JUNE 2020

SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

ADVANCES in Steinert's disease

>myotonic dystrophy type 1
>DM1

Steinert disease or myotonic dystrophy type 1 is a rare disease of genetic origin. It affects the muscles, which become weak (dystrophy) and difficult to relax after contraction (myotonia). It also affects other organs (heart and respiratory systems, digestive system, hormone secretions and nervous system): it is a so-called multi-system disease.

This document has been translated into English from *"Avancées dans la maladie de Steinert"*, published by the French Muscular Dystrophy Association (AFM-Téléthon). It presents news from the past year about research into myotonic dystrophy type 1: international symposia, ongoing clinical trials or studies, scientific and medical publications...

It can be downloaded from the AFM-Téléthon English website, where other information can also be found regarding AFM-Téléthon projects to develop treatments for rare diseases.

WEB www.afm-telethon.com

AFMTÉLÉTHON
INNOVER POUR GUÉRIR

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▪ We would like to thank all the individuals affected by this disease who have taken the time to review or amend all or part of this document.

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Steinert's disease or myotonic dystrophy type 1 (DM1) is a rare neuromuscular disease of genetic origin.
It is caused by abnormal repeats of a small DNA sequence (**CTG nucleotide triplet**), in the ***DMPK*** (dystrophia myotonica protein kinase) gene on chromosome 19. Normally, a repeat containing between 5 to 37 CTG triplets is found in the *DMPK* gene.

▪ In Steinert's disease, the number of these CTG repeats is abnormally high, ranging from 50 up to several thousand triplets. Generally speaking, the greater the expansion, the earlier the onset and the more marked the manifestations of the disease, although there isn't a perfect correlation between the two.

▪ Clinicians distinguish between five forms of the disease depending on the age of the patient when the disease first appears:
- at birth (congenital form),
- at 1 month to 10 years of age (childhood onset form),
- at 10 to 20 years of age (adolescent onset form),
- at 20 to 40 years of age (adult onset form),
- at over 40 years of age (late onset form).

Abnormal messenger RNA disrupts normal muscle cell function

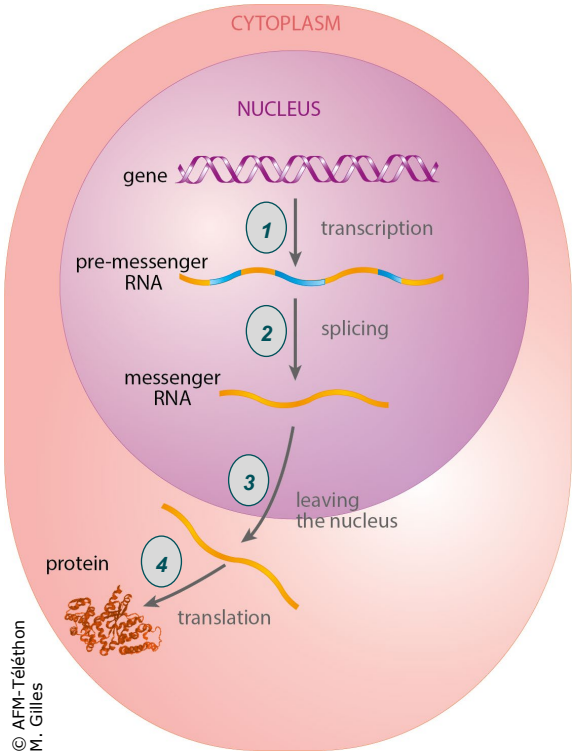
In order to produce the DMPK protein, assembly instructions are needed for these proteins. This is the role of the messenger RNA.
It is produced in the nucleus by copying the *DMPK* gene (transcription).
After maturation (splicing), the messenger RNA leaves the nucleus to serve as a guide in the production of DMPK proteins.

Genetic diseases *are diseases resulting from abnormalities in an individual's DNA, i.e. the information that determines how the body functions biologically. This information is contained in our cells in the form of chromosomes. We inherit this information from our parents and our children inherit it from us. This is why genetic diseases are often familial, i.e. several members of the same family may be affected by the same genetic disease.*

Gene expression *corresponds to the amount of protein produced based on this gene. A strongly expressed gene leads to the production of a large amount of protein, and a weakly expressed gene to the production of a small amount of protein.*

The ***nucleotide*** *is the base unit of the DNA molecule and comes in 4 different types (A, T, G and C). Each combination of 3 nucleotides (triplet or trinucleotide) on the gene corresponds to an amino acid in the protein.*

The role of messenger RNA in protein synthesis



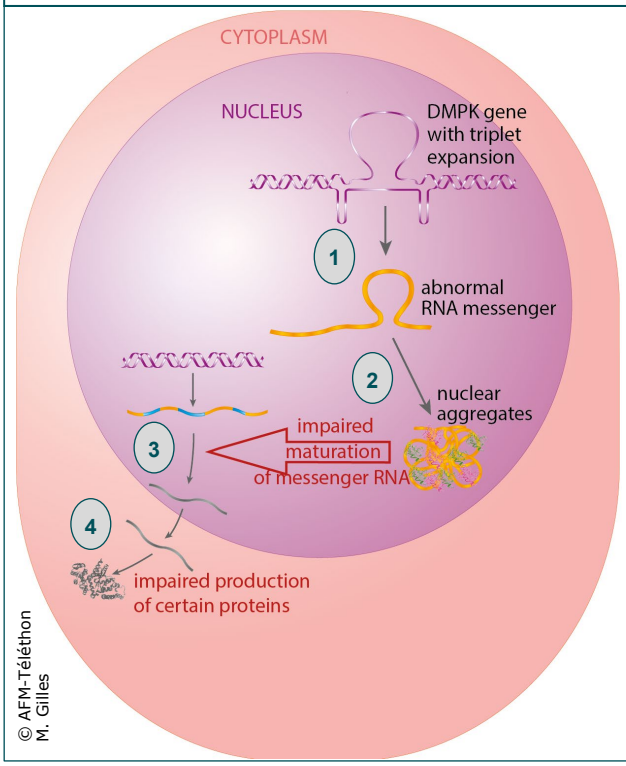
Messenger RNA is a copy of a gene. It contains the information needed to produce a protein.

***1.** Pre-messenger RNA is produced in the nucleus from the DNA sequence (transcription).*
***2.** It undergoes a maturation process (splicing), resulting in messenger RNA that can be used to synthesise a protein.*
***3.** Messenger RNA leaves the nucleus, heading into the cytoplasm where protein synthesis takes place.*
***4.** It is used as a 'template' by the cell machinery to produce a protein (translation).*
Each of these steps is controlled by so-called 'regulatory' proteins.

▪ In DM1, abnormal CTG triplet repeats are also copied in messenger RNA, where they form abnormal stem-loop structures. This mutated RNA no longer leaves the nucleus, but accumulates within the nucleus, creating nuclear aggregates that disrupt the functioning of two proteins in particular:
- the MBNL (Muscleblind-like) family RNA-binding proteins such as MBNL1, MBNL2 and MBNL3, depending on their tissue expression, are sequestered by this abnormal RNA;
- the activity of the CELF family RNA-binding proteins (CELF1 or CUGBP1) is impaired.

Because of their role in the maturation of other messenger RNAs, changes in MBNL and CEFL1 activity cause disruption in the expression of other genes (a snowball effect).

A toxic accumulation of messenger RNA



1. CTG *triplet expansion is transcribed into* CUG *triplets in the* DMPK *messenger RNA, forming abnormal messenger RNA.*
2. *Abnormal DMPK messenger RNA has a tendency to bind to proteins contained in the nucleus and to form aggregates (foci). This binding prevents these nuclear proteins from fulfilling their role.*
3. *Certain regulatory proteins increase in quantity, others decrease, which changes the maturation of many cell messenger RNAs (different from DMPK messenger RNA).*
4. *This disrupts the synthesis of a number of cell proteins.*

For more information about the mechanisms involved in Steinert's disease:
WEB Spotlight on... Steinert's disease research

Key events

An enhanced team to combat myotonic dystrophy - Repeat Expansions & Myotonic Dystrophy (REDs)

Since 2019, four teams have come together at the Institut of Myology, forming a single unified complementary team meant to pool efforts to combat this disease, accelerate research and generate new therapeutic avenues. These four teams were originally led by Denis Furling, an expert in myotonic dystrophy, Geneviève Gourdon, a specialist in CTG triplet repeats, Arnaud Ferry, a specialist in muscle physiology, and Guillaume Bassez, a neurologist and clinical scientist who is experienced in the field of Steinert's disease and who coordinates the DM-Scope registry.

WEB https://www.institut-myologie.org/recherche/myologie-centre-de-recherche/equipe-4-denis-furling/

Uniting the European myotonic dystrophy associations

The year 2019 saw the birth of a new patient association called Euro-DyMA (the European Myotonic Dystrophy Association), exclusively dedicated to type 1 and type 2 myotonic dystrophies and uniting the European patient associations involved in combating these diseases.

This association is headquartered at the Institute of Myology in Paris, a very short distance from the new REDs team. AFM-Téléthon is represented in this new association, in particular via the Steinert's disease (DM1/DM2) Interest Group.

WEB http://euro-dyma.eu/

Euro-DyMA: the European Myotonic Dystrophy Association
Trait d'union - The Steinert's disease (DM1/DM2) Interest Group Newsletter 2020 (Jan)

Medical/scientific conferences and workshops

There are several conferences dedicated to myotonic dystrophy, allowing researchers and clinicians engaged in this disease to exchange information regarding the progress of their research projects and to establish new collaborations.

