PW 12:
DM1 – Pathogenesis and treatment

PW12-142

THE BLOCK OF CA-DEPENDENT K+CHANNELS REDUCES MYOTONIA IN STEINERT DISEASE: AN IN VIVO PHARMACOLOGICAL STUDY

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Many studies have been carried out to clarify the mechanism underlying the abnormalities of sarcolemma in Myotonic Dystrophy type1 (MD) but univocal results have not been reported.
The first clinical evidence of specific channels involvement was suggested after the observation that the local treatment of muscle with apamin, a specific blocker of Ca-activated K^+-channels (SK), reduced the “myotonic runs” in MD (Beherens et al.,1994). Recently we showed a characteristic surface EMG pattern, strictly leaked to myotonia, in MD patients (Chisari et al.,2001).
In this study we evaluated the effect of the local administration of apamin on sarcolemma excitability alteration recorded through surface and needle EMG.
We applied a stimulation protocol to 8 MD patients and recorded an amplitude parameter (ARV) of surface EMG before and after the local injection of 50 µl of 10 µM apamin. Moreover, to verify the reliability of our approach, in two patients we recorded the needle EMG “myotonic runs” before and after the local injection of apamin.
According to Beherens et al., we observed a clear reduction of myotonic discharge recorded by means of needle EMG. On the other hand, in 2 out of 8 patients we observed a complete but transient normalization of the characteristic surface EMG pattern.
This work confirmed the role of SK in sarcolemma “instability” represented by the needle EMG “myotonic runs” and did not rule out the hypothesis that SK could play a specific role in the genesis of phenotypic expression of myotonia in MD. Of course further studies need to validate this hypothesis but we consider this approach a good starting-point to study ***in vivo*** muscle functional alteration in Myotonic Dystrophy type1.

PW12-143	**ABNORMALITIES IN DIAPHRAGM NEUROMUSCULAR JUNCTIONS AND IN THE PHRENIC NERVES ARE DETECTED IN A TRANSGENIC MICE MODEL OF MYOTONIC DYSTROPHY** PANAITE PA[1], GANTELET E[1], KRAFTSIK R[2], GOURDON G[3], KUNTZER T[1], BARAKAT-WALTER I[2] (1) Laboratoire de Recherche Neurologique, CHUV, Lausanne, SWITZERLAND. (2) Département de Biologie Cellulaire et de Morphologie, Université de Lausanne, Lausanne, SWITZERLAND. (3) INSERM U781, Hôpital Necker, Université René Descartes, Paris V, FRANCE.
To contact the author:: Petrica-Adrian.Panaite@chuv.ch .	Myotonic dystrophy (DM1) is caused by abnormal expansion of a polymorphic $(CTG)_n$ repeat, located in the DM protein kinase gene. Respiratory problems have long been recognized to be a major feature of DM1 disease and are probably the main factors contributing to mortality. Since several pulmonary impairments are associated with phrenic nerve and diaphragm dysfunction, we examined the diaphragm and the respiratory neural network in a reliable animal model of human myotonic dystrophy disease. The morphological and morphometric analysis of adjacent diaphragm muscle sections labeled with rhodamine alpha-bungarotoxin and neurofilament antibody revealed that the diaphragm end-plates had significantly smaller size and less complex shapes in DM1 mice than in control. Moreover, the mean density of ACh receptors on the postsynaptic membrane is significantly decreased in DM1 mice. The alterations observed in DM1 neuromuscular junctions indicate a possible denervation of diaphragm muscle. The analysis of both semi and ultra- thin sections taken from the middle trunk of phrenic nerve demonstrated there is a severe and significant decrease in the number of unmyelinated fibers in DM1 mice, however, there is no loss in the number of myelinated fibers. Also no pathological signs or loss in neuronal cells are detected either in medullary respiratory centers or in cervical spinal cord motor neurons. The absence of loss in the number of myelinated fibers in the middle trunk of phrenic nerve led to conclude that the denervation of end-plates is due to distal or intramuscular nerve degeneration. Since the neuromuscular junction are involved in the transmission of action potentials and the afferent phrenic unmyelinated fibers control the inspiratory activity, our results suggest that the respiratory impairment associated with myotonic dystrophy disease could be partially due to the pathological alterations in neuromuscular junctions and phrenic nerves.

PW12-144

THE RNA-BINDING PROTEIN STAUFEN : A NEW PLAYER IN MYOTONIC DYSTROPHY TYPE 1 ?

