



Progress and prospects in antisense oligonucleotide-mediated exon skipping therapies for Duchenne muscular dystrophy

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Abstract

Recent years have seen enormous progress in the field of advanced therapeutics for the progressive muscle wasting disease Duchenne muscular dystrophy (DMD). In particular, four antisense oligonucleotide (ASO) therapies targeting various DMD-causing mutations have achieved FDA approval, marking major milestones in the treatment of this disease. These compounds are designed to induce alternative splicing events that restore the translation reading frame of the dystrophin gene, leading to the generation of internally-deleted, but mostly functional, pseudodystrophin proteins with the potential to compensate for the genetic loss of dystrophin. However, the efficacy of these compounds is very limited, with delivery remaining a key obstacle to effective therapy. There is therefore an urgent need for improved ASO technologies with better efficacy, and with applicability to a wider range of patient mutations. Here we discuss recent developments in ASO therapies for DMD, and future prospects with a focus on ASO chemical modification and bioconjugation strategies.

Keywords Duchenn muscular dystrophy · DMD · Antisense oligonucleotide · Exon skipping · Dystrophin

Dystrophinopathy

Duchenne muscular dystrophy is a severe, X-linked inherited disorder caused by loss of the dystrophin protein affecting 1:3500–5000 boys worldwide (Hoffman et al. 1987). The disease results from a spectrum of loss-of-function mutations in the dystrophin gene (*DMD*) (Hoffman et al. 1987), the most common of which are whole exon deletions (Muntoni et al. 2003). *DMD* is one of the largest genes of the human genome, encoding a 14 kb, 79-exon long mRNA

which is translated into a 427 kDa dystrophin protein. In DMD, dystrophin deficiency results in vulnerability of muscles to contraction-induced damage (Petrof et al. 1993). As such, daily physical function initiates a detrimental cascade of degeneration-regeneration cycles, ultimately leading to muscle wasting (Cardone et al. 2023). Notably, the disease affects not only skeletal muscle, but also the heart, and almost all DMD patients develop a form of dilated cardiomyopathy, often leading to end-stage heart failure (Szabo et al. 2021). Currently, cardiac dysfunction is the main cause of death for dystrophic patients, typically in the third decade of life (Passamano et al. 2012).

Becker muscular dystrophy is an allelic form of DMD characterised by later onset, milder disease severity, and slower disease progression, with many patients remaining ambulant well into adulthood (with some never requiring wheelchair use) (England et al. 1990; Clemens et al. 2020a; Thada et al. 2023). In most cases, the difference between the DMD and BMD phenotypes can be explained by the ‘reading frame rule’ (Vengalil et al. 2017; Aartsma-Rus et al. 2006). Specifically, DMD is caused by frameshift mutations which lead to production of defective, prematurely terminated protein variants. Conversely, BMD patients typically maintain the translation reading frame, producing an internally deleted, yet partially functional, pseudodystrophin,

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which underlies the milder disease progression. A remarkable example of this phenomenon is the case of a BMD patient lacking 46% of the dystrophin gene who presented with only mild symptoms and was ambulant at the age of 61 (England et al. 1990).

Antisense oligonucleotide therapeutics

Antisense nucleotides (ASOs) are short, single-stranded nucleic acid polymers (~20–30 nucleotides in length) designed to bind to complementary target mRNA sequences via Watson–Crick base pairing (Roberts et al. 2023, 2020; Aartsma-Rus et al. 2017; Brad Wan and Seth 2016). The therapeutic potential of ASOs was first demonstrated in 1978 by Stephenson and Zamecnik who showed that short, synthetic DNA oligonucleotides can inhibit replication of the Rous sarcoma virus in a cell-free system (Stephenson and Zamecnik 1978). These results have paved the way for research into short oligonucleotide-based therapeutics, and eventually to the regulatory approval of ~15 ASO-based drugs over the past 26 years, the vast majority within the last decade (Lauffer et al. 2024). ASOs elicit gene regulatory functions via a variety of mechanisms including post-transcriptional control through transcript degradation, translation inhibition, or splice-switching (Lauffer et al. 2024; Dhuri et al. 2020). In the context of DMD, ASO-mediated exon skipping of the dystrophin pre-mRNA is one of the most promising therapeutic strategies (Roberts et al. 2023). This approach aims to convert the severe DMD phenotype into a less severe ‘BMD-like’ phenotype by paradoxically increasing the degree of internal deletion and restoring the translation reading frame in the dystrophin protein via the exclusion of a specific exon(s) from the *DMD* pre-mRNA. This leads to the production of an internally-deleted but largely functional pseudodystrophin protein (Roberts et al. 2023; Aartsma-Rus et al. 2009). Importantly, ASO-mediated exon skipping is a mutation-specific approach, theoretically

applicable to as many as ~83% of all DMD-causing mutations (Aartsma-Rus et al. 2009; Bladen et al. 2015).