The international Myotonic Dystrophy Consortium, IDMC-12

The International Myotonic Dystrophy Consortium (IDMC) meets every two years. The 12th edition of the International Myotonic Dystrophy Consortium (**IDMC-12**) took place between the 10th and the 14th of June 2019 in Gothenburg, Sweden. It received financial support from AFM-Téléthon.

Experts in this disease from around the world exchanged information regarding scientific advances in molecular mechanisms, animal models, databases, therapeutic avenues and clinical trials in myotonic dystrophy. A review of ongoing projects has confirmed that the pharmaceutical industry has a growing interest in myotonic dystrophy, with more than a dozen different pharmaceutical companies involved, mostly in programmes that are still at the pre-clinical stage.

WEB https://idmc12.org/

The annual *Myotonic* conference and workshop on central nervous system impairment in DM1.

- The annual conference of the *American Myotonic Association* saw a gathering, over a 3-day period in September 2019, of over 450 individuals,

***Myotonic**, the new name for the Myotonic Dystrophy Foundation – MDF – is an American not-for-profit organisation dedicated to myotonic dystrophy. Its mission is to contribute towards improving the quality of life of patients with myotonic dystrophy and to support research into a treatment for this condition.*
WEB www.myotonic.org

including 160 professionals involved in researching and treating Steinert's disease. Among them were 45 representatives from pharmaceutical companies, demonstrating the level of involvement of the pharmaceutical industry in Steinert's disease research.

WEB https://www.myotonic.org/2019-myotonic-annual-conference

The time for clinical trials has returned, in the United States primarily…

Trait d'union - The Steinert's disease (DM1/DM2) Interest Group Newsletter 2019 (Jan)

- A pipeline of drug candidates currently in development in myotonic dystrophy and arising from academic or pharmaceutical research, is available online, on the association's website:

WEB https://www.myotonic.org/sites/default/files/pages/files/Myotonic-Dystrophy-Drug-Development-Pipeline-as-of-19-May-2020-Full.pdf

- A workshop on central nervous system impairment was organised by the *Myotonic Association*, as part of its annual conference in September 2019.

WEB https://www.myotonic.org/sites/default/files/pages/files/Myotonic-CNSWorkshopAgenda-FNL-2019-08-22.pdf

This topic is regularly addressed during *Myotonic* conferences, and was the subject of a dedicated session in 2017 aimed at individuals suffering from Steinert's disease and their close caregivers. This meeting involved almost 350 participants, and provided a description of the signs of nervous system impairment in DM1 and their impact on quality of life. As with muscle weakness, the families are awaiting an effective treatment for central nervous system impairment, first and foremost for memory lapses and for feelings of "confused" thoughts. This requires, inter alia, a determination of which assessment tools are reliable and relevant in measuring cognitive impairment and its progression, particularly in the context of a clinical trial.

Patient Input to Inform the Development of Central Nervous System Outcome Measures in Myotonic Dystrophy.

White M.

Ther Innov Regul Sci. 2020 (Jan)

*The **central nervous system** consists of the brain (cerebrum, cerebellum and brainstem) and its extension, the spinal cord. It is protected by a bone structure (the neurocranium for the brain and the spinal column for the spinal cord). It analyses sensory information, coordinates movement and transmits commands for the muscles to contract.*

The ENMC workshop: "Myotonic dystrophies, molecular approaches for clinical purposes. Framing a European molecular research network"

- A workshop organised by the ENMC in October 2019 at Hoofddorp (in the Netherlands) brought together almost 30 participants (researchers, geneticists, molecular biologists, clinicians, patient associations including AFM-Téléthon, etc.), with the aim of identifying obstacles slowing down the development of new therapies in myotonic dystrophy and offering solutions to these obstacles.

Steinert's disease is characterised by a very diverse range of symptoms, even within a single family with several members affected. The mechanisms involved in the appearance of a specific symptom are not all known. Increased sharing of knowledge and expertise, and also research tools, would help to better understand the disease mechanisms and identify new therapeutic targets. The various participants would like to see the establishment of a European consortium to strengthen their interactions.

WEB https://www.enmc.org/download/myotonic-dystrophies-molecular-approaches-for-clinical-purposes-framing-a-european-molecular-research-network/

248th ENMC International Workshop: Myotonic dystrophies: Molecular approaches for clinical purposes, framing a European molecular research network, Hoofddorp, the Netherlands, 11-13 October 2019.

Wansink DG, Gourdon G, van Engelen BGM *et al.*

*The **European Neuromuscular Centre** (ENMC) is an international organisation that aims to support research in the field of neuromuscular disease. It regularly organises international meetings bringing together scientists and clinicians on a specific topic.*

WEB www.enmc.org/

Neuromuscul Disord 2020 (Apr)

National and international congresses on neuromuscular disease

The topic of Steinert's disease is also regularly addressed at French and international congresses dedicated to neuromuscular disease, such as the *Myology 2019* international congress (organised by AFM-Téléthon in March 2019 in Bordeaux), the annual meeting of the French Myology Society (organised in November 2019 in Marseille), or the International Congress of the *World Muscle Society* (October 2019 in Copenhagen, Denmark).

2020, a singular year

The COVID-19 pandemic has had an impact on Steinert's disease research: many research teams have put their laboratory work on pause, certain clinical trials have been discontinued provisionally, and congresses have been cancelled or postponed.

In response to the health crisis, healthcare professionals and associations have mobilised.

*The **FILNEMUS rare neuromuscular diseases healthcare network** is hosting, coordinating and encouraging interactions between participants in the diagnosis, treatment and research of new muscular diseases (reference centres and centres of expertise, diagnostic laboratories, research teams, associations for individuals affected by these diseases, etc.). It was created in February 2014, as part of the second Rare Diseases French National Plan, 2011-2014.*
WEB www.filnemus.fr

- The FILNEMUS rare neuromuscular diseases network, which acts as coordinator and host for French centres of expertise, has stimulated a great deal of action from the very beginning of the pandemic, and is adapting this action through biweekly e-meetings, in which doctors from AFM-Téléthon participate.
It has issued recommendations for doctors and patients, has posted (on its website) frequently asked questions & answers and self-rehabilitation materials to mitigate the closure of physiotherapy practices, and has issued alerts regarding the risks associated with administering hydroxychloroquine in neuromuscular diseases. It has also developed a national operational strategy for reference centres and centres of expertise, in order to ensure patients receive optimal and consistent treatment across France under the current pandemic.
- A survey organised by FILNEMUS, in collaboration with AFM-Téléthon, among individuals affected by neuromuscular disease, questioned more than 90 neuromuscular disease patients affected by COVID-19 in France. This survey will help to assess the impact of the pandemic (psychological impact, impact on home care, etc.).

WEB http://www.filnemus.fr/
WEB https://www.afm-telethon.fr/coronavirus

- The AFM-Téléthon Steinert's disease (DM1/DM2) Interest Group published an issue of its newsletter on COVID-19, including several interviews with myotonic dystrophy specialists.

Steinert's disease and COVID
Trait d'union - The Steinert's disease (DM1/DM2) Interest Group Newsletter 2019 (May)

- On the international stage, the American *Myotonic* association published recommendations on the respiratory care of patients with myotonic dystrophy during the pandemic. These were translated into French by the Neuromuscular Disease Network for Canada (NMD4C).

WEB https://www.myotonic.org/respiratory-care-recommendations-myotonic-dystrophy-patients-during-covid-19-pandemic

The publication of international recommendations

In order to ensure that every individual with myotonic dystrophy (DM) benefits from the best possible care, the American patient association,

Myotonic, is encouraging recommendations to be produced that can be referred to by care teams who are not (or not very) used to diagnosing and treating these diseases.

▪ Thus, in the last 12 months, *Myotonic* has published recommendations on management of children with DM1, respiratory care for DM1 and cardiological care in DM1 and DM2.
All these recommendations come from working groups involving a combination of clinicians and researchers from North America and Europe (including France), and are based mainly on the expert opinions and on the results of the few available controlled clinical studies. For each topic, the authors review all aspects of treatment, from the diagnostic stage to follow-up methods.

Consensus-based care recommendations for congenital and childhood-onset myotonic dystrophy type 1.
Johnson NE, Zapata-Aldana E, Angeard N, *et al.*
Neurol Clin Pract. 2019 (Oct)

Clinical Care Recommendations for Cardiologists Treating Adults With Myotonic Dystrophy.
McNally EM, Mann DL, Pinto Y *et al.*
J Am Heart Assoc. 2020 (Feb)

