

# RESEARCH STRATEGY 2017

#### PREFACE





Action Duchenne is delighted to inform you of our priorities for the next three years through the publication of our latest research strategy. As one of the longest standing parent-led Duchenne organisations, we have a proven track record of funding cutting-edge research and led the way with the first ever Duchenne-specific research strategy in 2013. We are delighted to have seen progress in all of the main areas we identified and this latest publication is a forward thinking strategy, building on what we set out four years ago. We very much see this as a vital piece in the puzzle of progressing areas of unmet need in Duchenne, in collaboration with all of our partners. We wish to thank our fantastic Duchenne community for all the support and inspiration you have given us over the last 15 years. Your vital contribution has meant that we continue to be at the forefront of these developments.

Diana Ribeiro, CEO Action Duchenne

The publication of our latest research strategy is an important step in the journey which Action Duchenne first embarked on back in 2001. Our overarching objective as a parent-led charity has always been to take a leading role in supporting research for potential treatments for those living with Duchenne and the delivery of a cure for this devastating condition. We would not have the array of clinical trials and emerging treatments that we see today without the financial support and campaigning undertaken by organisations such as Action Duchenne.

We are proud to have taken a leading role in the MDEX consortium which secured early government funding for exon skipping research back in 2003. We subsequently allocated significant funds to the initial Exon 51 trials and this year, supported the first ever gene therapy trials in the UK, which will see the delivery of a micro-dystrophin gene injected into the patient. We were also at the forefront of securing the Managed Access Agreement for Translarna and know that securing access to new treatments to families without delay is an absolute priority whenever research shows promise.

Our track record in identifying and funding the most promising new research is matched by the wonderful commitment and generosity of the Duchenne community and its supporters. We are also fortunate to have such a hardworking team of staff, trustees and volunteers, many of whom are parents and relatives of those living with Duchenne.

We are looking forward to the launch of our new research strategy at Action Duchenne's 15th international research conference in the knowledge that the translational research we have always supported is now opening up so many opportunities for participation in clinical trials across the UK and beyond.

Janet Bloor, National Chair, Action Duchenne Mark Silverman, National Vice-Chair, Action Duchenne



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#### **FOREWORD**





I am delighted to support the Action Duchenne strategy at such an exciting time in the development of therapies for DMD. There are significant challenges but with the focus on patient registries, support for new modalities, access to treatment and clinical trials, Action Duchenne is well placed to continue to be a driving force for an effective treatment for DMD boys of all ages.

Professor Dame Kay E. Davies CBE, FRS, FMedSci

As little as ten years ago, research and therapy development for Duchenne muscular dystrophy was sparse, poorly-funded and on the whole, far from clinical application. Pioneering researchers, now so familiar to us, are to be thanked for doggedly pursuing research studies in the field and progressing many fundamental breakthroughs in understanding. The families and young people living with Duchenne who took part in early research and clinical experiments did something nothing short of heroic. The early patient organisations, supported and in many cases led, by very determined families on both sides of the Atlantic, are to be thanked for recognising the worth of early research and making precious funds available. In this last decade, commercial pharmaceutical R&D has taken centre-stage and thankfully has the stomach to take on bigger trials, drug registration applications and win reimbursement debates. Many individuals within these organizations and at clinical trial centres across many countries, have contributed to where we are now.

Duchenne has one name but therapy solutions are diverse. Today, we have better understanding of the fundamental science of Duchenne, but not enough funds to pursue all avenues. Libraries of samples and patient data are proving invaluable, and must be curated to keep pace with the future possibilities of clinical and translational research. We have clinical trial opportunities, but not for all. We have realistic hope that new and future therapies will slow the disease and help the young enjoy adult lives, and in that context, the growing needs of a growing Duchenne adult population are to be understood and addressed.