Due to their inherent susceptibility to nucleases and poor target binding affinity, unmodified ASOs based on natural DNA and RNA chemistry have limited clinical utility (Roberts et al. 2020). As such, diverse ASO chemistries have been developed to improve their ‘drug-likeness’ (Roberts et al. 2020). The most commonly used nucleic acid chemistry in DMD exon skipping therapeutics is PMO (phosphorodiamidate morpholino oligonucleotide). PMOs consist of a six-membered morpholine ring (analogous to the five-membered arabinose ring found in native DNA/RNA) and an uncharged phosphorodiamidate backbone (analogous to the phosphodiester linkages). The non-natural chemical composition of PMOs means that they cannot be degraded by biofluid or tissue nucleases, and as such, these molecules exhibit high stability and a very favourable safety profile (Amantana and Iversen 2005; Summerton and Weller 1997). Indeed, PMOs have been administered to rodents at doses of up to 3 g/kg (Wu et al. 2010). As of 2024, four PMO antisense drugs have been approved by the FDA for treatment of DMD (Table 1): eteplirsen, golodirsen, viltolarsen, and casimersen (Lim et al. 2017; Roshmi and Yokota 2023; Clemens et al. 2020b; Heo 2020; Shirley 2021).

Eteplirsen (developed by Sarepta Therapeutics) was the first drug to receive marketing authorisation in 2016 (Lim et al. 2017), which marked a significant milestone in the development of therapeutics for DMD (Lim et al. 2017). This was the first gene-specific drug offered to DMD patients, which utilised a novel, targeted mechanism as opposed to the pleiotropic mode of action of corticosteroids, which are the standard-of-care in DMD management (Bushby et al. 2010). The clinical trials leading to the eteplirsen approval began in 2007 with a first phase 1/2 study conducted at Imperial College London demonstrating the safety and tolerability of the drug after intramuscular injection in patients (NCT00159250) (Kinali et al. 2009). A further, phase 2, dose escalation, intravenous injection trial

Table 1 FDA-approved ASO exon skipping therapies for DMD

ASO	DMD Target exon	Sequence (5' to 3')	Company	FDA approval	Dystrophin protein restoration	References
Eteplirsen	51	CTCCAACATCAAGGA AGATGGCATTCTAG	Sarepta	Sept 2016	0.9% after 180 weeks	Lim et al. (2017)
Golodirsen	53	GTTGCTCCGGTTCT GAAGGTGTTC	Sarepta	Dec 2019	1% after 48 weeks	Heo (2020; Servais et al. (2022)
Viltolarsen	53	CCTCCGGTTCTGAAG GTGTTC	NS Pharma	Aug 2020	5.9% after 25 weeks	Roshmi and Yokota (2023); Clemens et al. (2020b)
Casimersen	45	CAATGCCATCCTGGA GTTCTCTG	Sarepta	Feb 2021	4.25% after 48 weeks	Shirley (2021); Nicolau et al. (2024)

All ASO sequences consist of phosphorodiamidate morpholino oligonucleotide (PMO) chemistry

demonstrated a positive safety profile for eteplirsen, with no drug-related serious adverse events reported in the cohort of 19 ambulant DMD patients (NCT00844597) (Cirak et al. 2011). The exon-skipping efficacy, and thus therapeutic benefit, of the drug were variable in these studies with a maximum increase of 16% in dystrophin levels as measured by western blot in the phase 2 trial (Cirak et al. 2011). Follow-up studies reported more modest findings. Treatment with weekly injections of eteplirsen for almost 3.5 years resulted in the restoration of ~1% of dystrophin levels observed in healthy muscle (Lim et al. 2017). As such, the approval of eteplirsen by FDA in 2016 was highly controversial, as it was solely based on only minimal dystrophin restoration as a surrogate endpoint, without the evidence of functional benefit (Aartsma-Rus and Goemans 2019). Similarly modest results were obtained with other approved ASOs (Table 1) (Lim et al. 2017; Roshmi and Yokota 2023; Clemens et al. 2020b; Heo 2020; Shirley 2021; Servais et al. 2022; Komaki et al. 2018; Nicolau et al. 2024). For example, dystrophin restoration levels were the highest for viltolarsen, with 5.9% of dystrophin expression achieved after 25 weeks of treatment (Clemens et al. 2020b). Clinical trials for all of the FDA-approved exon skipping ASOs are currently ongoing (Vincik et al. 2024). Notably, none of the FDA-approved ASOs for DMD have been approved by European Medicine Agency, based on the same efficacy data (Aartsma-Rus and Goemans 2019).

