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Meeting Report

Report on the 3rd Ottawa International Conference on Neuromuscular Biology, Disease and Therapy – September 24–26, 2015, Ottawa, Canada

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Neuromuscular diseases (NMDs) represent a broad group of more than 150 genetic and acquired disorders [1], many of which are debilitating, progressive and cause premature death. Almost one million people in North America are believed to be affected by these disorders [2], which additionally have great socio-economic impact. For many NMDs, no cure or effective treatment exist. Indeed, the causative genetic mutations, and how they contribute to the disease state, or the autoimmune mechanisms underlying many of these disorders remains elusive. In addition, both the clinical and basic NMD research community still requires a more detailed understanding of the biological and biochemical workings of "normal" neuromuscular function. Collectively, we still have much to learn.

The 3rd Ottawa International Conference on Neuromuscular Biology, Disease and Therapy was convened September 24–26, 2015 in Ottawa, Canada. The goal of the conference was to bring together world leaders in NMD basic and clinical research to provide attendees an update on cutting-edge approaches to NMD diagnostics, complex NMD phenotyping, disease pathogenesis, and therapy development. A second goal of the conference was to provide a venue to enhance interactions and stimulate collaboration between the clinical and research worlds. It is only through the combined efforts of basic and clinical investigators that we can advance our understanding of NMDs and develop new, more effective, approaches to disease management and treatment.

CONFERENCE STRUCTURE

The Conference featured talks highlighting significant scientific breakthroughs and clinical care discoveries in NMD research, with sessions organized based upon disease types (e.g. SMA, dystrophinopathies, etc.). The organizing committee

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chose speakers who were (1) well-known leaders in their field and (2) had an established ability to engage and educate a varied scientific and clinical audience. The Conference featured 41 internationally recognized platform speakers (11 from Canada, 20 from the United States and 10 from Europe), and almost 300 attendees.

The conference was divided into ten sessions, with an opening session featuring the Keynote Speaker, Dr. Charles Thornton (University of Rochester). Sessions showcased high-level discussions highlighting cutting-edge advances in NMDs. Eight sessions included a progression of presentations from basic to translational to clinical, and speakers were advised to present their work for a general audience, to engage all attendees regardless of background or stage of career. In addition, we offered two concurrent breakout sessions to allow more in-depth presentations on recent advances in basic or clinical NMD research. Almost 100 abstracts were submitted for poster presentation, ten of which were advanced for a short platform presentation during the main scientific sessions. All posters were available for viewing throughout the entire conference, with two formal poster presentation sessions. Two networking events provided excellent opportunities for social interactions between attendees.

The Conference was hosted by the University of Ottawa Centre for Neuromuscular Disease (CNMD). CNMD was created in 1999 in recognition of the clear strength and leadership in NMD research in several Ottawa-area institutions, including the University of Ottawa (uOttawa), The Ottawa Hospital (TOH), Ottawa Hospital Research Institute (OHRI), Children's Hospital of Eastern Ontario (CHEO), CHEO Research Institute (CHEORI) and the uOttawa Heart Institute (uOHI). CNMD has now grown to include over 50 basic scientists and clinicians/clinician researchers and over 150 graduate students, postdoctoral fellows, residents and clinical fellows. All session moderators were members of CNMD.

OPENING DAY AND KEYNOTE SPEAKER

Opening remarks were provided by Drs. Robin Parks (OHRI, CAN) and Jodi Warman Chardon (The Ottawa Hospital, CAN), two of the conference organizers who emphasized the desire for a dynamic, informative and interactive conference. Dr. David Park, Director of the uOttawa Brain and Mind Research Institute (uOBMRI, CAN) and sponsor of the Keynote Speaker, outlined the efforts in Ottawa to unite and coordinate local area researchers from the various uOttawa faculties, resident hospitals, affiliated networks and local research institutes that study fundamental neuroscience biology and disease. Ms. Marla Spiegel, National Director of Research, Programs and Services at Muscular Dystrophy Canada (MDC) and sponsor of the Opening Day Social Event, provided a brief overview of MDC commitment to research excellence in NMD and patient care.

Keynote Speaker Dr. Charles Thornton (University of Rochester Medical Centre, USA) spoke on "Integrating bench and clinical research in therapeutic context." Dr. Thornton presented his 5-year odyssey in developing an antisense oligonucleotide (ASO) therapy to directly target toxic mRNAs generated through the CUG trinucleotide repeat in myotonic dystrophy type I (DM1) [3, 4]. Topics covered during Dr. Thornton's presentation included basic DM1 pathogenesis, therapeutic strategies under development, and key issues for DM1-directed ASO therapy development, such as allelic selectivity, potential cardiotoxicity, and effective measurement of target engagement and clinical response. Many of the issues and complications encountered during development of this therapy for DM1 will also be encountered when designing novel therapies towards other NMDs, and thus this address served as an excellent unifying presentation to set the tone for the Conference.

