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Meeting Report

New Directions in Biology and Disease of Skeletal Muscle 2014

Eugene J. Wyatt[a], H. Lee Sweeney[b] and Elizabeth M. McNally[a,c,*]
[a]*Department of Medicine, The University of Chicago, Chicago, IL, USA*
[b]*Department of Physiology, The University of Pennsylvania, Philadelphia, PA, USA*
[c]*Department of Human Genetics, The University of Chicago, Chicago, IL, USA*

Abstract. New Directions in Biology and Disease of Skeletal Muscle is a scientific meeting, held every other year, with the stated purpose of bringing together scientists, clinicians, industry representatives and patient advocacy groups to disseminate new discovery useful for the treatment of inherited forms of neuromuscular disease, primarily the muscular dystrophies. This meeting originated as a response to the Muscular Dystrophy Care Act in order to provide a venue for the free exchange of information, with the emphasis on unpublished or newly published data. Highlights of this years' meeting included results from early phase clinical trials for Duchenne Muscular Dystrophy, progress in understanding the epigenetic defects in Fascioscapulohumeral Muscular Dystrophy and new mechanisms of muscle membrane repair. The following is a brief report of the highlights from the conference.

Keywords: Muscular Dystrophy, spinal muscular atrophy, congenital muscular dystrophy, facioscapulohumeral muscular dystrophy

INTRODUCTION

The 2014 biennial New Directions in Biology and Disease of Skeletal Muscle Conference was held from June 29th thru July 2nd in Chicago, Illinois, USA. Over 250 attendees from academia and industry participated, featuring 159 posters and 40 oral presentations detailing the most recent advances in the understanding and treatment of neuromuscular disease. The keynote address was by **Fred Turek** (Northwestern University) who discussed the biology of circadian rhythms, a topic of relevance to muscle and muscle disease. Throughout the 4 day meeting, a broad spectrum of muscle disease topics were discussed, ranging from the initial identification of pathological mechanisms of disease, to the exploration and development of therapeutic targets, and ultimately their clinical implementation and evaluation.

*Correspondence to: E.M. McNally, Center for Genetic Medicine, Northwestern University, 303 E. Superior St., Chicago, IL 60611, USA. Tel.: +1 312 503 5602; Fax: +1 312 503 5603; E-mail: emcnally@uchicago.edu.

Industry workshop: Therapeutics in the clinic

The industry session began with **Diana Escolar** of Akashi Pharmaceuticals (formerly HALO Therapeutics) presenting the clinical development of HT-100, a delayed release halofuginone, for the treatment of Duchenne Muscular Dystrophy (DMD) [1]. Shown to attenuate pathological inflammation by suppressing T helper 17 (Th17) development, animal studies in the *mdx* mouse model of DMD are consistent with a more diverse anti-fibrotic, anti-inflammatory mechanism combined with pro-muscle regeneration effects [2]. Phase I open-label testing is now underway in a cohort of DMD boys, measuring tolerability and serum biomarkers. **Jon Tinsley** (Summit Corporation plc) discussed the efficacy of SMT C1100, a small molecule that increases compensatory utrophin levels, for the treatment of DMD. SMT C1100 reduced central nucleated fibers and serum CK levels in *mdx* mice, and protected against muscle damage from forced exercise [3, 4]. Phase Ib trials in a cohort of DMD boys, demonstrated tolerability and reduction