Enhancing ASO activity

Due to the limited efficacy of available drugs, the pursuit of improved ASO therapeutics in DMD continues. Here we will consider the two major approaches for ASO improvement; (i) chemical modification, and (ii) bioconjugation.

A major development in oligonucleotide chemistry is the incorporation of stereopure backbone linkages. While phosphodiester backbones are achiral, the incorporation of a sulphur to replace one of the non-bridging backbone oxygen atoms, as in the case of phosphorothioate modification, gives rise to chiral centres at every backbone linkage position. Control of the stereochemistry at each position has been reported to improve many oligonucleotide properties, with a stereopure enantiomer ultimately being more potent than the racemic bulk mixture (Kandasamy et al. 2022a). To this end, Wave Life Sciences developed a stereopure ASO with phosphorothioate backbone to induce *DMD* exon 51 skipping (suvodirsen) (Wagner et al. 2019). Despite promising pre-clinical results, suvodirsen failed to meet its primary endpoint (i.e., an increase in dystrophin protein expression) in a phase I clinical trial (NCT03508947), and its development was subsequently discontinued (Aartsma-Rus and Corey 2020). However, Wave Life Science have pursued

a second stereopure ASO designed to skip *DMD* exon 53 (WVE-N531). This compound is a mixmer ASO containing 2'-*O*-methyl and 2'-fluoro sugar modifications, and a mixture of stereoselective phosphorothioate and phosphoryl guanine (PN) backbone linkages (Kandasamy et al. 2022b). This pattern of ASO chemistry has been shown to improve delivery and overall therapeutic potency in animal models, including the severely affected dystrophin/utrophin double knock-out (dKO) mouse model of DMD (Kandasamy et al. 2022a; Tillinger et al. 2023). WVE-N531 is currently being evaluated in a phase 1b/2 trial (FORWARD-53, NCT04906460). Initial reports from this trial have been highly encouraging, with a mean level of exon skipping of 53% after three biweekly 10 mg/kg doses in the first three DMD patients treated, although dystrophin protein levels were negligible (Tillinger et al. 2023). Interim data from this trial after 24 weeks of dosing recently reported mean dystrophin protein expression levels of 9% (muscle content-adjusted) and 5.5% (unadjusted), with mean exon skipping levels of 57% (Wave life sciences announces positive interim data from FORWARD-53 Clinical Trial Evaluating WVE-N531 in boys with Duchenne muscular dystrophy amenable to exon 53 skipping - wave life sciences Available from: <https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-positive-interim-data-forward-53>).

Notably, a 2'-*O*-methyl ASO with phosphorothioate backbone, developed by BioMarin (drisapersen) was ultimately discontinued after demonstrating limited efficacy (i.e., lack of functional improvement) and adverse events including injection site reactions, thrombocytopenia, and proteinuria in a phase 3 trial (NCT01254019) (Markati et al. 2021; Goemans et al. 2018). The incorporation of phosphorothioate linkages was associated with dose limiting renal toxicity, which may prove to be a challenge for other therapeutic modalities, given the widespread usage of this chemistry in the nucleic acid therapeutic field. Nevertheless, other phosphorothioate containing ASOs have also been investigated. Daiichi Sankyo was developing renadirsen (DS 5141b) a fully phosphorothioate mixmer containing 2'-*O*-methyl and ethylene bridged nucleic acid (ENA) modifications for the skipping of *DMD* exon 45 (Ito et al. 2021), investigated in a phase 2 clinical trial (NCT04433234), although development of this drug is now discontinued. Furthermore, SQY Therapeutics is investigating a completely distinct chemistry, tricyclo-DNA. An ASO consisting of this chemistry, and conjugated to a palmitic acid, (SQY51) designed to skip *DMD* exon 51 is currently under investigation in a phase 1/2 clinical trial (NCT05753462/AVANCE1). Tricyclo-DNA is notable, as it has been reported to enable exon skipping in the brain, meaning that the neurological pathologies of DMD may be treatable (Goyenvallé et al. 2015; Zarrouki et al. 2022).

