aggregates or foci that sequester MBNL splicing factors leading to functional loss of MBNL and alternative splicing misregulations of a subset of pre-mRNAs. Thus, mis-splicing of *CLCN1*, *INSR* and *BIN1* pre-mRNAs were associated respectively to myotonia, insulin resistance and muscle weakness in DM1. Recently, we determine that abnormal splicing switch of *DMD* exon 78 in DM1 skeletal muscles compromises muscle fiber maintenance leading to ultrastructural abnormalities such as ringed fibers and sarcoplasmic masses. Finally, new abnormal spliced events have been identified in heart tissues of DM1 patients, and we showed that splicing alteration of *SCN5a* contributes to cardiac conduction abnormalities and arrhythmia, both symptoms of DM1.
Currently there is no cure for DM1 however several strategies are under development to reverse toxic CUGexp-RNAs dominant effects. Here we propose to neutralize RNA toxicity in DM1 cells by interfering with the abnormal CUGexp-RNA:MBNL interaction in order to release sequestered endogenous MBNL factor and restore its function. For this purpose, we have engineered a modified MBNLΔ polypeptide that keeps its RNA binding property but lacks its splicing activity. To evaluate its ability to inhibit CUGexp-RNA toxicity, we first expressed a GFP-MBNLΔ construct in DM1 muscle cells by using lentiviral vectors. We found that GFP-MBNLΔ colocalized with nuclear CUGexp-RNA foci and splicing misregulations as well as differentiation defects were corrected in DM1-treated muscle cells. To further assess this strategy *in vivo*, intramuscular injections of AAV-GFP-MBNLΔ vectors were performed in DM1 mice (HSA-LR) expressing 220CTG in skeletal muscles. As observed *in vitro*, colocalization of GFP-MBNLΔ with nuclear CUGexp-RNA foci in myofibers indicates that MBNLΔ is able to compete and release endogenous MBNL from these aggregates. More, splicing alterations of several transcripts were normalized or nearly corrected in injected HSA-LR mice and the myotonia was also abolished. In conclusion, we propose that a MBNLΔ-decoy gene therapy approach could represent an alternate or complementary therapeutic approach for Myotonic Dystrophy.

Structuring translational research in myotonic dystrophy: current approaches towards novel therapies
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Myotonic dystrophy type 1 (DM1) is the most prevalence autosomal dominant disease affecting the muscular function for which new treatments are being developed. Recent progress in understanding DM1 pathophysiology led to several molecular and pharmacological therapeutic approaches. Consequently, drug development and upcoming clinical trials further stress the need for dedicated translational research studies. This overview will present successful synergistic initiatives in France to foster collaborative research toward clinical trial readiness. This collaborative approach encompass various tools, infrastructure and network, including (1) the characterization of a DM mouse model, (2) the study of CUG expanded nuclear foci as therapeutic biomarker in mouse and human muscle, (3) a natural history of DM1 patients over 3 years, to prospectively better characterize neuromuscular outcome measures (4) a clinical network of reference neuromuscular centers, (4) the national DM-scope registry, (5) collaborative epidemiological and observational studies aiming at effective selection and enrolment of DM patients in clinical trials.

Plenary Session- Pharmacotherapy
• *Olivier DORCHIES (SWITZERLAND)* • *Zohar Argov (ISRAEL)* • *Ichizo Nishino (JAPAN)* • *Ana Ferreiro (FRANCE)*