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Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder that results in several characteristic symptoms including myotonia, muscle weakness and wasting, pain, cardiac defects, cataracts, cognitive impairments, and endocrine abnormalities. Converging lines of evidence have emerged to support the idea that an abnormal expansion of CUG nucleotide repeats in the 3'UTR of the myotonic dystrophy protein kinase (DMPK) mRNA is the main cause of these complex symptoms. Specifically, it is now believed that mutant DMPK transcripts cause a toxic RNA gain of function as they sequester through their 3'UTR expansion, RNA-binding proteins and transcription factors destined to normally regulate other target mRNAs and/or genes. Accordingly, it has become essential to identify proteins that interact with mutant DMPK transcripts and determine if their pattern of interaction is altered in diseased cells.
Staufen is a RNA-binding protein known to be involved in RNA transport. Here, we initiated a series of experiments aimed at determining whether Staufen participates in the complex DM1 pathology. Our results show that levels of Staufen protein are increased in muscles from a DM1 mouse model engineered to express a pathogenic transgene. Using immunoprecipitation analysis, we demonstrate that Staufen binds to DMPK mRNA in skeletal muscle cells. Interestingly, Staufen protein seems also involved in pre-mRNA splicing. As several mRNAs are known to be mis-spliced in DM1, we propose that Staufen may be responsible for some of these defects, and thus could contribute to the basic mechanisms underlying the complex phenotype associated with DM1.
This work is supported by the CIHR and AFM.

PW12-145	**INVESTIGATION OF NOVEL CANDIDATES THAT INTERVENE IN MYOTONIC DYSTROPHY TYPE 1** LAURENT FX[1], MARIE J[1] (1) Centre de Génétique Moléculaire , CNRS, Gif sur Yvette, FRANCE.
To contact the author:: marie@cgm.cnrs-gif.fr.	Myotonic dystrophy type 1 (DM1) is a multisystemic disorder caused by an expanded CTG repeat sequence in the 3' untranslated region of the DMPK gene. One of the most typical features is the disruption of alternative splicing of several pre-mRNA expressed in muscle and the brain. It has been proposed that the CUG repetitions would sequester and induce modifications of proteins involved in alternative splicing, such as the Muscleblind-like family (MBNL1-3) and the CUG-binding protein, two classes of proteins that regulate alternative splicing of several misregulated mRNA in the pathology. However, the sequestration of MBNL is not sufficient to explain all of the clinical phenotypes, suggesting that other factors could be involved in the DM1 pathogenesis. Thus, we have decided to identify molecular partners of MBNL1 and investigate the repertoire of proteins that bind to CUG repeats by affinity purification. We have cloned MBNL1 cDNA "40 isoform" with two different tags (the TAP-tag and the Histidin-Biotin tag), allowing us to purify the complexes by tandem affinity purification. Both constructions are well expressed in transient transfection in C2C12 cells and we are currently establishing inducible stable cell lines. Secondly, several plasmids containing CUG or CAG repeats of different lengths have been transcribed; the RNAs have been biotinylated, bound to streptavidin agarose and incubated with myogenic nuclear extracts. After elution, the proteins were analysed by SDS-PAGE electrophoresis. Preliminary results show that several proteins are specifically associated with the repeats according to the myogenic differentiation. We have identified 2 candidates; one is a nuclear factor involved in myogenic differentiation; the other is a splicing factor also required for mRNA export. We are currently testing these proteins for immunocolocalisation with nuclear foci in DM1 patient cells and analysing their expression in patients vs. control.