Dr Tina Flatau and Jo McCauley Action Duchenne Research Committee, Research Strategy lead members





As an adult living with Duchenne, current progress in research has definitely picked up pace within the last ten years, with real hope of treatments reaching the clinic in the near future. The community has begun to realise that individuals with Duchenne are living longer, with the need to tailor treatment for both ambulant and non-ambulant individuals being more important than ever. The new Action Duchenne strategy reflects this change supporting innovative research and current clinical trials, with a real focus on improving the quality of life of all those affected.

#### **Benjamin James** Member of Action Duchenne **Research Committee**

### **OVERVIEW**

The primary aim of Action Duchenne is to support innovative research that will one day lead to a cure for all those living with Duchenne muscular dystrophy (DMD). In 2013, Action Duchenne led the way with the first research strategy for the international Duchenne community. Our strategy identified groundbreaking advances in potential novel treatments which we were looking to support, including genetic replacement strategies. The four main recommendations were widely endorsed by the healthcare and patient community.

Action Duchenne has a proven track record in identifying promising areas of research, contributing towards advances in the field, whether this is translational research or clinical trials. Many of the significant advances have originated from initial Action Duchenne seed funding. For example, the MDEX consortium, the original think tank for exon skipping, originated in the UK with our involvement. The development of the UK DMD Registry, a significant part of the global TREAT-NMD global database, was another example of some of the pioneering work led by Action Duchenne. The UK DMD Registry collects most genetic data and a range of patient-centred information and is used to enhance clinical trial information and aid patient participation. The data has been used for studies published in high impact scientific peer-reviewed publications as well as for health economic purposes.

From the trials conducted to date, we can see a need to widen access to trials, to improve the applicability and precision of outcome measures, and to continue to provide high quality registry data. Action Duchenne intends to continue its investment in this valuable resource and sees an increasingly important role for the registry in driving international clinical trial development.

Action Duchenne has played a leading role in educating the patient and healthcare professional community. The charity has brought together the brightest minds across the sector enabling vital information to be shared and collaboration to occur. We continue to drive innovation in translational research developments, through vital partnerships with other organisations. In March 2017, Action Duchenne announced significant funding towards "UNITE-DMD". This international collaboration will assess the safety of gene therapy in Duchenne, in a phase I/II clinical trial that will take place in both the UK and France. These may be the first gene therapy trials for Duchenne in the UK and UNITE-DMD will be vital in testing the safety of this technology.

We have seen significant progress in potential clinical management strategies, improved and effective use of corticosteroids and development of novel treatment choices aimed at slowing disease progression. Action Duchenne is delighted with the progress made, but there are significant ongoing areas of unmet need for the wider Duchenne community. Action Duchenne is committed to fund state-



of-the art research that will lead to stepwise changes and clinically meaningful differences for those living with the condition and in the near future the hope of a cure.

Action Duchenne will re-evaluate the core strategic aims of the research strategy, in line with the progress made in three years time.

"Action Duchenne has a proven track record in identifying promising areas of research, contributing towards advances in the field, whether this is translational research or clinical trials."

## RECOMMENDATIONS

Considering the recent developments in the field, particularly in the paediatric setting, the challenges of quality of life for teenagers and adults living with Duchenne, have remained poorly unaddressed. A key focus of Action Duchenne will therefore be to facilitate access of translational research and clinical trial opportunities for the entire Duchenne population, beyond the paediatric setting and into adulthood.