A key advantage of FDA-approved PMO chemistry is the favourable safety profile resulting from their low plasma protein binding properties (Roberts et al. 2020; Brad Wan and Seth 2016), although this same characteristic also leads to rapid plasma clearance of the PMO via the kidneys (Roberts et al. 2020; Brad Wan and Seth 2016; Vincik et al. 2024; Tsoumpra et al. 2019; Betts et al. 2012). This results not only in the requirement for weekly dosing for prolonged periods, but also in limited uptake by targeted cells. As such, the efficient delivery of PMO to DMD muscle (and especially heart) remains an ongoing challenge for the field. An alternative approach for ASO improvement is via covalent conjugation to a delivery-assisting moiety. This has been most extensively studied in the case of PMOs, whereby the uncharged backbone enables facile synthesis of a variety of conjugates.

One of the most promising technologies for improved tissue targeting and uptake is conjugation of the PMO with cell-penetrating peptides (CPPs) (Tsoumpra et al. 2019; Betts et al. 2012). CPPs are short (< 30 amino acids), often cationic, sequences that possess the remarkable ability to cross cell membranes, making them valuable tools for delivering therapeutic molecules (McCloy and Banerjee 2018). A plethora of peptide-conjugated PMOs (PPMOs) have been developed and pre-clinically tested in the context of DMD (Tsoumpra et al. 2019). In comparison to unconjugated PMOs, PPMOs demonstrate enhanced efficacy as splicing correctors at lower doses, enabling systemic administration to achieve widespread dystrophin restoration in skeletal muscles and cardiac tissue (Tsoumpra et al. 2019). Multiple recent clinical trials of PPMOs for DMD are ongoing or have recently completed: Sarepta (NCT04004065/MOMENTUM, SRP-5051/vesleteplirsen), PepGen (NCT06079736, PGN-EDO51) and Entrada (ENTR-601-44-101, ENTR-601-44) (Roberts et al. 2023). The interim phase 2 data of vesleteplirsen (which consists of a PMO conjugated to the R₆Gly peptide) trial revealed mean 11% of exon skipping and 5.7% of dystrophin expression after 7 monthly doses (Sarepta Therapeutics Announces Positive Data from Part B of MOMENTUM, a Phase 2 Study of SRP-5051 in Patients with Duchenne Muscular Dystrophy Amenable to Skipping Exon 51|Sarepta Therapeutics, Inc. <https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-positive-data-part-b-momentum>). However, in November 2024, Sarepta announced the discontinuation of its vesleteplirsen programme on account of prolonged hypomagnesemia and a decline in the renal function marker eGFR (estimated glomerular filtration rate) in subsets of participants in the MOMENTUM trial (Community letter: update SRP-5051 program|Sarepta Therapeutics Available from <https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-positive-data-part-b-momentum>; Sarepta therapeutics

announces third quarter 2024 financial results and recent corporate developments|Sarepta Therapeutics, Inc. Available from: <https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-third-quarter-2024-financial>).

In the PepGen trial, a single PGN-EDO51 dose resulted in 2% of exon skipping in healthy volunteers (Larkindale et al. 2023). Interestingly, PepGen also observed transient hypomagnesemia in two PPMO-treated individuals, which resolved without intervention (PepGen reports positive data from phase 1 trial of PGN-EDO51 for the treatment of Duchenne muscular dystrophy|PepGen Available from: <https://investors.pepgen.com/news-releases/news-release-details/pepgen-reports-positive-data-phase-1-trial-pgn-edo51-treatment>). In contrast with the relatively simple amino acid composition of vesleteplirsen, the PGN-EDO51 is based on extensive iterative improvements of the Pip (PMO internalisation peptide) series of peptides developed through a collaboration between the groups of Mike Gait and Matthew Wood (Betts et al. 2012, 2015; Yin et al. 2011; Chwalenia et al. 2022). The latest versions of these peptides have been optimised to minimise renal toxicity without compromising exon skipping activity. It remains to be demonstrated whether PGN-EDO51 remains safe after prolonged treatment. Similarly, the PPMO compounds of Entrada are based on a cyclic peptide design, although more detailed chemical details of the structures of these compounds are not publicly available. Preliminary data from the phase 1 trial of ENTR-601-44 targeting *DMD* exon 44 (ENTR-601-44-101) in healthy volunteers suggested that the drug is safe, with exon skipping levels of up to 0.65% reported (Entrada therapeutics|Entrada therapeutics reports positive preliminary data in healthy volunteers from phase 1 ENTR-601-44-101 trial for Duchenne muscular dystrophy Available from: <https://ir.entradatx.com/news-releases/news-release-details/entrada-therapeutics-reports-positive-preliminary-data-healthy>). A phase 2 trial in amenable DMD patients is expected to be initiated in 2025.