SESSION 1: NEW INSIGHTS AND TRANSFORMATIVE GENETIC TECHNOLOGIES IN NEUROMUSCULAR DISEASE

Session 1 was moderated by Dr. Dennis Bulman (CHEORI, CAN), with a session exploring the impact of next generation sequencing (NGS) on the discovery of new, rare disease-causing genes. The session opened with Dr. Stephan Züchner (University of Miami Health System, USA) discussing how NGS, both exome and whole genome approaches, have accelerated the discovery of novel genes causing axonopathies, such as Charcot-Marie-Tooth Disease (CMT). Dr. Züchner also presented an overview of "The Genesis Project", a not-for-profit foundation set up to integrate and share the large data sets generated using NGS [5]. Currently, The Genesis Project has over 600 users from 44 countries, and includes a "Matchmaking" system to automatically connect research groups studying similar disease phenotypes

to hopefully accelerate novel gene identification. Dr. Hanns Lochmüller (Newcastle University, UK) spoke on the importance of integrating different types of data (NGS, transcriptome, clinical data, patient registries) to accelerate gene discovery and getting treatments to patients, highlighting the application of these approaches for congenital myasthenic conditions [6]. Dr. Lochmüller also described his work on a series of glycosyltransferases, each of which give a similar disease phenotype due to acting in series in the same glycosylation pathway, mutation of which ultimately impairs neuromuscular transmission. Finally, he stressed that identifying the disease causing gene can aid in assigning appropriate, mutation-specific targeted therapies and, conversely, can also prevent administration of potentially harmful treatments.

Dr. Bernard Brais (McGill University, CAN) reiterated the accelerated rate with which new disease-causing genes have been identified, since the field has transitioned from traditional positional cloning to NGS [7]. Dr. Brais presented pragmatic strategies to identify more challenging NMDs, such as those associated with later onset, undescribed or regional phenotypes, and variable penetrance or minimal pathology. For novel gene discovery, strategies such as NGS data sharing through international collaboration (including The Genesis Project), whole genome sequencing combined with RNAseq, regional exploitation for cohorts (some diseases are much more prevalent in certain populations [8]), and a general appreciation that there is still much we do not know so as to stay "humble". Dr. Kym Boycott (CHEORI, CAN) spoke about efforts to unite gene identification efforts for rare diseases across Canada, including FORGE (Finding of Rare Disease Genes) and Care for Rare. FORGE united 21 genetic centers across Canada and utilized NGS for children with rare disorders that remained undiagnosed in spite of extensive clinical investigations [7]. Over two years, FORGE selected 264 disorders for study (47 of these were neuromuscular), with disease causing variants found for 146 disorders (55% success rate, or one new gene per week over the two-year span) [9]. More recently, FORGE evolved into Care for Rare with an expanded mandate to become more international, to assess both pediatric and adult patients with undiagnosed rare genetic disorders, as well as identify new potential therapies through drug re-purposing screens. Dr. Boycott also discussed efforts to gain additional functional data on newly discovered genes through the creation of "The Rare Diseases: Models & Mechanisms Network", a service to link clinicians who discover novel disease-causing genes with basic researchers working on those same genes. The session ended with a Short Talk by Dr. Matthew Alexander from the laboratory of Dr. Louis Kunkel (Boston Children's Hospital/Harvard Medical School, USA) entitled "Generation, characterization, and corrective drug screening of an LGMD2I model zebrafish."

SESSION 2: CHALLENGES AND OPPORTUNITIES IN AMYOTROPHIC LATERAL SCLEROSIS THERAPY DEVELOPMENT

The title of the session was established by Dr. Michael Benatar (University of Miami, USA), who provided an excellent opening overview of the challenges faced in ALS research. These challenges include (1) the heterogeneous nature of the sporadic and inherited forms of ALS (e.g. many different genes cause ALS leading to different biology of disease); (2) lack of adequate outcome measures and the need for effective biomarkers [10, 11]; (3) inadequate animal models (e.g. the SOD1G93A mouse may not be the best model to represent the breadth of ALS); (4) difficulties in patient recruitment for clinical trials; and (5) therapeutic intervention usually happens too late in the disease (i.e. patients likely need to be treated at the presymptomatic stage). Dr. Brian Kaspar (The Research Institute at Nationwide Children's Hospital, USA) showed that, although ALS is thought of as a motor neuron disease, the root cause may be toxic effects of mutant microglia leading to death of the motor neuron [12]. This killing by mutant microglia appears to be highly dependent on SOD1 expression, as suppression of SOD1 in both familial and sporadic ALS lead to reduced killing in tissue culture. Intrathecal injection of AAV encoding a shRNA to SOD1 extended lifespan in the SOD1G93A mouse model of ALS.