Action Duchenne intends to fund and prioritise meaningful enablers in the following main areas:

- Promising and sound experiments and hypotheses, led by Duchenne investigators and other healthcare professionals, with the potential to generate novel and relevant data together. The wider healthcare community will be encouraged to think innovatively with new ideas, particularly with proposals that can progress into a late preclinical stage. The outcomes of which will be published and shared with the wider Duchenne community.
- Investment in the updated DMD Registry, in both capacity and in the tool itself, with a geneticist strategically leading its development and also leading the way with other databases in the UK. The new and updated UK DMD registry will collect more data, garner more support and input and ultimately assist with clinical trial recruitment, but also collecting more patient reported outcome measure data, which may be used for other clinical trials, for health economic reasons and to drive further Duchenne developments.
- The development of longitudinal outcome measures and biomarkers and the collection or application of robust natural history data. These will be identified by experts within the Duchenne and rare disease field with outcome measures that span the entire spectrum of the population, such as the performance of upper limb (PUL). This will play a crucial role in collecting good quality data for clinical trials, thus incentivising more companies to look at a wider population and with further investment, allow more centres to participate in clinical trials.
- Continuing our long-standing involvement in supporting the best possible multidisciplinary standards of care in the paediatric and adult populations. We will support timely intervention in an accident and emergency setting and the prevention of avoidable complications, ultimately leading to an extended and better quality of life.



Co-funding of other projects, as part of a consortium, in areas
of tissue collection and biobanking, to establish a viable bank of
tissue from patients, family members and controls. The biobank
with long-term investment, as well as infrastructure, could also
collect longitudinal biological samples (serum, plasma and urine).
These will elucidate disease evolution and the identification
of biomarkers to systematically monitor disease progression
and respond to experimental therapies. Samples in the tissue
bank could be linked with high quality and up-to-date deeply
phenotyped patient - as well as functional data, using validatable
outcome measures. The tissue bank will need to be accessible for
all partners involved to drive further innovation and collaboration.

## **POTENTIAL TIMELINES**

YEAR 1	SUPPORT EARLY STAGE TRANSLATIONAL RESEARCH	<ul> <li>Invest in the UK DMD registry, in both capacity and in making plans for the development of the registry, to collect more data that can be used for clinical trial recruitment and for patient reported outcome measures as well as health economic data</li> <li>Identify new plausible scientific hypotheses to fund, which may have merit in Duchenne and lead to state-of-the art treatment advances</li> <li>Engage young researchers, the rising stars in Duchenne, increase the knowledge base and therefore, further developments in this area</li> <li>Provide a forum where early stage science is pitched to a biopharma and investor audience for investment in new areas of translational research, the generation of novel data</li> </ul>
YEAR 2	SUPPORT DRUG DEVELOPMENT AND TRIAL CAPACITY	<ul> <li>Support natural history data collection</li> <li>With expert input, initiate at least one programme for development of a novel end point, applicable to the whole Duchenne population</li> <li>As above, collecting the novel data from the plausible endpoints, involving industry and regulator stakeholders</li> <li>Engage young researchers, the rising stars in Duchenne, increase the knowledge base and therefore, further developments in this area</li> <li>As above, engaging young scientists and healthcare professionals in the field. Expanding expertise, generating novel ideas and supporting infrastructure</li> </ul>
YEAR 3	DEVELOP CLINICAL TRIAL OPPORTUNITIES FOR TEENAGERS/ADULTS	<ul> <li>Report initial progress from a novel/non-ambulant applicable end point programme</li> <li>If not progressed as an outcome measure, support of the development of non/minimally invasive clinical trial biomarkers as surrogate outcomes for clinical work</li> <li>Assist in the promotion of tissue collection and biobanking samples, with other partners</li> <li>Consider research actions to support goals for increased life expectancy</li> </ul>