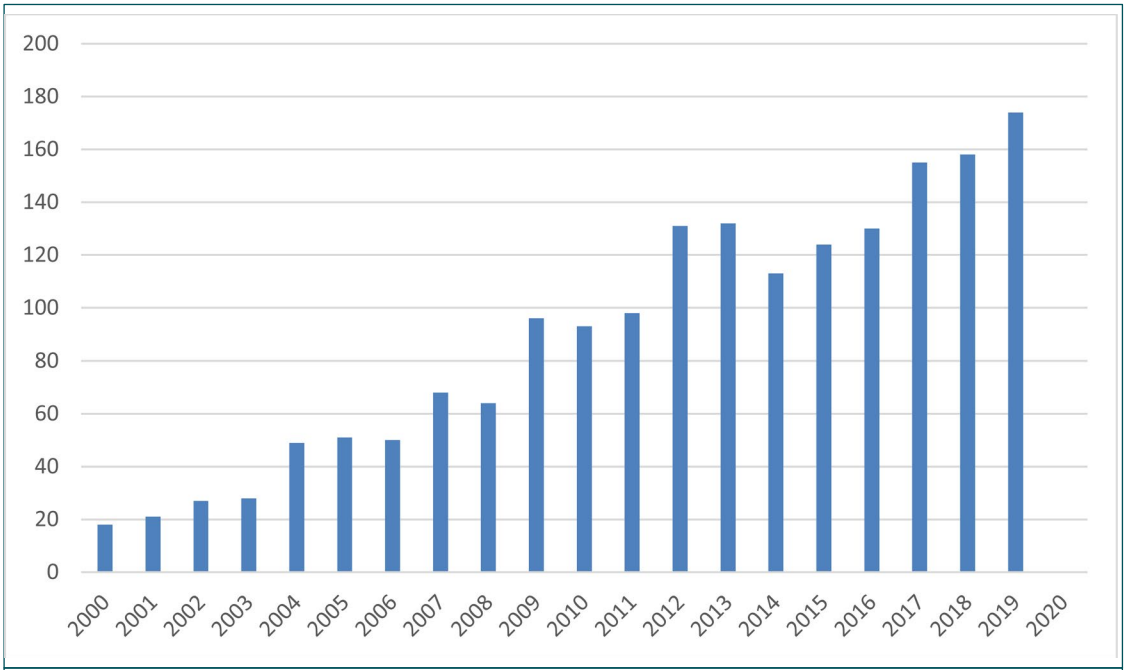
Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1.
Boentert M, Cao M, Mass D *et al.*
Respiration. 2020 (Apr)

▪ These reference documents are available in several languages on the *Myotonic* website.
WEB https://www.myotonic.org/toolkits-publications

A significant number of scientific publications

It is through articles in specialist journals that researchers working on Steinert's disease (DM1) communicate to the scientific and medical community their work and the conclusions or hypotheses they are able to draw from this work. The number of publications recorded each year on DM1 demonstrates the extent to which research in this area is active and diverse.

▪ Several major areas of research stand out:
- gaining a better clinical understanding of Steinert's disease (the consequences of this disease on the body, what medical examinations are used most often to follow-up a patient, in daily practice or during clinical trials, etc.);
- suggesting and evaluating different treatments and drug candidates in clinical trials;
- gaining a better understanding of the genetics of Steinert's disease;
- studying the disease mechanisms involved in the onset of the disease and suggesting new therapeutic avenues.



Number of medical/scientific publications on DM1 each year since 2000.
In the last 12 months, 180 articles on Steinert's disease were recorded in PubMed, the reference bibliographical database in the fields of medicine and biology. Year after year, research into DM1 is becoming more active.

Patient databases

The development of patient databases makes it possible to perform a survey (an exhaustive one in the case of a registry) of patients suffering from a particular disease, to clarify the natural history of the disease, to establish genotype/phenotype correlations and to help recruit patients into clinical trials.

*The so-called **natural history of a disease**, as doctors refer to it, is the description of different manifestations of that disease and their progression over time without the use of a treatment.*

The DM-Scope Observatory

The DM-Scope is a patient database, supported by AFM-Téléthon, which was established in France in 2008 for the purpose of collecting data relating to patients with myotonic dystrophy and supporting clinical research among these patients. It has become the largest database in the world for myotonic dystrophy.

- DM-Scope contains demographic, clinical and laboratory data for 3,359 patients with myotonic dystrophy: 3,174 patients with DM1 (363 children and 2,811 adults at the time of inclusion) and 185 patients with DM2 (1 child and 184 adults).

- In an article published in June 2019, a French/Québec consortium headed by researchers from the Institute of Myology in Paris presented a report on the status of this database.

Thanks to close cooperation between 55 neuromuscular reference centres or centres of expertise, DM-Scope is the most significant database in the world dedicated to DM1. It is responsible for 10 clinical studies (observational studies, fundamental research, recruitment of patients for clinical trials, etc.).

***Neuromuscular disease reference centres** provide specialist consultations in the field of neuromuscular disease that are approved by the French Ministry of Health. Besides the medical follow up of patients with neuromuscular diseases, reference centre consultations can be requested for their expertise in the area of diagnosis or treatment, for complex medical situations. They contribute to the conduct of clinical trials and to the improvement of professional*

DM-Scope French Observatory for myotonic dystrophy Studying the natural history of the disease, improving treatment, and promoting clinical research and the development of new therapies. (supported by AFM-Téléthon)		
Status	**Country**	**Date created**
Recruitment is ongoing	France	January 2008
As of June 2020: 3,174 patients with myotonic dystrophy type 1 have been included in the DM-Scope Observatory.		

The I-DM-Scope project

The objective of the French/Québec consortium called I-DM-Scope is to create an **international platform** for myotonic dystrophy in order to facilitate the setting up of multicentre studies, conduct natural history studies, identify biological markers, develop potential treatments, etc.

First established in July 2016, it combines the DM-Scope Observatory and the Québec database that encompasses the Québec and Saguenay regions.

The Q-DMR Québec myotonic dystrophy type 1 registry Better understanding DM1, facilitating the participation of patients in research projects and clinical trials		
Status	**Country**	**Date created**
Recruitment is ongoing	Canada	2002
As of April 2018: 1,410 patients have been included in this database.		

Other registries worldwide

The MDFR (Myotonic Dystrophy Family Registry) is an online database launched in 2013 by the American patient association, *Myotonic*, in order to collect medical and demographic information about patients with myotonic dystrophy (DM), to help researchers develop effective new treatments and to identify participants for potential research studies. The goal is to collect data for 3,000 patients aged 11 to 17 years, followed up over a 5-year period (due to end in February 2021).

Myotonic Dystrophy Family Registry (MDFR) Online collection of data on myotonic dystrophy (DM) [NCT02398786] (Sponsor: *Myotonic Dystrophy Foundation*)		
Status	**Country**	**Date created**
Recruitment is ongoing	United States	February 2013

WEB https://myotonicregistry.patientcrossroads.org

United States myotonic dystrophy database Connecting patients suffering from DM with research teams, collecting patient genetic and demographic characteristics. (Sponsor: *University of Rochester*)		
Status	**Country**	**Date created**
Recruitment is ongoing	United States	2000
As of January 2019, 850 patients with DM1 have been included in the database.		

Clinical advances

Observational studies help to better understand a disease, identify better diagnostic or monitoring tools, follow up the effect of a treatment in the longer term, etc. They are essential in being able to plan clinical trials.
The better the disease is described, the easier it will be to conclude with certainty at the end of a drug candidate trial whether or not the said candidate is effective. This also requires having high-performance tools at one's disposal to monitor this progress.

Impact of DM1 on the activities of daily living

▪ The PhenoDM1 study recruited 192 patients with DM1, the majority of which with the 'classic' adult-onset form of the disease, although all forms were included, from congenital to late-onset.
The study showed that patients with DM1 encounter difficulties performing several tasks of daily living in their home or during their leisure activities, in particular for activities requiring muscle strength, stability and coordination (walking uphill, running, carrying and dropping heavy objects, etc.). Despite these difficulties, the majority of daily tasks and activities (eating, washing, shopping, meeting friends, etc.) are possible and continue to be possible for a long time, even once the disease has progressed.

Activities of daily living in myotonic dystrophy type 1.
Landfeldt E, Nikolenko N, Jimenez-Moreno C *et al.*
Acta Neurol Scand. 2019 (Dec)

▪ Another study on the impact of the disease on the activities of daily living analysed motor function and executive function (skills allowing one to adapt to new situations: organising oneself, developing strategies in problem solving situations, etc.) among 66 young patients with DM1 (congenital and childhood-onset forms). Although it confirms that young patients with DM1 require more frequent help in performing the activities of daily living, the study suggests that this stems more from a deficit in executive functions than in motor function.

Daily activity performance in congenital and childhood forms of myotonic dystrophy type 1: a population-based study.
Eriksson BM, Ekström AB, Peny-Dahlstrand M.
Dev Med Child Neurol. 2019 (Nov)

▪ Danish researchers measured, over a period of 1 week, how long 67 patients with DM1 were physically active. They showed that the individuals who were most active were also those with a higher level of education, which could be explained, at least in part, by cognitive impairment.
Since the lack of physical activity observed among patients with DM1 could impact their well-being and their state of health (muscle wasting, fatigue, etc.), the authors recommend putting in place measures to encourage physical activity among patients with DM1, and remind readers of the results of the European OPTIMISTIC trial on the beneficial effects of cognitive behavioural therapy with respect to physical activity, social participation (with family, friends, work, etc.) and fatigue.

Physical activity in myotonic dystrophy type 1.
Knak KL, Sheikh AM, Witting N, Vissing J.
J Neurol. 2020 (Feb)

Cognitive behavioural therapy *is a form of psychotherapy that helps patients to resolve problems in daily living by acting on unfavourable attitudes or fears, or even phobias, that make these difficulties worse. It is an approach that is personalised and tailored to the objectives of*

Cognitive disorders

Cognitive disorders *encompass difficulties processing information (reasoning, memory, attention, language, writing, navigation, visual-spatial skills, planning, etc.) and knowledge acquisition. They can be present from birth, causing delays in psychomotor development. When they appear during childhood or adulthood, they cause difficulties at school and/or work.*

▪ A study looked at the progression of cognitive impairment over 11 years among 75 patients with DM1 (all forms of the disease, except the congenital form). It showed a gradual decline in visual memory and so-called "visual-constructive" skills (perceiving or reproducing spatial relationships between objects in order to structure a drawing, assemble the pieces of a puzzle, read a map and choose the best route, etc.).