PW12-146	**TAU MIS-SPLICING IN MYOTONIC DYSTROPHY TYPE 1: A BRAIN AND MUSCLE COMMON MOLECULAR MECHANISM ?** TRAN H[1], DHAENENS C[1], GHANEM D[1], CHARLET N[2], VAN BRUSSELS E[1], SABLONNIERE B[1], BUÉE L[1], CAILLET-BOUDIN ML[1], SCHRAEN-MASCHKE S[1], SERGEANT N[1] (1) INSERM U 837, Centre Jean-Pierre Aubert, Lille, FRANCE. (2) INSERM AVENIR group, IBGMC, Illkrich, FRANCE.
To contact the author:: tran@lille.inserm.fr.	Myotonic Dystrophy type 1 (DM1), the most common form of adult muscular dystrophy, is a multisystemic inherited disorder that affects skeletal muscle, heart and brain. DM1 is caused by a CTG expansion mutation located on the 3'untranslated region of the *dystrophia myotonica protein kinase* (*dmpk*) gene. The pathogenesis results primarily from a toxic gain of function of RNAs bearing long CUG tracks. Toxic RNAs accumulate in the nucleus and sequester RNA binding proteins. Their subsequent loss of function alters developmentally regulated alternative splicing, thereby causing specific symptoms of the disease. We previously showed in DM1 brain a modified splicing of Tau, consisting on a reduced inclusion of Tau exons 2/3. Tau is a microtubule associated protein expressed in brain and muscle. Tau is also the main component of neurofibrillary degeneration, a pathological lesion observed in DM1 brain and in other neurodegenerative disorders referred to as Taupathies. Interestingly, our analyses on DM1 muscle biopsies also revealed a mis-splicing of Tau primary transcript similar to the one observed in brain. This result suggests a possible common mechanism of alternative splicing in brain and muscle. To address this question, we investigate further the potential role of the splicing factor Muscleblind like 1 (MBNL1) on Tau splicing. MBNL1 is expressed in both tissues and was found sequestered by expanded RNAs. Herein, we show that depletion of MBNL1 expression by small RNA interferences reduces inclusion of Tau exons 2/3, as observed in DM1 brain and muscle tissue. Interestingly, we also show that ectopic expression of MBNL1 alone does not modify Tau splicing whereas co-expressed along with expanded RNAs it restores Tau mis-splicing. Altogether, our results suggest a potential common mechanism responsible of Tau mis-splicing in brain and muscle tissue where the splicing factor MBNL1 would be one of the main actors.

PW12-147	**<u>THE FALLACY OF FOCI: A HETERODOX VIEW OF MUTANT RNA IN MYOTONIC DYSTROPHY</u>** JUNGHANS R[1] (1) Boston University School of Medicine, Roger Williams Medical Center, Providence, USA.
To contact the author:: rjunghans@rwmc.org.	Dystrophia myotonia type 1 (DM1; myotonic dystrophy) is an autosomal dominant disorder due to a large CTG expansion in the 3' untranslated region (UTR) of the DM protein kinase (DMPK) gene. Transcription of this gene yields a long CUGn-containing mutant (mut) RNA, in which clinical disease is associated with repeats of n=100-5000. Phenomenologically, the expression of mut RNA is correlated with the morphologic observation of ribonucleoprotein (RNP) precipitates ("foci") in the nuclei of DMPK-expressing cells. There has been an abiding but unsupported concept that the identification of proteins in these foci is essential for a conclusion of protein-mut RNA interactions. In this presentation, I contend that this is an unwarranted inference. Revision of this view is essential to restoring confidence in diverse data on mut RNA binding to proteins not in foci that have been discounted because of non-conformity with this premise, data that are essential to a scientifically sound understanding of the underlying pathobiology of this disease. A new model of mut RNA-protein interactions is proposed with distinct binding properties for soluble and insoluble (foci) mut RNA that accommodates these data without exclusions. I acknowledge present or past support from the Association Francaise contre les Myopathies (AFM) and the Muscular Dystrophy Association (MDA).

PW12-148	**RNA METABOLISM DEFECTS IN MUSCLE AND BRAIN OF MICE CARRYING LARGE CTG REPEAT EXPANSIONS: AN ANIMAL MODEL TO EXPLORE THE MOLECULAR PATHOGENESIS OF MYOTONIC DYSTROPHY** GOMES-PEREIRA M[1], HUGUET A[1], ACQUAIRE J[1], NICOLE A[1], FOIRY L[1], MUNNICH A[1], GOURDON G[1] (1) Inserm U781, Hôpital Necker Enfants Malades, Université Paris Descartes, Paris, FRANCE.
To contact the author:: pereira@necker.fr.	Myotonic dystrophy (DM) is the most common form of adult muscular dystrophy, with a worldwide incidence of 1 in 8000. Although traditionally regarded as a muscle disease, DM has also emerged as a brain disorder. DM type 1 (DM1) is caused by the expansion of an unstable trinucleotide CTG repeat in the 3'UTR of the *DM protein kinase* (*DMPK*) gene. Repeat length correlates directly with disease severity and inversely with age of onset. Therefore, intergenerational expansion-biased repeat instability provides the molecular explanation for the increasing severity of the symptoms and earlier age of onset in successive generations of an affected family. Experimental evidence supports a *trans*-dominant effect of CUG-containing transcripts: toxic CUG repeats accumulate in nuclear foci, affecting the levels and/or localisation of key splicing regulators, and disrupt the processing of multiple downstream RNA transcripts. We have previously generated transgenic mice to investigate the mechanisms of trinucleotide repeat expansion and the molecular pathogenesis of DM1. DM300 mice carry a highly unstable 300-CTG expansion in the context of the human *DM1* locus. These animals recreate important aspects of the disease, including myotonia, myopathy, nuclear RNA foci accumulation in multiple tissues and misdistribution of tau protein isoforms in brain. Large intergenerational expansions or "big jumps" (ranging between 200 and 500 CTG in one single transmission) have been recently reported in DM300 mice, resulting in very large trinucleotide sequences (up to 1800 CTG repeats), reduced body size and splicing abnormalities, notably in muscle and brain. Interestingly, the extent of the splicing defects observed varies between muscles and brain regions. We are currently using our mouse model to investigate the relationship between key splicing factors and abnormal RNA metabolism in DM1. Transgenic mice carrying very large CTG repeat expansions provide a useful tool to dissect the molecular disease pathogenesis and to assess novel therapeutic schemes.