## BACKGROUND

Duchenne muscular dystrophy is caused by either inherited or spontaneous nonsense (unreadable code) mutations in the gene for the protein dystrophin, a critical element of the muscle stabilising DAPC (dystrophin-associated protein complex). A cornerstone of early clinical trials was the assumption that for DAPC treatments targeting the primary lack of dystrophin, the best biological measure or biomarker - would be to assess improvement in muscle quality, or at least measure the change in dystrophin levels in muscle fibres. This methodology requires a muscle sample (biopsy), tissue that will not regrow. Samples are taken to assess leg or arm muscles; cardiac (heart) muscle for instance is never assessed in this way. Various methods of assessing dystrophin expression and the condition of sliced muscle biopsies have never delivered reliable results. Using the current methods, a single tiny biopsy sample is not indicative of the quality of an entire muscle, nor all muscle in a person. Researchers have particularly highlighted the need to target and assess heart muscle performance; the inability of oligonucleotide (exon skipping) drugs to reach the heart is seen as a potential issue that may be addressed by other approaches such as utrophin upregulation. The limitations and undesirability of routine biopsies are wellrecognised, and the development of more precise, reliable and less invasive biomarkers of disease progression is a key enabler to better quality and more inclusive clinical trials.

Notably, clinical studies have almost exclusively enrolled younger children often targeting the optimum age window around 6-10 years. Each clinical study must have a key measure or 'primary end point' that is acceptable to regulators. In Duchenne, the 6 minute walking distance (6MWD) test became adopted as a 'validated' end point (it had been previously accepted by the FDA in separate studies for people with COPD or chronic obstructive pulmonary disease). The use of this key test excluded young children from trials, who were thought unlikely to comply correctly with the test, and young people and adults living with Duchenne who could not walk unaided or who were no longer ambulant. The 6MWD test is at its best when measuring the steep decline in walking ability that typically occurs in a short timeframe during the early teens, but variable layout of the test 'course', performance motivation and energy levels at the start of the test are all variables that reduce the precision of this measure in ambulant Duchenne subjects.

Ambulant trials can have a wider range of end points. The North Star Ambulatory Assessment and various timed function assessment are all widely used but to date, have not been accepted by regulators as a primary endpoint. The major goal is to get agreement in principal for a novel endpoint that can reasonably predict clinical outcome and in turn, generate further data. Across the wider population, there is progress in promoting magnetic resonance imaging (MRI) as a trial end point that correlates to muscle force, performance and disease progression [1]. Alternative end points and measures of physical ability still need development and validation as sources of reliable data across the all study populations, patient registries and natural history data must maintain pace with end point developments.



"Notably, clinical studies have almost exclusively enrolled younger boys often targeting the optimum age window around 6-10 years."

## **CLINICAL RESEARCH**

We are now seeing significant growth in Research and Development (R&D) and clinical trial options, to the extent that patients and their families struggle to make informed trial choices.

Many trials are underway and there is a short but significant list of treatments approved in Europe and the US.

- · Treatments approved for treating Duchenne include Eteplirsen (to skip exon 51) in the United States (under review in Europe), Ataluren/Translarna in Europe (review discussions continuing in the USA) and Deflazacort (Europe and now USA). We are not yet at the stage of having cures available, but the rich mixture of technologies in R&D raise the prospect of genuine breakthroughs in the not too distant future. Many companies and institutions are leading R&D efforts, however there is a high cost for pioneering development studies. These in turn translate into high treatment costs and therefore present a hurdle for reimbursement. Patient organisations and academic institutions have played a hugely important role in enabling clinical trials to happen, whether through fundamental disease research, endpoint developments, registries and direct funding of technologies as well as keeping Duchenne on the political and healthcare agendas.
- · The Duchenne population ranges in age from screened newborns to adults, but clinical trials to date have largely enrolled only from limited sub-groups. Widening the scope for studies requires a range of markers and end points that can be applied across the population to all ages, specific to the natural history stages of changing muscle status rather than the ability to correctly perform physical tests. Commercial developers have tended to leave academic researchers and patient organisations to establish new methodologies, supporting data sets and infrastructure such as centres of excellence and biobanking.
- · Adults living with Duchenne have been described in the literature as an 'emerging' and 'unforeseen' population [2]. The 2014 ENMC workshop [3] marked some formal recognition that older subjects have a distinct set of requirements, not just relating to disease and care needs. Some disease aspects overlap and muscle changes with age and subsequently the hope is that therapy developments will rapidly extend to the adult population.