Pharmacotherapy of Duchenne muscular dystrophy: an overview on nutraceuticals and repurposed drugs
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Duchenne muscular dystrophy (DMD) is a severe X-linked disorder caused by the lack of dystrophin, a large protein that confers mechanical stability to muscle fibres and ensures proper signalling across the sarcolemma. Boys affected by DMD develop progressive muscle wasting, cardiac and respiratory failure, and early death. Currently, corticosteroids are among the only drugs prescribed to boys with DMD. These drugs have limited efficacy and many adverse effects. Recently, there have been tremendous efforts towards gene and cell therapy to repair or replace the defective dystrophin gene. As these approaches are facing many hurdles, pharmacological strategies using small molecular weight compounds offer numerous advantages. This presentation will discuss briefly the pros and cons of gene therapy, cell therapy, and pharmacotherapy. It will then focus on dietary supplements (nutraceuticals) and repurposed drugs for time-effective translation of data obtained on animal models into clinical trials, hopefully, for the benefit of patients.
Of note, although DMD is a monogenic disease, many signalling pathways and cellular processes are altered downstream of the missing dystrophin. These include impaired calcium homeostasis, mitochondrial function, energy production, protein synthesis, kinase activity, regeneration from stem cells, and excessive production of reactive oxygen/nitrogen species, exposure to cytokines, inflammation, fibrosis, etc. Fortunately, most, if not all, of these features are not specific for DMD but are shared by other disorders such as inflammatory diseases, diabetes, age and cancer-related loss of muscle mass, heart failure, and fibrotic disorders. This situation offers the opportunity to mitigate DMD symptoms via a variety of pharmacological targets and using diverse classes of drugs and nutraceuticals that are already approved for human use and are readily available and affordable. The preclinical evaluation of nutraceuticals and repurposed drugs in DMD animal models and their facilitated translation into clinical trials will be illustrated using examples of our research as well as from other groups. These compounds are creatine, green tea polyphenols and other antioxidants, melatonin, pentoxifylline, rimeporide, losartan, halofuginone, Viagra and related compounds.
Finally, we will show that estrogenic signalling is a previously unrecognized pathway that critically controls dystrophic disease in model mice. Based on published and unpublished work from our group, we will show that tamoxifen, a drug used for more than 30 years to treat breast cancer, efficaciously ameliorates muscle function and structure in dystrophic mice and may become a symptomatic treatment for DMD boys in the next years.

Intravenous trehalose improves dysphagia and muscle function in oculopharyngeal muscular dystrophy (OPMD): preliminary results of 24 weeks open label phase 2 trial.

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Objective: To assess the safety and efficacy of weekly IV administration of Cabaletta (trehalose 9% solution) in OPMD after a 24 week open label phase 2 trial.
Background: Trehalose showed efficacy in reducing PABPN1 muscle aggregation and improving muscle function in a transgenic OPMD mouse model.Methods:25 genetically-confirmed OPMD patients received weekly infusion of 300 cc Cabaletta. Swallowing, muscle power and functional tests, and swallowing quality of life report (SWAL-QOL) were assessed at baseline and after 24 weeks.
Results: No serious drug-related adverse effects were noted. Time to swallow 80cc cold water (an OPMD validated dysphagia test) improved by 35.3% ($p<0.0001$). This was correlated with improvement in patient reported symptom severity ($p=0.05$). Validated swallowing related patient questionnaire (SWAL-QOL) score improved progressively from 54.0 points to 58.8 after 12 weeks to 61.4 after 24 weeks (12.1% improvement $p=0.0448$). Muscle strength measured in Kg by a hand-held dynamometer showed an increased power in all 5 tested muscle actions, and reached significance for knee and foot extension. When a lower limb composite (combining hip flexion, knee extension, foot dorsiflexion) power was calculated the percent increase in strength was 13.4% ($p=0.0059$). Arm lift test improved by 17.6% ($p=0.019$), while the improvement in sit-to-stand (14.1%) and 4-stairs climb tests showed an improvement trend which did not reach significance.
Conclusions: Preliminary findings show that IV trehalose is safe and improves swallowing and muscle power that are major disabilities in OPMD. The objective measured improvement in drinking time is matched by the QOL reports. This is the first time in OPMD that a pharmacotherapy shows early improvement of multiple recorded end points. A phase 3 placebo controlled study is soon to be launched.