Several PMO-bioconjugation strategies have been explored which target the ubiquitously-expressed transferrin receptor 1 (TFRC, Trf1), in order to promote uptake in skeletal and cardiac muscle tissues (Roberts et al. 2023). Avidity Biosciences is developing antibody oligonucleotide conjugates (AOCs) consisting of a monoclonal antibody targeting TFRC and a PMO designed to skip *DMD* exon 44 (i.e., Delpacibart zotadirseb, del-zota, or AOC 1044). This compound is currently under investigation in a phase 1/2 clinical trial (NCT05670730/EXPLORE44) with interim findings showing exon skipping levels of 1.5% after a single 10 mg/kg dose in healthy volunteers (Avidity biosciences reports positive data demonstrating AOC 1044 delivers unprecedented concentrations of PMO in muscle following a single dose in healthy volunteers

from phase 1/2 EXPLORE44TM trial for Duchenne muscular dystrophy Available from: <https://www.prnewswire.com/news-releases/avidity-biosciences-reports-positive-data-demonstrating-aoc-1044-delivers-unprecedented-concentrations-of-pmo-in-muscle-following-a-single-dose-in-healthy-volunteers-from-phase-1-2-explore44-trial-for-duchenne-muscular-dystrophy-302013456.html>.

Similarly, Dyne Therapeutics are developing DYNE-251, a Fab fragment targeting TFRC conjugated to a PMO designed to skip *DMD* exon 51. Dyne has recently reported positive preclinical findings from their platform technology (known as FORCE) (Desjardins et al. 2022). DYNE-251 is currently under investigation in a phase 1/2 clinical trial (NCT05524883/DELIVER) with interim data showing that patients treated at the 20 mg/kg dose exhibited 8.7% of healthy dystrophin levels (muscle content adjusted) and 3.7% (unadjusted) and functional improvements at 6 months post treatment for patients treated with both 20 mg/kg and 10 mg/kg monthly doses (Dyne reports positive phase 1/2 data for Duchenne agent DYNE-251 Available from: <https://www.neurologylive.com/view/dyne-reports-positive-phase-1-2-data-duchenne-agent-dyne-251>; Dyne therapeutics presents data at world muscle society congress highlighting promise of FORCETM platform to address underlying causes of neuromuscular diseases Dyne Therapeutics, Inc. Available from: <https://investors.dyne-tx.com/news-releases/news-release-details/dyne-therapeutics-presents-data-world-muscle-society-congress>).

A discrepancy between RNA and protein levels has been a common observation across clinical programmes (Roshmi and Yokota 2023; Tillinger et al. 2023). For example, viltolarsen induced an 43.9% increase in exon-skipping which resulted only in production of 5.9% of the healthy dystrophin levels (Roshmi and Yokota 2023). It is well known that RNA and protein levels correlate poorly in general (Ideker et al. 2001; Roberts et al. 2015), although for genetic therapies a close relationship is often taken for granted. However, it is important to note that such inconsistencies between levels of corrected transcripts and restored dystrophin protein may be a consequence of technical issues related to assay design, the timing of sample collection (i.e., there potentially being a lag between RNA level correction and the accumulation of dystrophin protein), differences in protein stability when comparing full-length healthy dystrophin with internally-deleted pseudodystrophins restored by exon skipping, or potentially other pathobiological features which may cause an obstacle to therapeutic success that are as yet under-appreciated (e.g., post-transcriptional repression of dystrophin expression via *trans*-acting factors in dystrophic muscle).

Competition from microdystrophin gene therapy

Up until 2023, ASO-based drugs were the only option to treat the underlying cause of DMD. This changed with the approval of the delandistrogene moxeparvovec (elevidys, SRP-9001), an AAV-based gene replacement therapy developed by Sarepta Therapeutics (Hoy 2023). This drug encodes a minigene version of dystrophin, known as microdystrophin, in which large regions of the dystrophin open reading frame have been deleted in order for it to be small enough to be packaged into an AAV genome (Roberts et al. 2023). A phase 2 trial of elevidys demonstrated restoration of almost 40% of microdystrophin protein levels in patients at week 12 post-infusion (assessed by western blot) (Mendell et al. 2023). Despite relatively high levels of microdystrophin, improvements in clinical endpoints have so far been very modest. The strongest evidence for any benefit was in the 5–6 year age group, but the effect was much less apparent in older boys (Mendell et al. 2023). This raises the important question of whether microdystrophin(s), even when expressed at relatively high levels, are capable of replacing sufficient dystrophin function to allow meaningful clinical benefit.