Age-related cognitive decline in myotonic dystrophy type 1: An 11-year longitudinal follow-up study.
Labayru G, Aliri J, Zulaica M *et al.*
J Neuropsychol. 2019 (Aug)

▪ A study conducted among 31 patients with DM1 showed that these patients had more difficulty making decisions than healthy subjects. The authors suggest that this deficit in the decision-making process could be linked to the dopamine pathways, which could present a possible therapeutic target.

Ventral tegmental area dysfunction affects decision-making in patients with myotonic dystrophy type-1.
Serra L, Scocchia M, Meola G *et al.*
Cortex. 2020 (Apr)

▪ Eleven patients with the adult-onset form of DM1 took part in a cognitive remediation programme, combined with cognitive training using virtual reality.
Several studies conducted in other diseases have shown the benefits of virtual reality in the treatment of cognitive impairment, in particular with respect to visual-constructive skills and executive function.
This study confirms the benefits of cognitive remediation in DM1 and presents virtual reality as a promising tool in the treatment of patients with DM1.

Look at the cognitive deficits in patients with myotonic dystrophy type 1: an exploratory research on the effects of virtual reality.
Maresca G, Portaro S, Naro A *et al.*
Int J Rehabil Res. 2019 (Nov)

▪ A neuropsychological study of children with the childhood-onset form of Steinert's disease was conducted in France. The data are currently undergoing analysis.

PsyDM1 study
Better characterising cognitive disorders in the childhood-onset form of DM1
(Sponsor: Institute of Myology)

Status	Number of participants (age)	Country	Follow-up period
Data currently undergoing analysis	30 (from 6 to 20 years)	France	1 day (cross-sectional study)

WEB www.afm-telethon.fr/essai-psydm1-dans-maladie-steinert-6537

Fatigue and sleepiness

Fatigue and sleepiness during the day are commonly reported in Steinert's disease, and have a significant impact on the daily lives of patients.
▪ In an article published in October 2019, Canadian specialists report on a survey conducted among 115 adult patients with DM1 living in the

Saguenay region (Canada). The aim of this study was to establish the prevalence of disorders related to fatigue and sleepiness, and their progression over a period of nine years. Other variables were included in the study, such as depressive state, changes in weight, pain, hypothyroidism or sleep disorders.
The authors observed that there was an increase in fatigue and daytime sleepiness over time, over the period studied, and they were able to correlate this with other predictive variables, such as overweight or hyperthyroidism. The medical treatment of these factors could, therefore, reduce fatigue.
Patients with the more severe forms, with significant CTG triplet expansion, would seem to be particularly at risk.

Predicting daytime sleepiness and fatigue: a 9-year prospective study in myotonic dystrophy type 1.
Laberge L, Gallais B, Auclair J *et al.*
J Neurol. 2019 (Oct)

▪ A Serbian study confirms that fatigue is very common in DM1. Out of the 64 patients with DM1, half experienced fatigue and excessive sleepiness during the day. Seven years later, 38 of these patients were questioned again: at that stage, 82% complained of fatigue and 60% of sleepiness. Fatigue seems to progress independently of muscle involvement.

Fatigue in myotonic dystrophy type 1: a seven-year prospective study.
Peric S, Bjelica B, Bozovic I *et al.*
Acta Myol. 2019 (Dec)

Gait disorders, falls

▪ A study monitoring falls over a 100-day period among 102 patients with DM1 showed that these patients fell 7 to 8 times more frequently than normal: 16% of patients with DM1 had at least two falls during the 100-day study period. The majority of these falls took place indoors, hence the importance of adapting the environment to reduce the risk of falls at home (installing anti-slip mats and handrails; removing any potential obstacles, etc.). The patients most at risk of falling are the most elderly, the least active and those with the greatest muscle weakness.

High incidence of falls in patients with myotonic dystrophy type 1 and 2: A prospective study.
Berends J, Tieleman AA, Horlings CGC *et al.*
Neuromuscul Disord. 2019 (Aug)

▪ The Mini-BESTest test is being used increasingly to assess balance disorders. A Canadian team has shown, based on a study among 59 patients with the adult or late-onset form of DM1, that it could be applied to DM1 to estimate the risk of falling.

Validity of the Mini-BESTest in adults with myotonic dystrophy type 1.
Duchesne E, Hébert LJ, Mathieu J et al.
Muscle Nerve. 2020 (Apr)

Involvement of central nervous system

While it is known that central nervous system impairment is involved in cognitive disorders and is a factor in sleep disorders in Steinert's disease, an increasing number of studies are showing that it also plays a role in gait and balance disorders.

▪ A Swiss team has analysed gait, mobility and cognitive skills among 19 patients with either childhood, adolescent and adult-onset forms of DM1. To see how cognition and gait may interact with one another, they asked participants to perform two tasks at the same time (walk and describe the colour of some text in front of them, for example). This makes it possible to test what happens when one needs to concentrate on two different tasks at the same time. The authors observed gait deviations among patients with DM1 that were different to those observed among healthy subjects. Furthermore, patients with DM1 made more mistakes on the cognitive task, with attention focused more on walking in order not to stumble.
This study shows that cognitive impairment interferes with motor skills.

Characterizing cognitive-motor impairments in patients with myotonic dystrophy type 1.
Filli L, Schwegler S, Meyer C et al.
Neuromuscul Disord. 2020 (May)

▪ Two other studies, one looking at motor reflexes in the legs and the other at electrophysiological parameters while walking, reinforce the idea that gait disorders in DM1 are not due solely to muscle weakness (in particular in the feet) and that central nervous system impairment also plays a role.

*The **electrophysiological study** of the muscle is a medical examination intended to record the electrical activity in a muscle (electromyogram) or in a nerve (nerve conduction velocity test). It consists of collecting – using fine needles that serve as electrodes, implanted in the muscle – the electrical signals transmitted by the nerves or emitted by the muscle fibres at rest, and also during and after movement.*

Myotonic dystrophy type 1 alters muscle twitch properties, spinal reflexes, and perturbation-induced trans-cortical reflexes.
Shields RK, Lee J, Buelow A *et al.*
Muscle Nerve. 2019 (Nov)

Paving the way for a better understanding of the pathophysiology of gait impairment in myotonic dystrophy: a pilot study focusing on muscle networks.
Naro A, Portaro S, Milardi D *et al.*
J Neuroeng Rehabil. 2019 (Sep)

▪ An Italian team reports that it has tested the use, in a female patient with DM1, of a rehabilitation exoskeleton during physiotherapy sessions, over a period of 2 months. This rehabilitation resulted in an improvement in walking skills, balance skills and muscle strength in the lower limbs. Electroencephalogram and electromyogram studies suggest an improvement in central nervous system impairment too. These results, while seemingly promising, need to be confirmed across a wider number of cases.

*An **electroencephalogram** involves the recording of electrical activity in the brain using electrodes placed on the surface of the scalp. This examination is commonly given whenever epilepsy or brain activity dysfunction is suspected. It is used to study brain electrical activity when the brain is at rest or is stimulated by sensory excitement (sight, hearing, touch, etc.) or mental activity.*

Overground exoskeletons may boost neuroplasticity in myotonic dystrophy type 1 rehabilitation. A case report
Simona Portaro, Antonino Naro, Antonino Leo *et al.*
Medicine (Baltimore). 2019 (Nov)

A multi-system disease

Steinert's disease is a multi-system disease. It affects the muscles and can also affect other organs: the heart, respiratory system, digestive system, hormone (endocrine) system and nervous system.
The descriptions presented below relate to signs that may be encountered in Steinert's disease. A particular sign or symptom will appear in one person at a specific point in the progression of the disease, whereas it may appear sooner, later or not at all in another person.

Do not hesitate to report any complaint
During the annual checkup, it is important to address any difficulties or discomforts experienced, even if they do not seem to you to be related to the disease. This helps doctors guide treatment to the best of their ability.

▪ Italian clinicians have described hormone impairment based on the observation of 63 patients with DM1. They concluded that hormone and metabolic impairment is common in DM1 and that it is therefore necessary to check for this systematically during the medical follow-up, in order to put in place a tailored treatment as soon as it is needed.

Hormonal and metabolic gender differences in a cohort of myotonic dystrophy type 1 subjects: a retrospective, case-control study.
Spaziani M, Semeraro A, Bucci E *et al.*
J Endocrinol Invest. 2019 (Nov)

▪ A study conducted among 36 patients with DM1 has shown greater bone fragility, related to hormone and muscle impairment: 15 of these patients had experienced fractures related to bone fragility.

Fragility fractures and bone mineral density in male patients affected by type 1 and type 2 myotonic dystrophy.
Passeri E, Sansone VA, Sconfienza LM *et al.*
Neuromuscul Disord. 2019 (Nov)

▪ Seventy-five patients with DM1 answered a questionnaire regarding bulbar disorders (difficulty swallowing and aspiration problems) and 28 underwent a swallowing videofluoroscopy. The results show that patients with DM1 have more problems swallowing and that this impacts negatively their quality of life.

Swallow-related quality of life and oropharyngeal dysphagia in myotonic dystrophy.
Pilz W, Passos VL, Verdonschot RJ *et al.*
Eur Arch Otorhinolaryngol. 2020 (Apr)

▪ A survey conducted among 152 patients with DM1 showed that 68% of them had experienced difficulties related to anal incontinence in the previous month (inability to retain intestinal gas and/or faecal incontinence) and 37% had had to modify their lifestyle habits.