Inclusion body myositis – current status

Ichizo Nishino, MD, PhD, Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP)

Inclusion body myositis (IBM) is the most common form of idiopathic inflammatory myopathy in patients over 50 years of age in Western countries. It is characterized clinically by progressive muscle weakness and atrophy especially in quadriceps and finger flexor muscles and pathologically by cytotoxic T-cell invasion into endomysium and non-necrotic muscle fibers, together with MHC-1 expression in myofibers, and by rimmed vacuole formation for which p62 is involved. However, the pathogenesis of the disease is not still clear.

Interestingly, the prevalence of IBM appears to be quite different in different regions of the world. For example, in most South East Asian countries, IBM is quite rare, suggesting the presence of certain genetic factor. In fact, MHC ancestral haplotype 52.1 has been associated with Japanese IBM patients. Nevertheless, the number of IBM patients seems to be increasing in Japan based upon the frequency of the diagnosis of IBM on muscle pathology in NCNP which is functions as a referral center for muscle disease and collects about 70% of muscle biopsies in the whole country. This suggests that environmental factors, such as aging, life style change, and chronic virus infection, may also contribute to the development of IBM. In line with this assumption, we recently found that the prevalence of chronic hepatitis C virus (HCV) infection is high in IBM patients, suggesting that development of IBM is most likely multifactorial.

Autoantibodies to Cytosolic 5'-nucleotidase 1A (cN1A or NT5C1A) have been reported to be specifically increased in blood from IBM patients, raising a possibility that this antibody may be a useful diagnostic marker of IBM. We measured anti-cN1A antibodies in plasma from patients with IBM together with those with other inflammatory and non-inflammatory myopathies. Interestingly, anti-cN1A antibody was positive in 20% of patients with immune-mediated necrotizing myopathy associated with anti-SRP antibody, suggesting that the anti-cN1A antibody may not be specific to IBM.

There is no therapy proven to be efficacious to IBM. Currently being conducted is the phase 2/3 clinical trial to test the efficacy of BYM338, anti-ActRII antibody, which is expected to block myostatin cascade and thus prevent muscle atrophy. If successful, this will be the first efficacy-proven agent against IBM.

A first clinical trial in SEPN1-related myopathy: the SELNAC study

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SEPN1-Related Myopathy (SEPN1-RM) is a congenital muscle disease due to mutations of the *SEPN1* gene, encoding selenoprotein N (SelN). SEPN1-RM is characterized by a relatively preserved ambulation, contrasting with severe trunk

muscle weakness that can lead to death due to respiratory failure. No treatment is currently available, and clinical trial readiness in SEPN1-RM has been so-far hindered by the lack of sensitive and reliable biomarkers and outcomes.
We have shown previously that SelN is implicated in redox homeostasis, and that the antioxidant N-acetylcysteine (NAC) restores the phenotype in cultured cells from SelN-devoid patients. Recently, a preclinical study using the *sepn1 KO* mouse line allowed us to: i) describe so-far unknown phenotypical abnormalities which represent measurable outcomes; ii) identify muscle and systemic biomarkers iii) confirm the therapeutic efficiency of NAC *in vivo* in this SEPN1-RM model; iv) validate an optimum dose/effect.
Based on the results above, which improved dramatically clinical trial readiness in SEPN1-RM, we have designed the first trial in this rare condition. Given that this is a rare disorder and that there is no data about NAC use in human SEPN1-RM patients, we decided to start with a phase II-III pilot trial (SELNAC) which will take place at the Raymond Poincaré Hospital (URC Paris-Ouest, France). The SELNAC study is a randomized, double-blind, placebo-controlled cross-over trial which will include 24 adult patients (age: 18-60 years) with known *SEPN1* mutations, and 24 healthy controls. We will measure the biological and functional response to NAC, including quantification of biomarkers, body mass and motor and respiratory function studies.
Thus, the SELNAC trial will use a safe, available and inexpensive drug to treat an incurable genetic disease. This study represents the first clinical trial in SEPN1-RM, and also the first drug treatment targeting a primary pathophysiological mechanism in a congenital myopathy.