"We are not yet at the stage of having cures available, but the rich mixture of technologies in R&D raise the prospect of genuine breakthroughs in the not distant future."

#### **ANNEXES**

#### HIGHLIGHTS OF DUCHENNE TREATMENTS IN DEVELOPMENT

Duchenne therapy approaches in development that Action Duchenne may fund, can be broadly categorized as:

- 1. Restoration of the DAPC complex
- 2. Improve muscle condition and reduce the consequences of muscle stress

#### 3. Gene therapies

[Author's note: clinical trials news and data from public-domain sources. Reference citations added for information only.]

#### 1. Restoration of the DAPC complex

Most progress has been made with treatments aimed at correcting the underlying genetic fault that interrupts healthy dystrophin production, acting at the stabilizing muscle membrane structure, the DAPC.

Nonsense mutations - Ataluren/Translarna gained a conditional marketing authorisation in Europe in 2014 based on a phase 2b trial, for the treatment of ambulant patients (>=5 years) with Duchenne caused by a nonsense mutation. Ataluren, classified as a readthrough compound (RTC), suppresses nonsense mutations and is potentially applicable to 11-13% of all patients if it is eventually used for all Duchenne age groups. Studies have included Becker muscular dystrophy patients. The drug has been granted FDA orphan drug designation and discussions continue regarding USA market approval. A number of subsequent RTC drugs such as RTC13 have been identified and are undergoing preclinical evaluation [4].

Exon-skipping - Eteplirsen/Exondys51 a morpholino antisense oligonucleotide, achieved conditional (accelerated) FDA approval in September 2016 in the United States, contingent on another confirmatory study. In Europe, Eteplirsen is currently under review with the EMA's CHMP and is due to start NICE HST (highly specialized technology) evaluation in October 2017. Exon-skipping therapies are mutation-specific and aim to produce a shortened but partly functional dystrophin gene. Eteplirsen targets confirmed mutations which can be corrected by exon-51 skipping, and is applicable to about 13% of the Duchenne population. Other exon-skipping treatments also in development using the same technology, include mutations amenable to skipping exons 8, 35, 43, 44, 50, 55 and 52, with exon 53 and 45-skipping drugs in clinical development. Another morpholino antisense oligonucleotide in development is NS-065/ NCNP-01 aimed at mutations amenable to exon 53 skipping and now in a Phase II clinical study in Japan.

So-called 'next generation' exon-skipping WVE-210201 is due to enter clinical development in 2017, using nucleic acid-based exon skipping technology. It may have potential to offer more effective dystrophin restoration but is still to be proven in humans.

Ezutromid/ SMT C1100 is currently in a Phase II trial as a utrophin modulator. This is a small molecule (non-biologic) drug approach to promote utrophin, functionally similar to dystrophin, to compensate for the absence of dystrophin in potentially 100% of Duchenne patients. As a small molecule, cardiac muscle penetration is a theoretical advantage in terms of heart muscle health, but previous issues with bioavailability are being addressed in the current study.

Human recombinant biglycan /TVN-102 also acts via utrophin, activating a compensatory pathway to increase utrophin levels. The drug has already achieved orphan designation from the FDA and further data will be generated over the next year to file an IND.

#### 2. Improve muscle condition and reduce the consequences of muscle stress

There are very many 'downstream' therapies in development and a number are highlighted here to illustrate the breadth of current work.

The longest-established are the anti-inflammatory corticosteroids such as prednisone/prednisolone and deflazacort. These have all been shown to improve clinical performance and prolong ambulation, but there are well-known long-term side effects to contend with, and there have been concerted efforts to determine optimum treatment regimens [5]. In studies, deflazacort has prolonged ambulation with a better side effect profile than older steroids. Deflazacort has been available in Europe for some time and an NDA in the United States was approved early in 2017. VBP15 is currently in Phase II clinical development as a novel corticosteroid with enhanced potency and lower side effects [6].