The prevalence of faecal incontinence in myotonic dystrophy type 1.
Petty RKH, Eugenicos MP, Hamilton MJ *et al.*
Neuromuscul Disord. 2019 (Jun)

▪ A study conducted among 35 children aged 3 to 13 years, with the congenital form of DM1, shows that muscle wasting tends to decrease in the oldest patients. The more the children grow up, the more their muscle mass approaches that of healthy children of the same age.

Body Composition in Patients with Congenital Myotonic Dystrophy.
Ceballos-Sáenz D, Zapata-Aldana E, Singeris S *et al.*
Muscle Nerve. 2019 (May)

▪ In an article published in August 2019, Dutch and French teams, including a team from the Institute of Myology in Paris, worked together to study the medical records of 33 patients with a diagnosis of DM1 and presenting highly asymmetric scapular winging and/or complex shoulder mobility disorders (scapular dyskinesis), all of which could mimick another neuromuscular disease, such as facioscapulohumeral muscular dystrophy (FSHD).
Among the 33 files analysed, 3 involved congenital forms of DM1, 6 involved childhood-onset forms and 24 involved adult-onset forms. Unexpectedly, a diagnosis of FSH muscular dystrophy (FSHD) was made in 3 patients, in addition to the DM1 diagnosis.

Facioscapulohumeral muscular dystrophy *(FSHD) is a rare muscular disease of genetic origin. It manifests as a decrease in volume and a weakness of the face muscles and the upper limbs in patients as adults or adolescents. The aim of treatment is essentially to prevent complications and improve patient comfort.*

The co-existence, in a single patient, of genuine DM1 and FSHD has already been reported in the literature and can be suspected clinically if the symptomatology is predominantly scapular.

Scapular dyskinesis in myotonic dystrophy type 1: clinical characteristics and genetic investigations.
Voermans NC, van der Bilt RC, IJspeert J *et al.*
J Neurol. 2019 (Aug)

Finding the good outcome measures for clinical trials

▪ In an article published in August 2019, the OMMYD (Outcome Measures for Myotonic Dystrophy) consortium reported on the state of progress of its work, intended to optimise outcome measures in DM1. A battery of tests was proposed: the 6-minute walk test, the 10-metre walk test, the 10-metre run test, the 30-second sit and stand test and the 9-hole peg test. This study involved 213 patients with DM1. It was possible to follow up 98 of them over a period of 1 year.
There is a fairly good correlation between these tests, body mass index and disease severity, thus accounting for their benefit in upcoming therapies. It should, however, be noted that the figures observed sometimes varied significantly between the first and second test attempt.

Analysis of the functional capacity outcome measures for myotonic dystrophy.
Jimenez-Moreno AC, Nikolenko N, Kierkegaard M *et al.*
Ann Clin Transl Neurol. 2019 (Aug)

▪ Work has been conducted to determine the most reliable tests to evaluate muscle strength, balance and mobility in DM1.
Seventy-three adult patients with DM1 (excluding the congenital form) underwent a series of examinations at an interval of 1 week to see which ones were least likely to vary between attempts (this would reflect variations in external conditions rather than the parameter being evaluated).
The authors recommend the use of a portable dynamometer to evaluate muscle strength, timed tests for balance (for example using a stopwatch to measure the time a person takes to sit up from a chair, walk 3 metres, turn around, head back to the chair and sit down) and for mobility, the walk test timed over a distance of 10 metres.

Intrarater reliability and validity of outcome measures in myotonic dystrophy type 1.
Knak KL, Sheikh AM, Andersen H *et al.*
Neurology. 2020 (May)

*A **biological marker**, also referred to as a biomarker, is a measurable characteristic that indicates a normal or pathological biological process. The identification of new biological markers for a disease is very important in monitoring the progression of the disease and the efficacy of new treatments, whether these markers are physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

▪ Circular RNAs are not translated into proteins. These circular RNAs are difficult to detect using conventional sequencing methods, and so have long been considered to be intermediate products of the alternative splicing of genes, and to be of no interest.
Italian researchers, in collaboration with a team from the Institute of Myology (Paris), studied these circular RNAs in DM1, using new sequencing programs (RNA-Seq). In an article published in April 2019, they reported that levels of these circular RNAs are elevated in the muscles and blood of patients with Steinert's disease. Although their role in the onset of DM1 is still in dispute, they could, in time, be used as biomarkers for the disease.

Dysregulation of Circular RNAs in Myotonic Dystrophy Type 1.
Voellenkle C, Perfetti A, Carrara M, *et al.*
Int J Mol Sci. 2019 (Apr)

▪ Several messenger RNA molecules are modified in DM1 and have been proposed as biomarkers. Researchers have developed an analysis tool that encompasses the modifications observed with several messenger RNA molecules, and that could be used in the context of a clinical trial.

Towards development of a statistical framework to evaluate myotonic dystrophy type 1 mRNA biomarkers in the context of a clinical trial.
Kurkiewicz A, Cooper A, McIlwaine E *et al.*
PLoS One. 2020 (Apr)

Therapeutic cannabis and myotonia

The symptomatic treatment of myotonia is based on a few therapeutic drugs used over the long term: mexiletine, lamotrigine, carbamazepine and phenytoin. However, this does not always give satisfactory results.

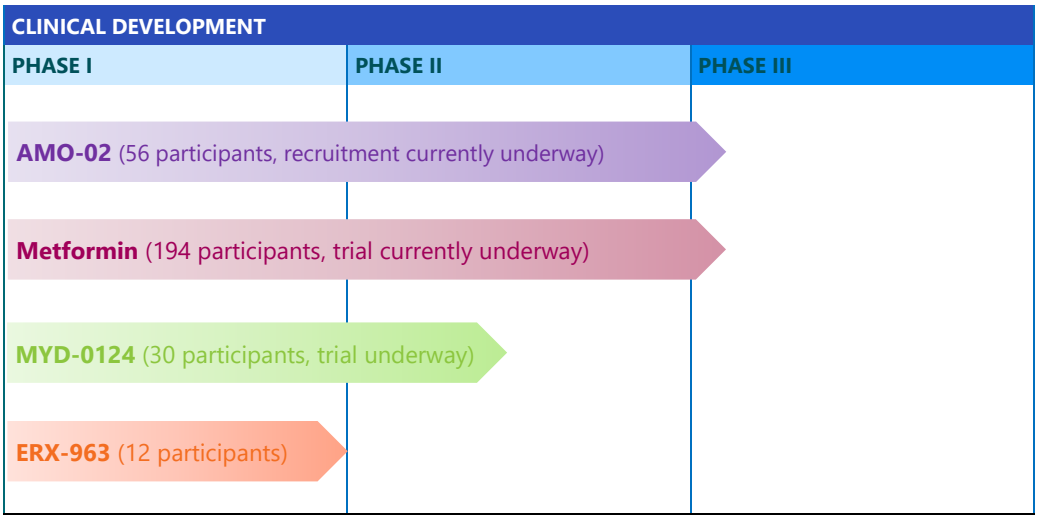
▪ In an article published in October 2019, German clinicians reported the results of an open-label pilot study conducted among 6 participants, 4 with DM1 or DM2, and 2 with myotonia congenita involving an abnormality of the gene coding the chloride channel.

Over a period of four weeks, the study participants ingested oil with increasing doses of CBD (cannabidiol) and THC (tetrahydrocannabinol), the two active ingredients in cannabis used for therapeutic purposes. The analysis of the clinical parameters, with respect to myotonia (including the Myotonia Behaviour Scale, MBS) and also to muscle pain, tends to support the fact that the product has a positive effect. The authors recommend further trials, this time in a randomised manner, and involving a larger sample of patients.

A role for cannabinoids in the treatment of myotonia? Report of compassionate use in a small cohort of patients.
Montagnese F, Stahl K, Wenninger S, Schoser B.
J Neurol. 2019 (Oct)

Clinical trials

Clinical trials are used to evaluate the effects of a potential treatment (a drug candidate, a medical device, etc.) in a disease, to make sure it is well tolerated and effective in this disease.
Four drug candidates are being trialled in Steinert's disease (or myotonic dystrophy type 1, DM1).



AMO-02

AMO-02 (or tideglusib) is a drug candidate being developed by *AMO Pharma*. By inactivating GSK3beta, AMO-02 normalises the activity of CUGBP1, a regulatory protein abnormally activated in DM1, thus improving general cell function.

- Laboratory studies show that AMO-02 (or tideglusib) reduces cell abnormalities related to DM1 (decrease in the quantity of mutated *DMPK* RNA, re-establishment of the maturation of messenger RNA regulated by CUGBP1 and MBNL) in muscle cell samples taken from patients with DM1 (congenital and adult-onset forms) and in mice models.
The drug was injected into mouse models of DM1, and it extended their lifespan and improved their growth and their neuromotor activity.

Correction of GSK3β in DM1 reduces the mutant RNA and improves postnatal survival of DMSXL mice.
Mei W, Wen-Chin W, Lauren S et al.
Mol Cell Biol. 2019 (Aug)

Correction of RNA-Binding Protein CUGBP1 and GSK3β Signaling as Therapeutic Approach for Congenital and Adult Myotonic Dystrophy Type 1.
Timchenko L.
Int J Mol Sci. 2019 (Dec)

- AMO-02 was evaluated over a 3-month period in a phase II trial among 16 patients with DM1 presenting with either congenital or childhood-onset forms. The preliminary results announced by a press release in 2018 showed that the product was well tolerated and that there was an improvement in cognitive skills and ability to perform daily tasks, and a decrease in experienced fatigue.

- AMO Pharma announced, in a press release on 9 January 2020, that it was starting recruitment for a phase II/III trial of AMO-02 in the congenital form of Steinert's disease. This new trial will evaluate, over a period of 5 months

and 2 weeks, the efficacy and safety of AMO-02 in 56 participants. It will be conducted in Canada, the United States and the United Kingdom.