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in serum enzyme levels of creatine kinase (CK), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). **Michael Jirousek** of Catabasis Pharmaceuticals detailed their Safely Metabolized And Rationally Targeted (SMART) Linker platform, combining salicylate and docosahexaenoic acid (DHA) to synergistically inhibit NFkB signaling. Animal studies in *mdx* mice and GRMD dogs demonstrated reduced NFkB signaling, increased muscle weight, and decreased inflammation. **Carl Morris** of Pfizer's Muscle Biology and Protein Therapeutics Rare Disease Research Unit overviewed the development of antibodies and peptides aimed at inhibiting myostatin, also known as Growth and Differentiation Factor 8 (GDF8). Newer compounds with improved specificity for myostatin or its receptor are anticipated to have an improved safety profile compared to previous antibodies [5]. Initial results demonstrated tolerability and increased muscle mass that was maintained over time, supporting the initiation of phase II trials. **Stuart Peltz** (PTC Therapeutics) presented an overview of stop codon read through for the treatment of DMD caused by nonsense mutations. Ataluren, a small molecule that interacts with the ribosome, promoted read through of premature nonsense stop signals and production of full-length, functional protein [6]. In a phase IIb clinical trial, ataluren (40 mg/kg/day) demonstrated clinical benefit in ambulatory DMD patients ≥ 5 years old, as determined by the 6MWT [7]. Recently, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion regarding conditional marketing authorization of ataluren for nonsense mutations in ambulatory DMD patients aged five years and older. **Pat Furlong** from Parent Project Muscular Dystrophy (PPMD) detailed new guidelines for the evaluation of therapies for muscular dystrophy presented to the Food and Drug Administration (FDA).

Clinical trials: Experiences and future planning

Alessandra Ferlini from the University of Ferrara presented data from a multi-institute EU FP7 BIO-NMD consortium that evaluated blood and serum samples for differentiating markers of DMD or the less severe Becker Muscular Dystrophy (BMD) [8]. Using a multiplex antibody array, they identified several markers that segregated with disease and disease severity; they also developed SNP arrays to predict severity and response to treatments such as steroids. Blood biomarkers of special interest include carbonic anhydrase III (*CA3*); myosin light chain 3 (*MYL3*); mitochondrial associated malate dehydrogenase (*MDH2*); and electron transfer flavor protein (*ETFA*). **Laurent Servais** (Institut de Myologie) described new technological advancements, specifically a grip strength assay to measure disease progression in DMD patients. The assay uses ActiMyo, a more sensitive actigraph, to measure disease progression, especially in non-ambulant patients. **Charles Thornton** (University of Rochester) discussed gene therapy strategies, using anti-sense oligonucleotides (ASO) to treat myotonic dystrophy type 1 (DM1), demonstrating long term knockdown of the expressed CUG repeat expansion in mice [9]. This strategy is now being developed for phase I human trials. **Kathryn Swoboda** (University of Utah) provided an update on clinical outcomes measurement for Spinal Muscular Atrophy (SMA) for both ASO read frame correction of SMA2, and the administration of virally-delivered SMN.

Spinal Muscular Atrophy, SMA: Disease models and preclinical discovery

Charlotte Sumner (Johns Hopkins University) organized the session. She presented an overview of spinal muscular atrophy (SMA) and discussed the animal models developed to investigate the mechanisms of disease. Genetic mutations leading to a deficiency of survival motor neuron 1 (*SMN1*) cause proximal SMA, the most common form of disease [10, 11]. Humans produce SMN from a second locus (*SMN2*), albeit at lower levels due to frequent skipping of exon 7 during transcription that leads to the production of a truncated rapidly degraded protein (SMNΔ7) [12]. Transgenic expression of human *SMN2* in $SMN^{-/-}$ mice rescued lethality and improved the phenotype in a dose dependent manner; however, two copies still resulted in postnatal reduction of motor neurons, impaired muscle function, and death; recapitulating the most severe human phenotype [13]. Permutations of this original genotype have since been created in animal models to mimic the variable pathogenesis and disease severity of the human disorder. Additionally, inducible SMN expression in $SMN^{-/-}$ mice revealed a temporal and tissue specific requirement of SMN necessary for proper neuromuscular development and neuromuscular junction (NMJ) maturation [14–16]. **Adrian Krainer** (Cold Spring Harbor Laboratory) described recent animal studies that used ASO to induce exon 7 inclusion in the SMN2 transcript, generating full length SMN. Muscle fiber size, heart weight, and NMJ preservation increased with systemic