PW12-149	**IDENTIFICATION OF EARLY DEVELOPMENTAL ALTERATIONS IN MYOTONIC DYSTROPHY TYPE 1 USING A HUMAN PGD-DERIVED EMBRYONIC STEM CELL LINE** AUBERT S[1], GIRAUD-TRIBOULT K[1], ROCHON-BEAUCOURT C[1], DENIS J[1], LAUSTRIAT D[1], BAGHDOYAN S[1], GIDE J[1], FURLING D[2], CHAMPON B[1], KASSAR-DUCHOSSOY L[1], MARTINAT C[1], SERMON K[3], PESCHANSKI M[1], PIETU G[1] (1) INSERM/UEVE U861 I-Stem, AFM, EVRY, FRANCE. (2) INSERM/UMR S 787, PARIS, FRANCE. (3) Department of Embryology and Genetics, Vrije Universiteit Brussel and UZ Brussel, BRUSSEL, BELGIUM.
To contact the author:: saubert@istem.genethon.fr.	In order to address early developmental events associated with the mutation in Myotonic Dystrophy type 1 (DM1), we took the opportunity of an existing human embryonic stem cell line (hES) derived from an embryo after pre-implantation genetic diagnosis (PGD) [Mateizel, I.,et al. *Hum Reprod* 2006]. The mutant (VUB03_DM1) carrying the mutation (expanded CTG repeat in the 3' UTR of the *DMPK* gene) and two control (SA01 and VUB01) hES cell lines were specified towards neural progenitor cells (NPC) and mesenchymal precursors (MPC) which would give rise after lineage-specific differentiation to cell types affected by the pathology, namely the central nervous system and skeletal muscle. Molecular analysis of these two progenies exhibited alterations previously described in patient DM1 cells. In both mutant NPC and MPC cells, we observed the DMPK mRNA accumulation in the nucleus co-localizing with Muscleblind 1 (MBNL1) protein, a splicing factor. We also detected abnormal alternate splicing of the insulin receptor gene (*INSR*) in both NPC and MPC mutant cells. To confirm these results, we performed first the MBNL1 knock-down expression in both mutated and normal MPC. Thus, we demonstrated that the abnormal *INSR* splicing was specifically linked to the down-expression of MBNL1. In parallel, after transfection of a $(CTG)_{960}$ construction into control MPC we observed that the presence of the $(CTG)_{960}$ repeats generated foci, which were able to trap the MBNL1 protein in the nucleus. Moreover this model reproduced the abnormal splicing of *INSR*. In conclusion, this study demonstrates that DM1 hES cell line displayed some features observed in patients and that DM1, though a disease with relatively late clinical onset, is associated with “early developmental” alterations. It underlines the importance of PGD-derived ES cell lines as cellular tool to decipher molecular mechanisms of DM1.

