morgan JE, Muntoni F. (2009). Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. Lancet Neurol. 8(10):918-28. doi: 10.1016/S1474-4422(09)70211-X.

**(R4).** Cirak S, Arechavala-Gomeza V, Guglieri M, Feng L, Torelli S, Anthony K, Abbs S, Garralda ME, Bourke J, Wells DJ, **Dickson G**, Wood MJ, Wilton SD, Straub V, Kole R, Shrewsbury SB, Sewry C, Morgan JE, Bushby K, Muntoni F. (2011). Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet. 378(9791):595-605. doi: 10.1016/S0140-6736(11)60756-3.

**(R5).** Frank D, Schnell FJ, Akana C, El-Husayni SH, Desjardins CA, Morgan J, Charleston JS, Sardone V, Domingos J, **Dickson G**, Straub V, Guglieri M, Mercuri E, Servais L, Muntoni F. (2020). **Increased Dystrophin Production With Golodirsen in Patients with Duchenne Muscular Dystrophy** Neurology. pii: 10.1212/WNL.0000000000009233.

**(R6).** Le Guiner C, Servais L, Montus M, Larcher T, Fraysse B, Moullec S, Allais M, François V, Dutilleul M, **Malerba A, Koo T**, Thibaut JL, Matot B, Devaux M, Le Duff J, Deschamps JY, Barthelemy I, Blot S, Testault I, Wahbi K, Ederhy S, Martin S, Veron P, Georger C, **Athanasopoulos T**, Masurier C, Mingozzi F, Carlier P, Gjata B, Hogrel JY, Adjali O, Mavilio F, Voit T, Moullier P, **Dickson G**. (2017). Long-term microdystrophin gene therapy in a canine model of Duchenne muscular dystrophy. Nat Commun. 8:16105. doi: 10.1038/ncomms16105.

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

Research undertaken at RHUL led to the development of gene therapies for DMD patients, providing effective treatment of their disease. This has major impact in four key areas: it has increased options for drug therapies for patients living with DMD; it has changed clinical practice in the treatment of DMD; it has improved quality and length of human life in treated patients;

and it has increased company revenues for drug companies who have commercially exploited the research.

**Increasing drug treatment options for DMD Patients:** Treatment options for DMD have been limited to controlling symptoms and providing palliative care. Current recommended management is daily corticosteroid administration to control the inflammation that arises within skeletal muscle as a result of the disease; long term corticosteroid treatments carries serious body-wide side effect risk. Research at Royal Holloway has been instrumental in advancing the drug treatment options for patients that are specifically targeted to address the genetic basis of DMD. The president of British Society for Gene and Cell Therapy confirms that "*Royal Holloway ……. was the **first to demonstrate** that (AOs) could be used to induce therapeutic exon skipping in cellular and animal models of DMD….and has directly led to …….the design of the first ever registered gene-therapy drug [ExonDys51]".* **(S1).** The Director of Research and Innovation at Muscular Dystrophy UK (MDUK) believes that *"The research [at Royal Holloway] has resulted in ….. treatments that… stabilise and…. provide an effective cure for Duchenne muscular dystrophy"* (**S2)**.

**Changing clinical practise:** In contrast to corticosteroid treatment, ExonDys-51 and VyonDys-53 effectively restore dystrophin protein expression in skeletal muscle in treated patients. On the basis of this **proven efficacy** seen in **clinical testing** sponsored by Sarepta Therapeutics Inc. **(S9)**, **accelerated FDA approvals** for ExonDys-51 was received in September 2016 **(S3**), and for VyonDys-53 in December 2019 **(S3),** allowing their prescribed medicinal use in 15% of patients worldwide (n=45,000) and 8% of patients worldwide (n=24,000) respectively. The dystrophin protein expressed is demonstrated to be functional; treatment with ExonDys-51 for more than 2 years has been reported to **prevent further deterioration** in muscle function **(S3)**. For a severe progressive disease like DMD, this imparts paramount therapeutic benefit. A neurologist at Ohio State University describes the benefit of these treatments: "*Exon skipping is now an acceptable and important addition to combating the effects of this debilitating disease. Not only is the **natural history of DMD significantly improved but the side effect profile is minimal**, making this an **attractive treatment** for clinicians"*. **(S4).**

**Improving life expectancy and quality of life**: The restored dystrophin protein expression seen with ExonDys-51 treatment has been shown to **improve life expectancy (S5).** In patients whose treatment began before loss of lower limb function, **ambulation is maintained (S5)**. In older wheelchair-bound patients, ExonDys-51 acts to **preserve upper limb and diaphragm functionality (S5)**. This genetic medicine leads to an **enhanced quality of life** in all treated patients. The Professor of Medicine at John Walton Muscular Dystrophy Research Centre, Newcastle University, who was involved in the clinical trials of both ExonDys-51 and VyonDys-53, explains: "*Studies suggest that these gene therapies [developed by The Royal Holloway team] will **preserve respiratory muscle function and hand dexterity** as the disease progresses which is **vital for the quality of life** for older patients*." **(S6)**.