ASO delivery compared with intracerebroventricular (ICV) injection alone, implicating the therapeutic benefit of combined treatment of the peripheral and central nervous system [17]. In addition, he showed that ASO crossed the blood brain barrier after subcutaneous injections, and demonstrated long-term effects on exon 7 inclusion and expression, SMN localization, and attenuation of muscle pathology even in the presence of decoy oligonucleotides. **Chien-Ping Ko** (University of Southern California) reviewed his findings on the critical role that central synapse loss plays in the pathology of SMA, revealing a decreased numbers of glutamanergic central synapses and increased levels of microglia associated with SMNΔ7 motorneurons [18]. He also described a small molecule splicing modifier, specific to SMN2, which promoted exon 7 inclusion and prevented motor neuron loss and muscle atrophy in SMNΔ7 mice [19]. Finally, **Livio Pellizzoni** (Columbia University) explained the broader role SMN plays as a molecular chaperone for snRNP complex formation and RNA processing, in an effort to understand how selective motor system dysfunction results from reduced levels of the ubiquitously expressed SMN protein [20].

Congenital muscular dystrophies

Mutations in Collagen VI isoforms (*COL6A1-3*) can cause both severe Ullrich congenital muscular dystrophy (UCMD) and mild Bethlem myopathy [21–23]. **Carsten Bönnemann** (National Institutes of Health) discussed how these varied mutational effects are further complicated by the multifaceted roles played collagen VI in the extracellular matrix (ECM). Therapeutic approaches discussed include anti-apoptotic treatment (including omigapil, discussed later by Marcus Ruegg) and allele specific knock-down of mutant transcripts to attenuate dominate negative effects. Merosin-deficient congenital muscular dystrophy (*MDC1A*) is caused by mutations in laminin-α2 that disrupt the mechanical linkage between the ECM and the muscle fiber [24–26]. **Marcus Ruegg** (University of Basel) discussed studies using mini-agrin, a truncated ECM binding agrin isoform, to prevent muscle degeneration due to mechanical over load; or omigapil, an inhibitor of apoptosis, to prevent muscle fiber loss. Treatment with both compounds had a synergistic effect on muscle regeneration, fiber size, and force generation; providing a new

therapeutic strategy for treatment of MDC1A [27]. Walker-Warburg syndrome (WWS) is a heterogeneous dystroglycanopathy caused by autosomal recessive mutations that impair glycosylation of α-dystroglycan (α-DG). **Tobias Willer** (University of Iowa) detailed an inventive complementation assay used to identify genes previously unlinked to dystroglycanopathy [28]. Cell fusion complementation experiments in fibroblasts from 11 subjects with unknown WWS mutations were followed by targeted sequencing and resulted in the identification of five new causative genes in WWS.

Nemaline myopathy (NM) is a heterogeneous disorder caused by mutations in genes encoding thin filament components of the sarcomere [29, 30]. Broad based sequencing has now been used to identify new genes for NM in cases that were previously genetically unresolved [31]. **James Dowling** (Toronto Sick Kids), who also organized the session, reported on the morpholino knockdown of leiomodin 3 (*lmod3*) in zebrafish. Studies showed LMOD3 localized to the actin filament, and knockdown induced a nemaline phenotype. Further analysis indicated LMOD3 interacts with tropomodulins whose levels are reduced in NM patients. **Rhonda Bassel-Duby** (University of Texas Southwestern) discussed the role of *KLHL40* in thin filament function and NM. Previous work identified *KLHL40* as a Mef2C-regulated gene expressed in skeletal muscle and heart [32]. *KLHL40* mutations were recently shown to cause NM in humans, and loss of *KLHL40* in mice leads to a NM-like phenotype, comparable to that of patients with NM lacking *KLHL40* [31]. Studies showed that KLHL40 localized to the thin filament, bound nebulin (NEB) and LMOD3, promoted stability of NEB and LMOD3, and blocked LMOD3 ubiquitination [33]. Together, the results suggest KLHL40 is essential for the maintenance of sarcomere structure and muscle contractility. **Michael Lawlor** (Medical College of Wisconsin) presented data showing ActRIIB inhibition of myostatin had a favorable effect on muscle mass in a NM mouse model, pointing to one potential mode of therapy of NM.