PW12-150	**P16 PROMOTES PREMATURE SENESCENCE OF DM1 MYOBLASTS** GASNIER E[1], BIGOT A[1], MOULY V[1], FURLING D[1] (1) UMRS787 – Groupe Myologie; Inserm / UPMC-ParisVI; Institut de Myologie, Paris, FRANCE.
To contact the author:: erwan.gasnier@chups.jussieu.fr.	Myotonic Dystrophy type I (DM1) is caused by a CTG expansion in the 3'-UTR of the DMPK gene and is characterized by progressive muscle weakness and wasting. Large CTG repeats affect the differentiation program and we have showed that the proliferative capacity of the cDM1 myoblasts was significantly reduced when compared to non-affected cells. DM1 myoblasts have not exhausted their proliferative capacity but have a premature replicative arrest. Analysis of several markers suggests that a mechanism of premature senescence triggers this early arrest. We found that an early accumulation of the cdk inhibitor p16 is associated with this phenotype in DM1 cells. We show that an inactivation of p16 activity in DM1 myoblasts was able to inhibit premature senescence and to restore proliferative capacity : DM1 cells overexpressing CdK4 that binds and inhibits p16, can make the same number of division as control cells. Our results also indicate that the accelerated telomere shortening measured in DM1 satellite cells may not contribute to the aberrant induction of p16. We propose that deregulation of the mitotic clock is a consequence of a stress related to the amplified CTG repeat that promotes premature senescence mediating by a p16-dependent mechanism in DM1 muscle cell precursors. The mechanism of p16 regulation in the DM1 cells is currently under investigation in order to determine how the CTG mutation interferes with the p16 pathway.

PW12-151	**USE OF HUMAN EMBRYONIC STEM CELLS-DERIVED MOTONEURONS TO STUDY THE MOLECULAR AND CELLULAR MECHANISMS OF MYOTONIC DYSTROPHY TYPE 1** MARTEYN A[1], LECUYER C[1], SERMON K[2], PIETU G[1], PESCHANSKI M[1], MARTINAT C[1] (1) INSERM/UEVE UMR 861, ISTEM, AFM, Evry, FRANCE. (2) Centre for Medical Genetics, Brussels, BELGIUM.
To contact the author:: cmartinat@istem.genethon.fr.	Human embryonic stem cell lines (hES) provide an invaluable resource for the understanding of molecular and cellular mechanisms implicated in the development of monogenic diseases. Indeed, hES cell lines carrying the causal mutation and derived from affected embryos discarded through a preimplantation genetic diagnostic (PGD) process can be used as a cellular tool for this pathological modelling application. Thus, a mutant hES (VUBO3) was derived, at the AZ-VUB (Brussels, Belgium), from a blastocyst carried out through a PGD for Myotonic dystrophy type 1 (DM1). DM1, characterized by dystrophic and myotonic symptoms, is caused by an abnormal (CTG)n repetition located in the 3'-untranslated region of the *DMPK* (Dystrophy Myotonic Protein Kinase) gene. This mutation leads to pathological RNA pre-messenger expression, which, accumulate in the nucleus, sequestrate several RNA-binding proteins, implicated in the alternative splicing process. Thus, abnormal regulation of alternative splicing, and subsequently to the misexpression of different proteins can be observed during the pathological process of this disease. Although the knowledge of DM1 molecular mechanisms is expanding, the general DM1 physiopathology is still poorly understood, as the one underlying myotonia, the delay of muscular decontraction after motoneuron stimulation. By using the mutant hES cell line VUB03, we analyzed the effect of this mutation in the differentiation and survival of hES-derived motoneurons. In comparison with three wild type hES cell lines, no significant difference was observed. Nevertheless, the expression of mature cholinergic markers, and other genes involved in the axonal guidance seem to be altered in VUB03-derived neurons. The analysis of alternative splicing of these genes indicated abnormalities that might be implicated in the modulation of their expression. The effect of these genetic modulations on the establishment of the neuromuscular junction is under processed.

PW12-152	**ALTERED ALTERNATIVE SPLICING OF MBNL1 IN MYOTONIC DYSTROPHY TYPE 1** LEMERCIER C[1], BUTLER-BROWNE G[1], FURLING D[1] (1) UMRS787 – Groupe Myologie; Inserm / UPMC-ParisVI; Institut de Myologie, Paris, FRANCE.
To contact the author:: camille.lemercier@chups.jussieu.fr.	Myotonic dystrophy (DM1) is an autosomal dominant neuromuscular disease caused by an expanded trinucleotide repeat (CTG, n >50) located in the 3'UTR of the DMPK gene. The classic adult form is characterized by myotonia, progressive muscle weakness and wasting and the severe congenital form is associated by impairment in skeletal muscle development. The variable and progressive phenotype observed in DM1 patients is caused by a complex molecular pathogenesis. An increasing body of evidence suggests that the nuclear accumulation as discrete foci of mutant DMPK transcripts containing CUG expansions may contribute to the DM1 physiopathology. MBNL1 proteins bind specifically to these CTG expanded repeats and their normal functions in the regulation of alternative splicing of pre-mRNAs are altered. In addition, the MBNL1 knockout mouse model reproduces RNA splicing abnormalities that are characteristic of DM1 disease suggesting that MBNL1 deregulation plays a role in the development of the pathology. Interestingly, MBNL1 itself is also subject to alternative splicing. In this study we will determine if MBNL1 splicing is altered in the muscle of DM1 patients. We have analysed the expression of the different isoforms of MBNL1 during normal human muscle development and in DM1 patients. Preliminary results will be presented.