AMO Pharma Announces Initiation of Planned Pivotal Clinical Trial for Myotonic Dystrophy Following $35m Fund Raise
AMO Pharma, *Press release dated 9 January 2020.*

Phase II/III trial Evaluating the safety and efficacy of AMO-02 [NCT03692312] (Sponsor: AMO Pharma)				
Status	**Number of participants (age)**	**Country**	**Follow-up period**	**Start – End**
Recruitment currently underway	56 (aged 6 to 16 years)	Canada, United States, United Kingdom	22 weeks	April 2020 – August 2021

Metformin

In 2015, a team from I-Stem, the French research and development laboratory dedicated to pluripotent human stem cells, created and supported by AFM-Téléthon, showed that metformin, a drug already marketed in insulin-resistant diabetes, corrects splicing defects in cells taken from patients with DM1.

▪ A phase II trial supported by AFM-Téléthon, the Myomet trial, was conducted in France between 2013 and 2017 among 40 ambulatory adult patients, aged 18 to 60 years, with myotonic dystrophy type 1. The results were published in October 2018.
Metformin was well tolerated over the 48-week period of the trial by the 23 patients, who followed the trial to the end.
At the end of the trial, participants taking metformin (n=9) had shown an increase in the distance they walked over a 6-minute period (6-minute walk test or 6MWT) of 32.9 metres (± 32.7 m), versus an increase of 3.7 metres (± 32.4 m) among participants taking the placebo (n=14). The other parameters, including myotonia and muscle strength, did not change.

Improved mobility with metformin in patients with myotonic dystrophy type 1: a randomized controlled trial.
Bassez G, Audureau E, Hogrel JY, Arrouasse R, Baghdoyan S, Bhugaloo H, Gourlay-Chu ML, Le Corvoisier P, Peschanski M.
Brain. 2018 Oct 1;141(10):2855-2865.

Benefits of metformin on risk of cancer

▪ An American study shows that metformin appears to reduce the risk of cancer among patients who suffer from DM1 and are diabetic. The American researchers looked at correlations, among 913 patients with DM1, between risk of onset of type 2 diabetes and risk of cancer, depending on whether metformin was being taken or not. They showed that there is:
- a higher risk of type 2 diabetes among patients with DM1 compared to the general population,
- an increased risk of malignant tumour in patients who have DM1 and who are diabetic,
- a statistically reduced risk of malignant tumour in patients who have DM1 and diabetes, and who takes metformin.

***I-Stem**, the Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, is a research centre exploring stem cells for therapeutic purposes, supported by AFM-Téléthon.*
I-Stem is working on cell therapy to restore function to tissues or organs using stem cell transplant, and also on tools developed from stem cells to better understand rare disease mechanisms and to discover new medicines.
WEB www.istem.eu
WEB www.institut-biotherapies.fr/

These findings could provide an additional argument for treating DMA patients with metformin in a targeted manner.

Diabetes, Metformin, and Cancer Risk in Myotonic Dystrophy Type I.
Alsaggaf R, Pfeiffer RM, Wang Y *et al.*
Int J Cancer. 2019 (Nov)

▪ These results are especially important given that studies have reported a higher risk of developing cancerous or benign tumours in patients with DM1.
An American study conducted among 927 patients with DM1, identified a higher risk, compared to the general population, of these patients developing benign tumours (thyroid nodules, benign brain tumours, colorectal polyps, salivary gland adenomas or benign skin tumours).

Benign tumors in myotonic dystrophy type I target disease-related cancer sites.
Alsaggaf R, St George DMM, Zhan M *et al.*
Ann Clin Transl Neurol. 2019 (Aug)

Metformin acts on the metabolism

▪ Starting with a review of publications on changes to the insulin pathway in DM1, Dutch authors have hypothesised that metformin's mechanism of action within the cell involves the insulin signalling pathway.
Insulin is a hormone that is produced by the pancreas and that acts, via the blood circulation, on the liver, the muscles and the adipose tissue (fatty cells) in order to regulate the storage of carbohydrates and fat by the body. This insulin signalling pathway is involved in growth and ageing, and in the body's response to stress. It causes a number of proteins to respond inside the cells.

*Cell **signalling pathways** transmit messages within a cell in order to modulate its activity (growth, division, differentiation, death, etc.). Messages can originate from other cells in the body or from the external environment.* Their arrival at a cell receptor triggers a cascade of reactions that will modify the cell's behaviour.

Insulin Signaling as a Key Moderator in Myotonic Dystrophy Type 1.
Nieuwenhuis S, Okkersen K, Widomska J et al.
Front Neurol. 2019 (Nov)

▪ In an article published in April 2020, Spanish researchers reported that they had identified abnormalities in the functioning of the mitochondria and the energy metabolism in the fibroblasts and the blood cells of patients with DM1. Adding metformin to these cells in culture caused these abnormalities to disappear.
The role of mitochondria in DM1 is not known. The authors hypothesize that impairment of the metabolism and of the functioning of the mitochondria, resembling accelerated ageing, would seem to exist in DM1 and that metformin could partly correct this.

*The **mitochondria** act as 'power plants' for the cells. Thanks to their respiratory chain, they provide the energy that is used by the cell. The number of mitochondria inside a cell varies – it depends on the cell's energy needs – and can range from several hundred to almost a million. A muscle fibre is highly demanding of energy and contains several thousand mitochondria*

Myotonic Dystrophy type 1 cells display impaired metabolism and mitochondrial dysfunction that are reversed by metformin.
García-Puga M, Saenz-Antoñanzas A, Fernández-Torrón R *et al.*
Aging (Albany NY). 2020 (Apr). 12(7):6260-6275.

An Italian trial currently underway

A new metformin trial is currently underway in Italy, among 194 patients with DM1 who are being followed up for a period of 2 years.

Phase III trial Evaluating safety and efficacy of metformin (MetMyd) [EudraCT number 2018-000692-32] (Sponsor: *DIP. Medicina dei sistemi università degli studi di Roma tor Vergata*)				
Status	**Number of participants (age)**	**Country**	**Follow-up period**	**Start – End**
Currently underway	194 (aged 18 to 64 years)	Italy	2 years	May 2019

MYD-0124

MYD-0124 is an antibiotic (erythromycin) that has a beneficial effect on myotonia in mice with DM1. This small molecule seems to be capable of binding to the *CUG* repeats in mutated *DMPK* RNA, causing the release of MBNL regulatory proteins and the correction of messenger RNA maturation abnormalities that are the targets of the MBNL proteins.

▪ A clinical trial is currently underway in Japan.

Phase II trial Evaluating the safety and efficacy of MYD-0124 [JPRN-jRCT2051190069] (Sponsor: *Mochizuki Hideki*)				
Status	**Number of participants (age)**	**Country**	**Follow-up period**	**Start – End**
Currently underway	30 (aged 20 to 55 years)	Japan	6 months	September 2019

*In a **phase II** clinical trial, a medicinal product, previously shown to be well tolerated (during a phase I trial), is being administered to a group of patients with the aim of determining the treatment's therapeutic efficacy, optimal doses and its safety (what method of administration and maximum dose are tolerated?).*
➤➤ Clinical trials and neuromuscular diseases, Knowledge & Understanding reference documents, AFM-Téléthon.

▪ It should be noted that researchers are studying, in the laboratory, the additional benefits of combining furamidine and erythromycin.
Furamidine is also a small molecule that acts on the RNA of the mutated *DMPK* gene.
Their work has shown positive results, both in a mouse model for DM1 and in muscle cells (in vitro) from patients with the disease.

Combination Treatment of Erythromycin and Furamidine Provides Additive and Synergistic Rescue of Mis-Splicing in Myotonic Dystrophy Type 1 Models.
Jenquin JR, Yang H, Huigens RW 3rd *et al.*
ACS Pharmacol Transl Sci. 2019 (Aug)

ERX-963

ERX-963 is a small molecule developed by Expansion Therapeutics for the purpose of binding to the CUG repeats of the mutated *DMPK* RNA and releasing the MBNL-family proteins.
A trial was conducted in the United States to evaluate the safety of this drug candidate among 12 adult patients with DM1.

Phase I trial Evaluating safety and efficacy of ERX-963 [NCT03959189] (Sponsor: *Expansion Therapeutics*)				
Status	**Number of participants (age)**	**Country**	**Follow-up period**	**Start – End**
Data currently undergoing analysis	12 (aged 18 to 65 years)	United States	2 years	June 2019 – April 2020

Non-invasive ventilation

In the field of respiratory care, a French study supported by AFM-Téléthon assessed the early introduction of non-invasive ventilation among patients with Steinert's disease. The data are currently undergoing analysis.

DYVINE study – Assessing the safety and efficacy of the early introduction of non-invasive night-time mechanical ventilation [NCT0122561] (Sponsor: *Assistance Publique - Hôpitaux de Paris*)				
Status	**Number of participants (age)**	**Country**	**Follow-up period**	**Start – End**
Data currently undergoing analysis	77 (18 years and older)	France	5 years	October 2010 – December 2018

WEB www.afm-telethon.fr/essai-dyvine-dans-maladie-steinert-1411

Advances in Genetics

Instability of the CTG repeats

The genetic abnormality involved in Steinert's disease (or myotonic dystrophy type 1, DM1) is the abnormal repetition of a small DNA sequence, made up of CTG nucleotide triplets, in the *DMPK* gene.
The number of CTG repeats is not stable: it can vary from one generation to the next within the same family, and even in a particular affected individual, it varies over time and across different organs (and even within the same organ, across different cells). In general, the number of repeats increases with time.