Idebenone/Raxone is a short chain benzoquinone adenosine triphosphate production modulator and cofactor for NAD(P)H, acting at a mitochondrial level to reduce oxidative stress and elevate energy levels in muscle. The drug has completed Phase II and Phase III studies and shown significant benefit in preserving respiratory function. This received a Negative Opinion from the CHMP for its Marketing Authorization Application, in September. Santhera (who develop the drug) plan to appeal this opinion and seek re-examination.

To promote muscle health, there are selective androgen receptor modulators (SARMs) such as DT-200, which has completed a number of Phase I studies but not been tested yet in Duchenne patients. DT-200 is designed to be selective for skeletal muscle, to promote muscle growth and strength with fewer excess androgen side-effects. Another approach is to use the oestrogen receptor modulator, tamoxifen. In a mouse model of Duchenne, this drug showed remarkable improvements in skeletal, cardiac and diaphragm muscle strength and performance. Thought to be due to an oestrogen-receptor dependant mechanism in muscle, treated mice had lowered CK and improved levels of various structural muscle indicators. An open-label study to treat Duchenne boys with tamoxifen started in 2016.

A Phase III study is in progress with tadalafil, a phosphodiesterase5 inhibitor, aimed to improve muscle condition by stimulating nNOS (nitric oxide synthetase) to increase blood flow to affected muscle.

Specifically targeting fibrosis, a Phase II clinical study is ongoing with FG-3019, a connective tissue growth factor (CTGF) monoclonal antibody in non-ambulatory Duchenne patients. The study aims to investigate useful endpoints such as preserving or improving pulmonary function in non-ambulatory Duchenne patients, sustaining and regaining upper body muscle strength and slowing or reversing cardiomyopathy. Still at the preclinical stage, AT-300 is a modulator of stretchactivated calcium channels, aimed at restoring calcium regulation in cardiac and skeletal muscle.

Blocking NFkB, a promotor of muscle degeneration and inflammation, edasalonexent/CAT-1004 is undergoing Phase I/II studies with MRI (T2 and fat fraction) as primary end point. Another experimental drug, NBD peptide, also aims to block NFkB and is at the preclinical stage.

Histone deacetylase inhibitor (givinostat/ITF2357) targets the muscle repair process and aims to boost muscle strength. An openlabel Phase II study is nearing completion in Italy and a placebocontrolled Phase III study is due to start this year.

Myostatin is a protein that restricts muscle overgrowth, and myostatin inhibitors are in clinical development for Duchenne, with potential applicability for all patients. Domagrozumab/PF-06252616 has completed enrollment of a Phase II study, and BMS-986089/ RG6206 is in a Phase II/III clinical trial currently recruiting. A Phase I/II gene therapy clinical study in Duchenne to assess AAV delivery of follistatin 344, is due to complete in September 2017. The gene therapy, administered by injection to the legs, is aimed at increasing muscle strength and preventing muscle wasting and fibrosis. Encouraging interim results from an ongoing Becker study have already been reported for follistatin.

There are a number of developments to address heart muscle degeneration. The flavonoid antioxidant epicatechin stimulates mitochondria and muscle regeneration, and is being dosed to nonambulant Duchenne subjects in a US trial to investigate its effects specifically on cardiomyopathy. Also in the US, a Phase III study is ongoing to look at potential cardiac benefits in Duchenne using aldosterone inhibitors spironolactone and eplerenone, both already used to treat heart failure in the general population. Another Phase II-III clinical trial is underway in the US to investigate the effects of dosing the natural antioxidant coenzyme Q10 (CoQ10), particularly active in heart muscle cells, with or without spironolactone, to patients with Duchenne, Becker and Limb Girdle muscular dystrophy.

A 2017 review of pharmacological advances for in Duchenne surveys the various drug treatments in research and on the market. [7]

#### 3. Gene therapies to correct the genetic fault

Gene therapies can be sub-classified as: gene replacement; gene editing; and gene renewal [8].