PW12-153	**PROGRESSIVE ATROPHY OF THE SKELETAL MUSCLES IN A DM1 MOUSE MODEL** VIGNAUD A[1], FERRY A[1], GOURDON G[2], HUGUET A[2], BUTLER-BROWNE G[1], FURLING D[1] (1) UMRS787- Groupe Myologie ; Inserm / UPMC-Paris6; Institut de Myologie, Paris, FRANCE. (2) Inserm U781, Hôpital Necker-Enfants Malades, Paris, FRANCE.

To contact the author:: furling@ext.jussieu.fr.	Myotonic dystrophy type 1 (DM1) is caused by the amplification of a CTG repeat and is characterized by a wide spectrum of clinical manifestations affecting skeletal muscle such as progressive weakness, wasting and myotonia. In order to investigate the role of the CTG mutation in the development of the disease, a transgenic DM1 mice, carrying the CTG expansion and producing an abnormal human DMPK with 350 repeats has been developed by Gourdon's group. These mice reproduce some features of the human disease, such as myotonia. In the present study, we have characterized the functional properties of the skeletal muscles of these transgenic mice. A progressive decrease of force production (weakness) with age was measured in the *tibialis anterior* TA of the DM1 mice. This weakness is progressive and a significant 30% decrease in the force was measured in 10-month old DM1 mice. However, the ratio force/mass did not seem to be different between non-transgenic and transgenic mice, indicating that the weakness is caused by a loss in muscle mass. To determine if the muscle wasting in DM1 mice is associated with an active process, we have examined by northern blot the expression of the atrogin-1, a muscle-specific ubiquitin-ligase required for muscle atrophy. Our results showed that the expression of atrogin-1 is significantly increased in both 3- and 10-month old transgenic mice when compared to age-matched control. Its expression also increases with age confirming the progressive muscle atrophy of the DM1 mice. In conclusion this mouse model reproduces the progressive muscle atrophy that is observed in human patients and may be used to evaluate therapeutic strategies.

PW12-154	**ACETYLSALICYLIC ACID AS A POTENTIAL TREATMENT FOR THE CONGENITAL FORM OF MYOTONIC DYSTROPHY** PUYMIRAT J[1], BEAULIEU D[1], CHAPEDELAINE P[1] (1) CHUQ Research Center, Quebec, CANADA.
To contact the author:: jack.puymirat@crchul.ulaval.ca.	Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy in adult. One characteristic of DM1 is the presence of a congenital form (CDM1), which is almost exclusively of maternal origin. It is the most severe form of DM1 with high neonatal mortality. The phenotype of the CDM1 differs in several aspects from that observed in the adult form and histological examination of skeletal muscles revealed that the changes are those of a failure of development of muscles rather than an active degeneration. To date, little is known about the mechanisms by which the expansion causes the delay in CDM1 muscle development. We recently identified prostaglandin-E2 (PGE-2), as a soluble factor produced specifically by CMD1 myoblasts, which blocks myogenic differentiation. The level of Cox-2 is specifically increased in skeletal muscle derived from CDM1 but not from DM1 or DM2. Treatment of normal myoblasts with PGE-2 blocked their differentiation in a dose-dependant manner. Because COX-2 inhibition also alters cellular production of other PGs, we targeted microsomal PGES (mPGES-1), an enzyme that acts downstream of COX-2 and that affect PGE2 production only. Inhibition of mPGES-1 by specific shRNAs completely abolished the production of PGE2 in the culture medium and restores the ability of CDM1 myoblasts to fuse. The literature describes several molecules that block the synthesis of PGE-2 and are thus candidates to correct the CDM1 phenotype. Among these molecules, acetylsalicylic acid, which is known to act as inhibitors of cyclo-oxygenase enzymes, restores myoblast differentiation. This drug has already received regulatory approval for treatment, making phase 2 and 3 clinical trials possible.