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

anti-HMGCR autoantibodies both have predominantly skeletal muscle involvement. This is contrast to patients with other forms of myositis, who most often have multisystem disease including the skin, lungs, and/or joints.

Although anti-SRP and anti-HMGCR positive myositis patients share certain clinical features, these diseases are different. For example, only anti-HMGCR myositis can be triggered by statin exposure. Furthermore, most anti-HMGCR myositis patients have the class II HLA allele DRB1*11:01; this allele is not an immunogenetic risk factor for myositis patients with autoantibodies recognizing SRP or other myositis-specific autoantigens. It is also important to recognize that ~15% of anti-SRP and anti-HMGCR patients have significant inflammatory cell infiltrates on muscle biopsy but are otherwise indistinguishable from patients with the same autoantibody who have necrotizing muscle biopsies. Given these observations, we conclude that IMNM may have significant limitations as a disease category. Indeed, we propose that "anti-SRP myositis" and "anti-HMGCR myositis" be recognized as distinct diseases defined by the presence of one of these two autoantibodies.

GNE myopathy – mechanism and therapy
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GNE myopathy, also called distal myopathy with rimmed vacuoles (DMRV) or hereditary inclusion body myopathy (hIBM), is an autosomal recessive muscle disease affecting adolescents and adults. The disease is characterized clinically by preferential involvement of tibialis anterior muscle and relative sparing of quadriceps, and pathologically by the presence of rimmed vacuoles, which are a pathological hallmark of aggrephagy, in addition to scattered atrophic fibers. Up to this time, no cure is available for this myopathy.

GNE myopathy is caused mostly by missense mutations in the *GNE* gene that encodes a protein with the activity of two enzymes in sialic acid biosynthesis, UDP-GlcNAC 2-epimerase and ManNAc kinase, resulting in the reduction of the sialic acid levels in serum and skeletal muscles. We generated a model mouse for GNE myopathy that expressed human *GNE* with the missense mutation p.D207V, but lacks the endogenous mouse *GNE*. This model mouse exhibited hyposialylation in serum and various organs which predated the skeletal muscle weakness, atrophy, rimmed vacuole formation, and deposition of amyloid and various proteins within the myofibers, supporting the concept that the hyposialylation causes the degenerative myopathy.

To see whether GNE metabolites ameliorate the phenotype, we treated our mice with ManNAc, NeuAc, and sialic acid conjugate, sialyllactose from around 15 weeks of age and continued to around 55 weeks. Interestingly, by any agent, clinicopathological manifestations were almost completely suppressed even at age 55 weeks when all mice are expected to show all clinicopathological features. Our results indicate that sialic acid deficiency is the cause of GNE myopathy and that the disease can be suppressed by sialic acid supplementation.

Following the animal study results, slow-release tablets of sialic acid up to 6000 mg/day were tested in phase 2 trial in the US and Israel. it seems efficacious with apparent dose-dependent effect especially in upper extremities, suggesting that less affected muscles may show better efficacy. Currently, phase 3 trial is being conducted in US, Canada, UK, and Israel, and sites in France, Italy and Bulgaria are scheduled to be added further, hopefully leading to the market release of the first fundamental therapeutic agent against GNE myopathy in a few years.

Symposium- Parallel Symposium FSHD
• *Sabrina Sacconi (FRANCE)* • *Silvère Van Der Maarel (THE NETHERLANDS)* • *Rossela Tupler (USA)*

Are FSHD1 and FSHD2 merging diseases?
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Facioscapulohumeral muscular dystrophies (FSHD) are characterized by typical pattern of muscle weakness, often asymmetric distinguishing them form other myopathies and including:
- Facial muscle weakness: Involving *orbicularis oculi* and *orbicularis oris* muscles
- Fixator scapulae weakness: (i.e., trapezius involvement later followed by serratus anterior, latissimus dorsi and pectoralis major, with sparing of spinati and subscapularis muscles (Tasca et al, 2014)
- Posterior leg and anterior foreleg muscle weakness: The most affected muscles are hamstrings followed by the tibialis anterior and the medial gastrocnemius. Psoas is frequently spared and vastus-, gluteal- and peroneal muscles are affected only late in the disease (Olsen et al, 2006)
- Abdominal muscles: giving rise to Beevor sign and lumbar hyperlordosis.

Nevertheless, FSHD shows a wide spectrum of clinical involvement ranging from very severe, progressive muscular weakness often associated with additional features (extra muscular involvement, dysphagia, respiratory muscle weakness..) to mild and slowly progressive forms and even asymptomatic cases.

Genetic/ epigenetic diagnosis of FSHD has been recently improved by the discovery of the genetic/epigenetic heterogeneity of this disease, which has been recently classified in two subtypes:
- FSHD type 1 (FSHD1) characterized by autosomal dominant inheritance of D4Z4 contracted permissive allele on chromosome 4 (≥1, <11 repeated units) that can be found in 90-to 95% of FSHD patients;
- FSHD type 2 (FSHD2) characterized by digenic inheritance of permissive non-contracted allele on chromosome 4 (>11 repeated units and pathogenic dominant mutation on *SMCHD1* (Structural Maintenance Of Chromosomes Flexible Hinge Domain Containing 1) gene located on chromosome 18.