In terms of gene replacement (also referred to as triple-transsplicing), AAV viral gene therapies are promising but still at the experimental trial stage for Duchenne. These approaches can use a mini-or micro-dystrophin gene slotted into an adeno-associated virus (AAV) vector. The AAV has been used therapeutically and with success in other diseases. Using a piece of the dystrophin gene means that a truncated, Becker-like benefit could be achieved, as potentially with exon-skipping. Early studies with local (arm) administration have shown that viral therapy in Duchenne can be safe with careful immunosuppression but trials have yet to show that systemic (whole body) dosing can be accomplished. A trial of local administration of the AAV-MCK-µDys vector is ongoing in the USA led by Professor Jerry Mendell (ref NCT02376816). A recently completed study in a canine model of Duchenne using AAV vector SGT-001 was deemed successful and promoted dose-dependent micro-dystrophin production for up to two years after administration by injection. The developers plan a human trial starting in 2017.

BMB-D001 is the mini-dystrophin gene therapy based on rAAV technology, for Duchenne. The therapy is just entering phase I/II trial. UNITE-DMD is a four-year collaboration into gene therapies for Duchenne, led in France and the UK by international researchers and supported by MDUK, Action Duchenne and AFM-telethon and pharmaceutical companies. The programme aims to support preclinical development of gene therapies and a phase I/II trial.

Gene editing There are several systems of nuclease-based gene editing, of which CRISPR (clustered regularly spaced palindromic repeats) is the best known, but other systems such as transcription activator-like effector nucleases (TALENs), meganucleases (MN) and zinc finger nucleases (ZFNs) are also used. Research and preclinical successes to date have included: rescue frame shift mutation in a dog model; expression of full-length dystrophin mRNA in human Duchenne myoblast cells; target insertions-deletions of different sizes and restore the reading frame; remove exon51 from a sample human transcript, restoring reading frame [9]; TALENs and CRISPR to achieve a permanent restoration of Duchenne reading frame in patient-derived muscle cells [10]. Both muscle cells and muscle-precursor satellite cells should be targeted for lasting effect. In a study reported in 2016, muscle satellite cells were successfully edited, opening the possibility of correcting mutations in muscle by replacement from the subject's own (edited) satellite cells [11]. This would improve clinical function and muscle quality by gradual replacement. According to Professor Jerry Mendell, CRISPR-mediated removal of one or more exons from the genomic DNA could benefit up to 80% of Duchenne patients, and early treatment would be advocated alongside effective newborn screening [12].

In practical terms, there are some crucial elements to validate for gene editing to be adopted. One of these is the reliable and speedy cleavage of the targeted DNA and another is the validation of nonspecific or off-target cleavage of the human gene. In February 2017, Cure Duchenne's technology investment arm invested USD\$5million seed funding to work on CRISPR technologies to cure Duchenne alongside other neuromuscular diseases.

Stem cell technology reprograms adult cells to have the characteristics of stem cells (induced pluripotent stem cells, or iPS cells).

One stem cell therapy in the clinic is CAP-1002 in a phase I/II clinical trial for Duchenne patients with cardiomyopathy, where improvements in heart and arm function are being measured. The company is cautiously optimistic about results to date and they plan a repeat dose trial later in 2017, having received rare paediatric disease designation and orphan drug designation.

Still at the research stage, scientists at UCLA in the United States have combined iPS technology with gene editing, making stem cells from Duchenne subjects (using skin cell samples) and then editing a large section of the gene using CRISPR, correcting the gene fault before re-transplantation into a Duchenne mouse model [13]. The Duchenne muscle regenerated with the dystrophin gene corrected and dystrophin production was restored. This technology could be applicable to up to 60% of Duchenne subjects and future clinical development will be followed with interest.