▪ A number of research projects are being undertaken to better understand the mechanisms underlying this instability and the reason why these repeats are more unstable in certain individuals and/or certain organs. A review appeared in January 2020 on the subject.

DM1 Phenotype Variability and Triplet Repeat Instability: Challenges in the Development of New Therapies.
Tomé S, Gourdon G.
Int J Mol Sci. 2020 (Jan)

▪ A Dutch team has studied the instability in the size of the CTG repeats from one generation to the next in 146 families. In each family, none of the parents had DM1 symptoms, but one of them presented a number of CTG repeats that was higher than normal, but not pathological (more than 37 repeats, but less than 80).
Their observations show that in these patients who are non-symptomatic, but who have a greater-than-normal number of CTG repeats, the length of the CTG repeats has a tendency to increase to a greater extent in men than in women. Furthermore, these men have a higher risk of transmitting to their children a number of CTG triplet repeats greater than 80, the pathological threshold. This is an additional risk that needs to be taken into account during genetic counselling.

Parental repeat length instability in myotonic dystrophy type 1 pre- and protomutations.
Joosten IBT, Hellebrekers DMEI, de Greef BTA *et al.*
Eur J Hum Genet. 2020 (Mar)

▪ It is possible to estimate the number of CTG repeats present on the *DMPK* gene that have been transmitted from parent to child, via a gamete (sperm cell or ovum), based on a blood sample collected during their lifetime, at the time of diagnosis. Generally speaking, the greater the expansion, the earlier the onset and the more marked the manifestations of the disease, although there isn't a perfect correlation between the two. Other factors are also involved.

▪ Two studies, one European, conducted among 250 people participating in the OPTIMISTIC trial, and the other Canadian, conducted among 192 people, have investigated the factors influencing symptom severity.
When the CTG triplet repeat is interrupted by other triplets (most commonly CCG or CGG), its size is more stable over time, depending on the organ in question. Individuals who present such variations within the CTG repeat develop less severe disease symptoms.
In addition to these genetic factors, other factors may also be involved (age, height, weight, gender, etc.).

***Genetic counselling** is aimed at individuals facing a genetic disease, whether or not that individual, or someone close to them, has the disease. The aim is to inform them of their risk of developing and/or transmitting the disease in the future and to assess the possibility of prenatal or pre-implantation diagnosis and the pre-screening of individuals at risk (pre-symptomatic diagnosis).
Genetic counselling is often undertaken prior to reproductive planning. It can also be undertaken without any direct link to such planning, to alleviate any concerns regarding one's own genetic status.
Genetic counselling can be accompanied by a psychological consultation, to help the person anticipate the impact of the test result on their future, and to allow that person to articulate any questions or concerns they may have with respect to themselves, their family and their future.*

Genetic determinants of disease severity in the myotonic dystrophy type 1 OPTIMISTIC cohort.
Cumming SA, Jimenez-Moreno C, Okkersen K *et al.*
Neurology. 2019 (Aug)

Allele length of the DMPK CTG repeat is a predictor of progressive myotonic dystrophy type 1 phenotypes.
Overend G, Légaré C, Mathieu J *et al.*
Hum Mol Genet. 2019 (Jul)

Methylation of the *DMPK* gene

Epigenetic factors *are factors relating to the organisation of the (more or less condensed) DNA molecule, but not to its contents (the nucleotide sequence is maintained). Epigenetic changes in gene expression can occur spontaneously, in response to the environment, and can be reversible. They can also be*

Methylation is an epigenetic change to DNA. Methylation of a DNA nucleotide base, i.e. addition of a methyl (CH3) group to the cytosine, influences gene expression.

▪ A high degree of methylation of the *DMPK* gene seems to be involved in the congenital form of DM1. Based on a literature review, authors have proposed a model to explain the special features of the congenital form of DM1 (the mutated *DMPK* messenger RNA is produced to a particularly high degree) combining a significant number of CTG repeats and hypermethylation in the region of the DNA containing the CTG expansions. Their model also explains why the congenital form of the disease is transmitted more frequently by women.

Molecular genetics of congenital myotonic dystrophy.
Lanni S, Pearson CE.
Neurobiol Dis. 2019 (Jul)

▪ In an article published in May 2019, a Canadian team focused on the effects of *DMPK* gene methylation in the adult-onset form of the disease. Ninety patients with this 'classic' form of DM1 participated in the study, in which clinical data (muscular and respiratory weakness) and molecular data (size of the CTG expansion, measurement of *DMPK* gene methylation) were cross-referenced.
The authors reported that the degree of methylation of the *DMPK* gene seemed to be correlated with muscle strength and, to a lesser degree, with respiratory parameters (vital capacity and maximum inspiratory pressure). These results could have an impact on genetic counselling and long-term care.

DMPK gene DNA methylation levels are associated with muscular and respiratory profiles in DM1.
Légaré C, Overend G, Guay SP *et al.*
Neurol Genet. 2019 (May)

Pre-implantation diagnosis

Pre-implantation diagnosis establishes, in the context of in vitro fertilisation, a diagnosis regarding the embryo before its implantation in the uterus (in general two to three embryos are implanted to increase the chances of initiating a pregnancy). This is a complex procedure that requires, at the same time, certain medically assisted reproductive techniques and a genetic diagnosis of cells taken from the embryo. The success rate is still fairly low (on average only 20 to 30% of pregnancies reach full term).

▪ French doctors have published a follow-up of 115 pre-implantation diagnostic procedures in 48 couples where one of the partners has DM1 (30 women and 18 men with DM1). Twenty-seven pregnancies reached full term (a success rate of 26.8% for women with DM1 and 32.3% for men with DMI).

The doctors also noted that the sperm was lower quality in men with DM1 and they recommend regular monitoring and the freezing of sperm if necessary.

CTG expansion in the DMPK gene: semen quality assessment and outcome of Preimplantation Genetic Diagnosis.
Puy V, Mayeur A, Levy A *et al.*
J Clin Endocrinol Metab. 2020 (Jan)

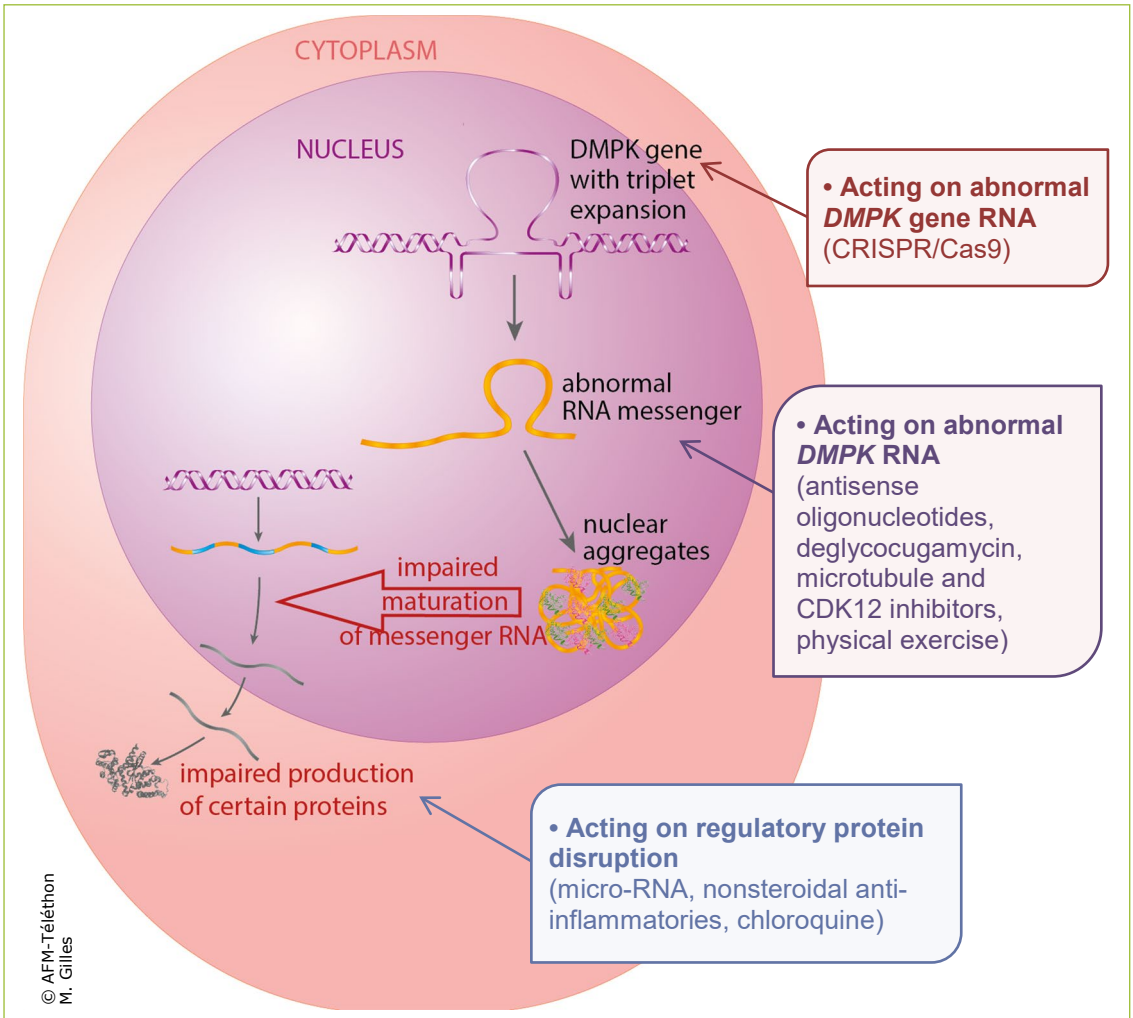
Exploring therapeutic avenues

Advances in our knowledge of molecular mechanisms and the natural history of Steinert's disease (DM1) allow us to consider different possible therapeutic avenues.