Inflammation in muscle injury and disease

Fayyaz Sutterwala (University of Iowa) provided an overview for the role innate immunity plays in the pathogenesis and exacerbation of muscular dystrophy, specifically focusing on nucleotide-binding domain leucine-rich repeat containing receptors (NLR) family pyrin domain containing 3 (*NLRP3*), whose activation results in the formation of a multiprotein complex termed the NLRP3 inflammasome. The mechanism by which NLRP3 is activated remains unknown; however, evidence supports a role for potassium efflux, reactive oxygen species (ROS), and purinergic receptor (P2X7) binding of ATP released from necrotic cells [34, 35]. Additionally, mitochondria play a role in the activation of the NLRP3 inflammasome through the binding to cardiolipin [36]. Thus, inhibiting NLRP3 inflammasome activation may have beneficial effects in preventing the damage mediated by the sterile inflammatory response in neuromuscular disease. **James Tidball** (University of California Los Angeles) detailed the complex balance of type 2 innate immune response in the *mdx* mouse. Interleukin-10 (IL-10) levels are increased in *mdx* muscle, and ablation increased muscle damage, likely mediated by an IL-10 regulated switch of muscle macrophages from cytolytic M1 to repair promoting M2c phenotype [37, 38]. Eosinophil-derived major basic protein (MBP) was found to attenuate cytotoxic T-lymphocytes (CTLs) production in *mdx* muscles; however, prolonged MBP release promoted fibrosis in certain muscle groups in the latter stages of disease [39]. Collectively, the results showed the initiating signal, muscle group, microenvironment, and duration of the response determine the benefit of type 2 innate immunity. **Renzhi Han** (Loyola University) organized the session on inflammation, and described the underexplored inflammatory response in dysferlinopathies. Dysferlin deficiency in mice, a model for Limb Girdle Muscular Dystrophy type 2B, is associated with an increased expression of complement factors in muscle, and genetic disruption of the central component (C3) of the complement system ameliorated muscle pathology [40]. A recent study also implicated NLRP3 activation in this response, whereby NLRP3 activation by liposome-induced reactive oxygen species (ROS) production triggered increased macrophage Ca^{2+} influx via the transient receptor potential cation channel (*TRPM2*) [41]. These results provided multiple new targets aimed at attenuating the inflammatory response in dysferlinopathies. **Eric Hoffman** (Children's National Medical Center) compared the glucocorticoid receptor (GR) steroid prednisone to a Δ-9,11 anti-inflammatory compound VBP15. VBP15 inhibited TNFα-induced NFkB activity, improved muscle strength in DMD mice, and promoted repair of skeletal muscle cells upon laser injury [42, 43]. VBP15 significantly reduced GR transcriptional activity, including the genes implicated in a number of harmful glucocorticoid side effects. Such alternatives to glucocorticoid steroids could be very useful in treating multiple forms of muscular

dystrophy. Finally, **Kanneboyina Nagaraju** (Children's National Medical Center), organizer of the gene correction session, overviewed the "danger model" of disease amplification where necrotic dystrophic cells triggered the innate immune response via release of damage-associated molecular pattern (DAMP) ligands that activate Toll-like receptors (TLR)s [44]. In addition, studies showed skeletal muscle expressed TLRs and produced cytokines that exacerbate the inflammatory response, with TLR signaling in DMD muscle mediated by the TLR adaptor protein myd88 [45]. Future experiments blocking this pathway may have important therapeutic implications for DMD.

Genetics and Epigenetics of Facioscapulohumeral Muscular Dystrophy (FSHD)