In addition, the drugs have provided an impact in societal benefits and have given **hope** to patients, parents and carers, where there was none before. The [text removed for publication] of Genethon, a not-for-profit French company dedicated to the design and development of gene therapy treatments for rare diseases, said: [text removed for publication] **(S7)** The comment from one family is indicative of the feedback from carers on the significance of these treatments for their families: "*DMD diagnosis means…..you will have to watch your child's health deteriorate over time, and the hopes and dreams you had for your son in the future disappears entirely… Gene therapy for Duchenne families is the …. **saving grace.** This is what gives us hope for a different future from the current prognosis because there is nothing else*." **(S8).**

**Economic and commercial Impact**: RHUL's granted patents have been licensed to the pharmaceutical company Sarepta Therapeutics Inc. **(S9)**. As a result, up to mid-August 2020, Sarepta was the only company commercially supplying an AO-based gene therapy treatment for DMD. These license agreements have translated into notable financial return for this mid-sized pharmaceutical organisation. Following its approval in 2016, the company announced increasing annual net sales of ExonDys-51; these were **$154,600,000** in 2017, **$301,000,000** in 2018 (94%

increase on previous year) and **$381,000,000** in 2019 (26% increase on previous year), and projected sales of **$420,000,000** in 2020 **(S10).** VyonDys-53 was highlighted by Optum as the **top drug to watch** in 2019 **(S9)**. On the day of its approval, Sarepta's **share price soared by 32%** in value **(S10)**. Projected revenue from VyonDys-53 for 2020 is **$130,000,000 (S9),** and Evaluate.com has predicted that the sales will reach **$265,000,000 in 2022, and $360,000,000 in 2024 (S10).** The Director of R&I at MDUK states that *This work…… would also have a major economic impact for health care providers and social services* **(S2).**

**Additional economic benefit has been generated for Genethon**, the French company that manages the patent on RHUL's gene addition therapy, who announced the start of clinical trials on the 30th November 2020 **(S9)**. RHUL received a payment of $8,000,000 from Sarepta Therapeutics Inc. in early 2020 following **an exclusive license option agreement (S9).**

**5. Sources to corroborate the impact**

**(S1)** Testimonial from Professor Uta Greisenbach, President of British Society of Gene and Cell Therapy entitled 'Impact statement for Royal Holloway Duchenne Team', dated 5th March 2020.

**(S2)** Testimonial from Dr Kate Adcock, Director of Research and Innovation, Muscular Dystrophy UK, dated 23rd October 2020.

**(S3)** Collated links to press releases from Sarepta Therapeutics Inc. related to the accelerated approval by the Food and Drug Agency of ExonDys-51 (dated 16th September 2016) and VyonDys-53 (dated 16th December 2019) for their prescribed use in DMD patients with appropriate mutations.

**(S4)** Testimonial from Professor Jerry Mendell, Curren-Peters Chair in Research, Professor of Paediatrics and Neurology, Nationwide Children's Hospital, Ohio entitled 'Professor George Dickson', dated 24th February 2020.

**(S5)** Collated links to three independent publications (Ann Neuro, 2016; J Neuromus Diseases, 2018; Medicine, 2019) led by Professor Jerry Mendell, a clinician involved in long-term (>2 years) treatments with ExonDys-51 describing the clinical benefits seen.

**(S6)** Collated letters/testimonials from Professor Volker Straub, Harold Macmillan Professor of Medicine, Newcastle University and Professor Laurent Servais, Professor of Paediatric Neuromuscular Diseases, Oxford University, clinicians involved in multi-centre, placebo-controlled international clinical trials testing ExonDys-51 and VyonDys-53, dated 4th March 2020 and 6th March 2020 respectively.

**(S7)** Collated letters from three biotech/biopharma company leads including [text removed for publication] of Genethon, [text removed for publication] of Synpromics (now AskBio) and Dr Takis Anathasopolous, Director and Head of Vector and Transgene Team, Gene and Cell Therapy, GlaxoSmithKline, dated 27th September 2018, 24th March 2020 and 29th February 2020 respectively.

**(S8)** Collated Letters/Testimonials from five DMD patients/parents/carers dated 19th September 2018, 6th February 2020, 12th February 2020, 31st March 2020 and 1st April 2020, including one from a mother whose son is being treated with ExonDys-51.

**(S9)** Non-exclusive license agreement dated 5th December 2013 between Royal Holloway and Bedford New College and Sarepta Therapeutics Inc. for US Patent Number 8,084,601 entitled 'Oligomers' (granted 27th December 2011). Press release by Genethon dated 9th January 2020 entitled 'Genethon announces expanded collaboration with Sarepta Therapeutics for continued development of an innovative gene therapy for Duchenne muscular dystrophy' and press release by Genethon dated 30 November 2020 entitled 'Genethon to start international clinical trial for treatment of Duchenne muscular dystrophy'.

**(S10)** Collated annual financial reports from Sarepta Therapeutics Inc. entitled 'NASDAQ_SRPT_2016', 'NASDAQ_SRPT_2017', 'NASDAQ_SRPT_2018' and 'Sarepta Therapeutics Announces Fourth Quarter and Full-Year 2019 Financial Results and Recent Corporate Developments' dated 26th February 2020, and website page links detailing share price and market potential of VyonDys-53 and link to an independent publication Nature Reviews: Drug Discovery, 2020.