Before they can be validated in humans as part of clinical trials, these therapeutic avenues must first be tested on cell and animal models.

The therapeutic avenues being investigated in Steinert's disease are intended to act at different levels:

- on the DNA (and the CTG repeats) of the abnormal *DMPK* gene,
- on the abnormal RNA (and CUG repeats),
- on the aggregates,
- on the sequestered proteins,
- or on the consequences of these abnormalities on cell function.



Therapeutic avenues in Steinert's disease

Several therapeutic avenues are being investigated in Steinert's disease. They act at different levels : on the DNA of the abnormal DMPK gene, on the abnormal RNA, on the aggregates or on the sequestered proteins.

Acting on the *DMPK* gene

The CRISPR-Cas9 system is a new high-performance tool for genome editing that can be used to excise CTG repeats in the *DMPK* gene.

▪ The Ana Buj Bello team at Généthon, in collaboration with the Denis Furling and Geneviève Gourdon team at the Institute of Myology, has developed and evaluated a gene therapy approach using CRISPR-Cas9.
Their work, supported by AFM-Téléthon, has shown that their approach can delete CTG repeats in the *DMPK* gene and eliminate toxic RNA aggregates in a cell model of the disease.
The gene therapy product was injected into the muscles of mice with DM1. A decrease in toxic mutated *DMPK* RNA aggregate was observed in the muscle cell nuclei of the diseased mice.
Based on these encouraging results, the researchers will pursue their work in order to improve the efficacy of this approach, and they are considering systemic administration as a way to treat the entire body.

Genome Editing of Expanded CTG Repeats within the Human DMPK Gene Reduces Nuclear RNA Foci in the Muscle of DM1 Mice.
Lo Scrudato M, Poulard K, Sourd C et al.
Mol Ther. 2019 (Jun)

▪ A Dutch team has shown that it is possible, using CRISPR-Cas9, to restore certain characteristics of precursor muscle cells affected by the congenital form of DM1 (2,600 repeats). These myoblasts were once edited were again able to properly differentiate and fuse to repair the muscle.

Recovery in the Myogenic Program of Congenital Myotonic Dystrophy Myoblasts after Excision of the Expanded (CTG)n Repeat.
André LM, van Cruchten RTP, Willemse M *et al.*
Int J Mol Sci. 2019 (Nov)

▪ Bearing witness to the growing number of studies on the subject, a literature review was published in July 2019, reviewing the first results and the difficulties still to be resolved.

CRISPR/Cas Applications in Myotonic Dystrophy: Expanding Opportunities.
Raaijmakers RHL, Ripken L, Ausems CRM, Wansink DG.
Int J Mol Sci. 2019 (Jul)

Acting on the *DMPK* RNA

Many approaches targeting the mutated *DMPK* messenger RNA are currently being developed. The objective of these approaches is to release the proteins abnormally trapped in the nuclear aggregates by acting on the abnormal *DMPK* RNA.

Optimised oligonucleotides

▪ A team from the Institute of Myology (Paris), in collaboration with British and Canadian researchers, has demonstrated, in a DM1 mouse model, that antisense oligonucleotides coupled with a specific peptide were better able to penetrate into muscle tissue.
These oligonucleotides are therefore able to penetrate more effectively into muscle fibres and their action is able to correct the molecular abnormalities and the myotonia found in these DM1 mice. Low doses of the product are sufficient to have an effective and long-lasting effect on the symptoms of the mice modelling DM1.

Peptide-conjugated oligonucleotides evoke long-lasting myotonic dystrophy correction in patient-derived cells and mice.

Klein AF, Varela MA, Arandel L *et al.*
J Clin Invest. 2019 (Sep)

▪ American researchers, in collaboration with Ionis Pharmaceuticals, have developed an antisense oligonucleotide (ISIS 486178) that targets the *DMPK* RNA, outside the repeated sequence. Injected into mice with DM1 via the systemic route, the product improved ability to run, myotonia and cardiac conduction disorders.

*The **systemic route** is a method of administration of a medicinal product. Injected intravenously or intra-arterially, the medicinal product is distributed rapidly to the entire body via the blood circulation (this is referred to as the systemic circulation).*

Systemic Therapy in a RNA Toxicity Mouse Model with an Antisense Oligonucleotide Therapy Targeting a non-CUG sequence within the DMPK 3'UTR RNA.
Yadava RS, Yu Q, Mandal M *et al.*
Hum Mol Genet. 2020 (Apr)

Cugamycin and deglycobleomycin combination treatment

▪ The repeated sequence of abnormal *DMPK* RNA has a very specific structure that can be recognised and targeted by small molecules.
Researchers have combined cugamycin, which recognises these structures, with deglycobleomycin, which cuts the messenger RNA. Deglycocugamycin was tested on a DM1 cell model, and showed encouraging results.

Precise Targeted Cleavage of a r(CUG) Repeat Expansion in Cells by Using a Small-Molecule-Deglycobleomycin Conjugate.
Angelbello AJ, DeFeo ME, Glinkerman CM *et al.*
ACS Chem Biol. 2020 (Mar)

CDK12 and microtubule inhibitors

▪ Two other mechanisms have been identified to reduce the quantity of abnormal *DMPK* RNA: inhibition of *CDK12*, involved in the transcription of certain genes with specific structures, and interference with microtubules, although the mechanism involved is not entirely understood. Beneficial effects of inhibitors of these pathways were observed both in cell models and in mice with DM1.

A CTG repeat-selective chemical screen identifies microtubule inhibitors as selective modulators of toxic CUG RNA levels.
Reddy K, Jenquin JR, McConnell OL *et al.*
Proc Natl Acad Sci U S A. 2019 (Sep)

CDK12 inhibition reduces abnormalities in cells from patients with myotonic dystrophy and in a mouse model.
Ketley A, Wojciechowska M, Ghidelli-Disse S *et al.*
Sci Transl Med. 2020 (Apr)

Physical exercise

▪ A study on physical exercise in mice with DM1 showed that the beneficial effects of endurance training on muscle mass was accompanied by a decrease in the quantity of abnormal *DMPK* RNA and a decrease in protein maturation abnormalities.

Endurance exercise leads to beneficial molecular and physiological effects in a mouse model of myotonic dystrophy type 1.
Sharp L, Cox DC, Cooper TA.
Muscle Nerve. 2019 (Sep)

Acting on disrupted regulatory proteins

In Steinert's disease, MBNL-family regulatory proteins are sequestered in the aggregates formed by abnormal *DMPK* RNA. These MBNL proteins regulate the maturation of other RNA and so influence the activity of many other cell proteins.

In DM1, sequestration of these MBNL proteins by abnormal nuclear aggregates reduces their availability, causing by extension a great deal of disruption in muscle cells.

▪ Several approaches are being studied to increase the quantity and/or activity of MBNL proteins. Positive results in cell and animal models have been reported with the use of micro-RNA and nonsteroidal anti-inflammatory agents.

MicroRNA-Based Therapeutic Perspectives in Myotonic Dystrophy.
López Castel A, Overby SJ, Artero R.
Int J Mol Sci. 2019 (Nov)

Inhibition of cyclooxygenase-1 by nonsteroidal anti-inflammatory drugs demethylates MeR2 enhancer and promotes Mbnl1 transcription in myogenic cells.
Huang K, Masuda A, Chen G *et al.*
Sci Rep. 2020 (Feb)

Micro-RNAs (miRNAs) *are small RNA molecules produced by the cell that are not translated into protein. Their role is to regulate the expression of genes by blocking the translation of the messenger RNA of these genes into protein. The expression of these miRNAs varies depending on the situation. In neuromuscular disease, certain miRNAs are expressed and not others, and the combination of miRNAs expressed differs depending on the neuromuscular disease and is specific to each disease.*

Acting on autophagy

Autophagy is a mechanism by which cells dispose of used or toxic elements they contain (performing a sort of cell cleaning function). Studies have identified that excessive activation of autophagy occurs in DM1 models. This is why one of the therapeutic avenues being investigated for this disease is the inhibition of this phenomenon.

▪ A study has shown that a drug that is known to block autophagy, chloroquine, increases the amounts of MBNL1 and MBNL2 available, and reduces cell disruption, characteristic of DM1, in mice and flies with DM1.

Increased Muscleblind levels by chloroquine treatment improve myotonic dystrophy type 1 phenotypes in in vitro and in vivo models.
Bargiela A, Sabater-Arcis M, Espinosa-Espinosa J *et al.*
Proc Natl Acad Sci U S A. 2019 (Nov)

▪ MicroRNA-7 (miR-7) microRNA is found in reduced quantities in DM1. Research on muscle cells modelling DM1 shows that re-establishing a normal level of miR-7 restores the ability of these stem cells to differentiate and fuse, thus improving muscle repair (without this repair mechanism, the muscle decreases in volume little by little). MicroRNA-7 seems to act on autophagy, by a mechanism independent of MBNL1.

miR-7 Restores Phenotypes in Myotonic Dystrophy Muscle Cells by Repressing Hyperactivated Autophagy.
Sabater-Arcis M, Bargiela A, Furling D, Artero R.
Mol Ther Nucleic Acids. 2019 (Nov)

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