For many years, FSHD remained a molecularly elusive form of muscular dystrophy, with linkage to 4q but without a clear molecular mechanism. **Silvere van der Maarel** (Leiden University Medical Center), organizer of the session, discussed the genetics of FSHD. FSHD1 results from a pathological chromatin state caused by a contraction of subtelomeric D4Z4 tandem arrays and a polyadenylation sequence which enables full length expression of the *DUX4* retrogene (DUX4-fl) coded in each unit [46–49]. FSHD2 is linked to mutations the *SMCHD1* gene (structural maintenance of chromosomes flexible hinge domain containing 1) whose function includes the establishment and maintenance of DNA methylation in the D4Z4 region, inhibiting *DUX4* expression [50, 51]. In addition, dual FSHD1 and FSHD2 lesions result in a more severe clinical phenotype, suggesting that *SMCHD1* can act as a modifier of FSHD1, with the two mutations sharing a common pathophysiological pathway [52]. **Peter Jones** (University of Massachusetts Medical School) further elucidated the epigenetic regulation of *DUX4* as FSHD 1 and 2 are associated with permissive chromatin environments including DNA hypomethylation and a reduction in heterochromatic histone marks [53–56]. This resulted in aberrant and toxic DUX4-fl expression in a subset of myogenic cells from FSHD patients [57–60]. **Scott Harper** (The Ohio State University) is working to establish new models of DUX4 expression in the mouse. **Jeffrey Miller** (Boston University) presented data on the potential pathological effects of DUX4-fl expression through inhibited protein turnover and aggregation of TDP-43, an RNA splicing factor whose aggregation has been implicated in the pathology of amyotrophic lateral sclerosis (ALS) [61]. **Louis Kunkel** (Children's Hospital Boston) described results from the first FSHD animal models created in zebrafish. Microinjection of human DUX4-fl mRNA into embryos resulted in developmental abnormalities and muscle deterioration recapitulating human FSHD, implicating *DUX4* in disease pathogenesis [62]. Using a tamoxifen inducible *DUX4* under the control of the myosin promoter in zebrafish, they observed variegated DUX4 expression that decreased over time, nuclear spreading of DUX4 expression, and reduced muscle activity. **Rabi Tawil** (University of Rochester) detailed the RNA-seq profiling of FSHD patients in the search for new biomarkers and insights into the pathology of disease [63]. Results indicated that differences between FSHD patients and controls were mediated by DUX4-regulated gene expression, with a subset indicative of immune cell infiltration. Obstacles to accurate marker identification included the variegated and transient nature of DUX4-fl expression in a subset of nuclei, and low level expression in asymptomatic controls. However, candidate markers were identified in the FSHD cohorts, initiating a list of biomarkers for the disease that will become more robust with additional investigation.

The Laminopathies

Mutations in *LMNA*, the gene encoding lamins A and C, produce a range of phenotypes that includes muscular dystrophy and cardiomyopathy. The lamins are nuclear envelope proteins involved in the maintenance of nuclear integrity, mechano-sensation, cell signaling, and chromatin organization [64]. LGMD1B is part of a wider array of disorders resulting from the mutation of nuclear envelope components, commonly referred to as laminopathies [65]. **Jan Lammerding** (Cornell University) observed impaired nuclear translocation of the mechanosensitive transcription factor megakaryoblastic leukaemia 1 (*MKL1/MRFT-A*) in *LMNA* null and *LMNA* N195K mutant fibroblasts [66]. Upon nuclear import MRFT-A activates genes regulating motility and contraction, including many cytoskeletal proteins, ultimately resulting in nuclear defects in *LMNA* mutant cells [66]. Ectopic expression of emerin, a nuclear envelope anchoring protein, rescued MRFT-A localization and subsequent transcription factor activity. Emerin rescue was dependent on phosphorylation, that required an intact linker of nucleoskeleton and cytoskeleton (LINC) complex that included nesprin (also known as *SYNE*) [66, 67]. **Gisèle Bonne** (INSERM-Institut de Myologie) described the role of yes-associated protein

(YAP), a ubiquitously expressed member of the Hippo cell proliferation pathway, in the mechano-sensing defects observed in *LMNA* mutant myoblasts [68]. Constitutive YAP activation in the absence of stretch was observed in cultured *LMNA* mutant myoblasts, indicative of dysregulated mechano-sensation, resulting in increased cytoskeletal tension at rest [68]. **Howard Worman** (Columbia University) reviewed the relationships among lamin associated peptide 1, emerin, and lamin A/C; and their role in pathogenesis for striated muscles [69, 70]. **Lori Wallrath** (University of Iowa) utilized the *Drosophila melanogaster* model system to investigate mutations in the lamin A/C IgG-fold domain. Expression of mutant forms of *Drosophila* lamin C displayed convincing muscle specific lethality, coupled with increased cytoplasmic protein aggregation and Nrf2/Keap-1 pathway activation. Muscle biopsies from LMNA mutant patients demonstrated similar findings.