## **PUBLICATIONS CITED:**

[1] Ricotti V, Evans MRB, Sinclair CDJ, Butler JW, Ridout DA, Hogrel J-Y, et al. (2016) Upper Limb Evaluation in Duchenne Muscular Dystrophy: Fat-Water Quantification by MRI, Muscle Force and Function Define Endpoints for Clinical Trials. PLoS ONE 11(9): e0162542. https://doi. org/10.1371/journal.pone.0162542

 J. Rahbek, B. Werge, A. Madsen, J. Marquardt, B.F. Steffensen,
 J. Jeppesen. (2005) Adult life with Duchenne muscular dystrophy: observations among an emerging and unforeseen patient population.
 Pediatr Rehabil, 8 (2005), pp. 17-28.

[3] Rahbek, Jes et al. Neuromuscular Disorders, Volume 25 (2014) Issue 9 , 727 - 738 . 206th ENMC International Workshop: Care for a novel group of patients – adults with Duchenne muscular dystrophy Naarden, The Netherlands, 23–25 May 2014.

[4] Namgoong, J. H. and Bertoni, M. (2016). Clinical potential of ataluren in the treatment of Duchenne muscular dystrophy. Degenerative Neurological and Neuromuscular Disease 2016:6, 37-48.

[5] Guglierii, M. et al (2017). Developing standardized corticosteroid treatment for Duchenne muscular dystrophy. Contemporary Clinical Trials 58 (2017) 34–39.

[6] Janelle M. Spinazzola & Louis M. Kunkel (2016) Pharmacological therapeuticstargeting the secondary defects and downstream pathology of Duchenne muscular dystrophy, Expert Opinion on Orphan Drugs, 4:11, 1179-1194, DOI: 10.1080/21678707.2016.1240613

[7] Guiraud, S and Davies, K. (2017). Pharmacological advances for treatment in Duchenne muscular dystrophy. Current Opinion in Pharmacology 2017,34:36–48 [8] Abdul-Razak H, Malerba A and Dickson G. (2016) Advances in gene therapy for muscular dystrophies [version 1; referees: 2 approved] F1000Research 2016, 5(F1000 Faculty Rev):2030 (doi: 10.12688/ f1000research.8735.1)

[9] Ousterout DG, Kabadi AM, Thakore PI, et al. (2015). Correction of dystrophin expression in cells from Duchenne muscular dystrophy patients through genomic excision of exon 51 by zinc finger nucleases. Mol Ther. 2015; 23(3): 523–32.

[10] Maggio I, Stefanucci L, Janssen JM, Liu J, Chen X, Mouly V, Gonçalves MA. (2016) Selection-free gene repair after adenoviral vector transduction of designer nucleases: rescue of dystrophin synthesis in DMD muscle cell populations. Nucleic Acids Res. 2016 Feb 18; 44(3): 1449-70

[11] Tabebordbar M, Zhu K, Cheng JK, et al. (2016) In vivo gene editing in dystrophic mouse muscle and muscle stem cells. Science 2016; 351:407-411

[12] Mendell, J. and Rodino-Klapac, L. (2016) Duchenne Muscular Dystrophy: CRISPR/Cas9 treatment. Cell Research (2016) 26:513–514. doi:10.1038/cr.2016.28.

[13] Young CS, Hicks MR, Ermolova NV, Nakano H, Jan M, Younesi S, Karumbayaram S, Kumagai-Cresse C, Wang D, Zack JA, Kohn DB, Nakano A, Nelson SF, Miceli MC, Spencer MJ\*, Pyle AD\*. A Single CRISPR-Cas9 Deletion Strategy that Targets the Majority of DMD Patients Restores Dystrophin Function in hiPSC-Derived Muscle Cells, Cell Stem Cell, 2016; 18: 1-8.

Action Duchenne Epicentre 41 West Street London E11 4LJ

T. 020 8556 9955 E. info@actionduchenne.org

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