Symposium- Parallel Symposium Inflammatory Myopathies
• *Olivier Benveniste (FRANCE)* • *Andrew Mammen (USA)* • *Ichizo Nishino (JAPAN)*

Recent progress in classification, clinical outcome definitions and treatments for idiopathic inflammatory myopathies
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Idiopathic inflammatory myopathies (IIM) form a heterogeneous group of acquired myopathies. Their global phenotype in term of intensity and distribution of weakness or extra-muscular organ involvement vary greatly among subgroups, which also results in differing prognoses. Based on clinical and muscle biopsy pathological criteria, five subgroups are classically described: polymyositis (PM), dermatomyositis (DM), immune mediated necrotizing myopathies (IMNM), inclusion body myositis (IBM), and non-specific myositis. Among some neurology clinics, PM appears to be relatively rare, with many patients being reclassified among overlap syndrome with myositis, or IBM or IMNM. Furthermore, more than 15 different myositis specific autoantibodies (MSA) are now described and measurable in routine, redefining even more homogenous group of patients with different physiopathology. In parallel, consensus in guidelines for conducting controlled, randomized clinical trials (RCT) for IIM have been developed and the necessity of consensus in clinical outcomes to measure impact of treatment appear fundamental. Three actors are here pivotal: the patients who aim to have a better quality of life, the clinicians who would like objective measures to assess treatment responses, and the regulatory agencies who have emphasized a preference for functional outcome measures and patient-reported outcomes. Knowing the metaphor of Neurologists coming from Mars and Rheumatologists from Venus “in the way that they may speak similar, yet different languages when describing the same myositis patients” for IIM classification, but also for clinical outcome assessment, a recent ENMC (the 213rd on outcome measures and clinical trial readiness) was held recently (Sept 2015). The conclusions were that the Myositis Disease Activity Assessment Tool (IMACS, developed by Rheumatologists) measures of disease activity and the new response criteria for DM and PM are globally well- designed and validated tools. But, this meeting also pointed out some weaknesses. These are 1) the way to evaluate muscle weakness and 2) the absence of well-validated performance-based observational functional scales. Furthermore, the development of applications permitting to evaluate the activity in real life of the patients is a very interesting approach that urgently needs validation. Based on the IIM physiopathology different from a subgroup to another, targeted therapeutic approaches are under development. The better categorization of IIM patients in more homogenous groups, the efforts in defining reliable outcomes and the development of targeted treatments will rapidly revolutionize the therapeutic approaches of IIM.

Immune-mediated necrotizing myopathy
Andrew L. Mammen, MD, PhD

In 1975, Bohan and Peter published classification criteria for myositis that are still widely used. According to that scheme, patients with proximal muscle weakness, irritable myopathy on EMG, elevated muscle enzyme levels, and inflammatory muscle biopsies who do not have a rash are defined as having polymyositis (PM). In contrast, those with these features who also have cutaneous manifestations are classified as having dermatomyositis (DM). More recently, it has been appreciated that some patients with autoimmune disease have abundant necrotizing muscle fibers, with minimal infiltration by inflammatory cells. Based on this observation, immune-mediated necrotizing myopathy (IMNM) was recognized as a unique category of myositis in the classification scheme published in 2004 by the ENMC. Given the different characteristic muscle biopsy features in DM, PM, and IMNM, distinct pathophysiological mechanisms are now thought to underlie each of these disease categories.
In addition to unique muscle biopsy features, it is now recognized that the majority of patients with myositis have one of more than a dozen “myositis-specific” autoantibodies and that each of these autoantibodies is associated with a distinct clinical phenotype. Specifically, patients with IMNM often have autoantibodies recognizing either the signal recognition particle (SRP) or HMG-CoA reductase (HMGCR). In addition to their similar biopsy features, patients with anti-SRP and