Notably, in a parallel microdystrophin study sponsored by Genethon, investigators observed up to 85% of dystrophin positive myofibres by immunofluorescence 8-weeks post injection (First clinical trial results of gene therapy (GNT0004) for Duchenne muscular dystrophy presented at international myology (2024) Congress Available from: <https://www.genethon.com/first-clinical-trial-results-of-gene-therapy-gnt0004-for-duchenne-muscular-dystrophy-presented-at-international-myology-2024-congress/>). However, the gene replacement approach is likely to result in diminished pseudodystrophin production with time due to vector genome loss, epigenetic silencing of the transgene, and the dilution effect of non-transduced nuclei as a consequence of muscle growth and repair. Notably, repeat administration with AAV is currently challenging as the patient is effectively immunised to the treatment after the first dose (Mendell et al. 2023). Moreover, AAV poses a substantial safety risk with some clinical trials previously reporting fatal immune adverse effects using high doses of the viral vectors (including with the Pfizer microdystrophin) (High-dose AAV gene therapy deaths 2020). As such, the search for efficacious and safe DMD therapeutics is far from over, with ASOs, gene therapy, utrophin (a natural dystrophin paralogue) upregulation (Tinsley et al. 2011), and CRISPR-Cas9 (Tabebordbar et al. 2016; Hanson et al. 2022; Long et al. 2016) all showing promise (Roberts et al. 2023). While most of these strategies mimic dystrophin protein (gene replacement) and target the dystrophin mRNA (ASOs) or gene (CRISPR-Cas9), numerous aspects of dystrophin biology remain underexplored and poorly understood. For example, relatively little is known

about the specific mechanisms governing correct dystrophin localisation to the sarcolemma. Our group has shown that the pattern of dystrophin coverage across the sarcolemma is an important consideration for effective restoration of muscle integrity (Westering et al. 2020), and that various therapeutic interventions restore dystrophin with distinct distribution patterns (Westering et al. 2020). Specifically, ASO-mediated exon skipping induced a uniform pattern of dystrophin distribution, whereas CRISPR-Cas9-mediated exon deletion resulted in a patchy pattern of dystrophin at the sarcolemma (Chwalenia et al. 2022; Hanson et al. 2022; Morin et al. 2023). As such, ASO therapy may present an advantage over other modalities in some cases, in terms of the uniformity of sarcolemmal dystrophin coverage post treatment.

Conclusions

In conclusion, while great progress has been made in the field of ASO-mediated exon skipping therapies for DMD, there is still a need for better drug delivery and improved efficacy. These challenges may be addressed through the use of novel ASO chemical modifications and bioconjugation.

In this special *festchrift* issue, we recognise the career achievements of Professor Jenny Morgan. While Prof Morgan's contributions to the field of satellite cell biology and myoblast transfer are widely recognised as world leading (Morgan et al. 1990, 1989; Watt et al. 1987; Partridge et al. 1989; Boldrin et al. 2015), she has also made key contributions to the field of ASO-mediated exon skipping. Prof Morgan was a founding member of the MDEX consortium, which was instrumental in the development of eteplirsen, and was a major contributor and co-author on the first studies to demonstrate dystrophin exon skipping in human DMD patient muscle (Kinali et al. 2009; Cirak et al. 2011). In addition, she has made numerous important contributions to this field, including development of a standardised method to assess exon-skipping in eteplirsen-treated patients and, more recently, in relation to the clinical evaluation of the exon 53 skipping compound golodirsen (Rossi et al. 2023; Anthony et al. 2012). An immortalised myoblast cell line derived from the *mdx* mouse (H2K-*mdx*) developed by Prof Morgan has become a widely-used cell model for screening exon skipping compounds that is still in use today (Morgan et al. 1994). Collectively, these contributions have been critical for the clinical realisation of exon skipping as a highly novel DMD therapeutic modality, and form the foundations on which future developments are built.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests M.J.A.W. is a founder, shareholder, and consultant for PepGen Ltd, a biotech company that aims to commercialise PPMO technology. The other authors declare no competing interests.

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