Limb Girdle Dystrophies (LGMDs)

LGMD1D is caused by heterozygous mutations in *DNAJB6*, a ubiquitously expressed molecular chaperone, most commonly associated with protein folding and proteosomal turnover [71–73]. **Bjarne Udd** (University of Helsinki) showed morpholino-mediated reduction of *DNAJB6* led to myofiber detachment in zebrafish that resulted from dysfunction of the cytoplasmic isoform [73]. Further study implicated both increased protein aggregation and myofibrillar disintegration; the later mediated through an interaction with BAG3. **Ralph Knöll** (Imperial College of London) presented the relationship between telethonin, the protein implicated in LGMD2G, titin, and the p53 pathway. **Isabelle Richard** (Généthon), organizer of the session, showed that adenoviral mediated calpain-3 gene therapy rescued skeletal muscle defects in calpain-3 deficient mice, but resulted in cardiotoxicity [74, 75]. Promoter and miR driven selective skeletal muscle expression eliminated the cardiac defects. They postulated that skeletal muscle expression was tolerated due to the presence of restrictive calpain binding sites on titin, while cardiomyopathy resulted from unrestricted calpain-3 activity in the absence of an M-line [76–78]. **Sandra Cooper** (University of Sidney) showed that a dysferlin cleavage product, and not the full-length protein, was recruited to the sarcolemma after ballistic injury. This cleavage was dependent on calpain digestion of dysferlin at site encoded by exon 40a, not often recognized in most assays [79, 80]. Antibodies against this epitope showed co-localization with MG53 at the site of repair, further elucidating the intricate process of membrane repair.

Presented in the "New and Notable session" were studies on sarcolemmal membrane repair. **Joel McDade** (University of Michigan) showed that recruitment of sarcolemmal dysferlin to an active zone of membrane repair after damage was dependent on the subcortical actin-cytoskeleton [81]. **Alexis Demonbreun** (University of Chicago) presented data showing that annexin 6 is recruited to the active repair zone of injured sarcolemma along with genetic evidence that *Anxa6*, the gene encoding annexin A6, is a modifier of muscular dystrophy [82]. **Jyoti Jaiswal** (Childrens National Medical Center) described a cell-based approach to examine membrane repair using a glass bead wounding/repair assay [83]. Differentiated dysferlin deficient cells had a reduction in lysosomes at the sarcolemma and demonstrated repair deficits in response to injury, as well as a reduction in the release of acid sphingomyelinase. Exogeneous acid sphingomyelinase rescued the repair deficit in dysferlin deficient cells [84]. Together these data highlighted precise molecular features of muscle membrane repair relevant to muscle injury and muscular dystrophy.

Gene correction and therapies for neuromuscular disease

Francesco Muntoni (University College London) reviewed the methods used in the evaluation of dystrophin as a marker for the efficacy of exon skipping therapy for the treatment of DMD. **Luis Garcia** (University of Versailles) presented a novel chemical approach for anti-sense oligonucleotide mediated exon skipping in *mdx* mice. **Rachelle Crosbie-Watson** (University of California Los Angeles) provided and overview on the impact dystrophin/utrophin, $\alpha 7\beta 1$ integrin, and ECM interactions have on therapeutic interventions [85]. Previous studies showed that transgenic expression of sarcospan (*SSPN*) increased utrophin and $\alpha 7\beta 1$ integrin sarcolemmal expression and ameliorated DMD pathology [86, 87]. Using a double-knockout approach, they demonstrated that both utrophin and $\alpha 7\beta 1$ integrin expression are required for SSPN amelioration of disease in *mdx* mice. Overall, these results suggest the upregulation of both adhesion complexes and sarcospan would increase the therapeutic potential compared with a single component. **Jennifer Strande** (Medical College of Wisconsin) described the derivation of induced pluripotent stem cells (iPSCs) from urine samples, and

demonstrated the ability to generate mutation specific *in vitro* culture systems that can be differentiated into desired lineages and used for cell based therapies, drug discovery, biomarker screening, personalized therapy, and mechanistic evaluation [88].

CONCLUSIONS

The "New Directions" meeting closed after 4 days with a continued emphasis on the presentation and sharing of newly published and unpublished findings with the goal of promoting new therapy development for muscle disease.

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