Dr. Guy Rouleau (McGill University, CAN) provided an update on genes associated with ALS, including GLE1, C9ORF72, and TBK1. The latter gene was identified in a large whole genome sequencing effort of almost 3000 ALS patients, which also identified more traditional ALS-associated genes such as SOD1 and TDP43 [13]. Dame Pamela Shaw (University of Sheffield, UK) reiterated the difficulty in applying a single therapy for a disease caused by many different genes with different underlying biology, such as in ALS, and noted that, even for a

single disease gene, significant variability in disease course can occur. Analysis of two different mouse strains with the same SOD1G93A mutation but dramatically different lifespans led to the identification of NRF2, a key transcription factor regulating the expression of antioxidant response genes, as a potential therapeutic target for ALS [14, 15]. The session ended with a Short Talk by Carolyn Tallon from Dr. Mohamed Farah's laboratory (Johns Hopkins University Medical School, USA) entitled "Reducing BACE activity via pharmacological and genetic interventions improves neuromuscular junction remodeling in both ALS and partial motor axon injury models." This session was moderated by Dr. Johnny Ngsee (OHRI, CAN).

SESSION 3: CONCURRENT CLINICAL AND BASIC SESSIONS IN NMD

Although the Conference was designed to bring together scientists and clinicians of varying background to enhance discussion and collaboration, it was recognized that focused sessions for basic researchers or clinicians/investigators were necessary to highlight specific advances in these areas.

Session 3A: Recent developments in clinical NMDs

The session was moderated by Dr. Hugh McMillan (CHEORI, CAN). Dr. Richard Lewis (Cedars-Sinai, USA) opened the clinical session with a detailed review of the electrophysiological characterization of demyelinating neuropathies. Dr. Lewis highlighted the underlying pathological mechanisms of sodium channel dysfunction in neuropathies, and outlined features of physiological slowing of conduction velocity from segmental or diffuse loss of myelin and, in some instances, remyelination [16]. Electrodiagnostic features, such as marked conduction velocity slowing, prolongation of distal latency and compound muscle action potential (CMAP) duration, segmental conduction slowing, as well as temporal dispersion of CMAP on proximal stimulation, provide evidence of a demyelinating neuropathy [17]. Dr. Bjarne Udd (University of Tampere, Finland) presented a comprehensive approach to classifying myopathies with rimmed vacuoles by clinical presentation, molecular testing and analysis of vacuolar contents (i.e. proteinopathies) of muscle biopsy. This rapidly expanding class of myopathies includes both the sporadic inclusion body myositis variants, as well as the inherited rimmed vacuolar myopathies (RVM), including titinopathies, distal myopathies, myofibrillar myopathies and other less common myopathies with RVM (i.e. LGMD1D) [18]. A categorization of inflammatory myopathies based on pattern of pathology in muscle fibers, connective tissues, and vessels, as well as immune features and clinical correlates was presented by Dr. Alan Pestronk (Washington University School of Medicine, USA) [19]. The acquired inflammatory myopathies were characterized into the following categories by pathology including: a) immune myopathies with perimysial pathology (IMPP) with perimysium connective tissue damage; b) myovasculopathies with abnormal perimysial or endomysial vessels; c) immune myopathies with $C_{5b\text{-}9}$ complement deposition on endomysial connective tissue, with necrosis and regeneration of scattered muscle fibers; d) histiocytic inflammatory myopathies with focal invasion of muscle fibers by histiocytic cells; and e) inflammatory myopathies with vacuoles, aggregates, and mitochondrial pathology (IM-VAMP) characterized by morphologic abnormalities in myofibers with endomysial mononuclear cell inflammatory infiltrates, which would also include inclusion body myositis [19, 20].

Dr. Volker Straub (Institute of Genetic Medicine at Newcastle University, UK) closed the session with an informative overview of the challenges for molecular confirmation in the diagnosis of the limb girdle muscular dystrophies (LGMD), a heterogeneous group of genetic muscle disorders characterised by progressive weakness affecting mainly the shoulder girdle, pelvic, and proximal limb muscles [21]. Dr. Straub outlined the clinical diagnostic difficulties due to genetic and phenotypic heterogeneity, and described recent innovative diagnostic approaches to validate potentially pathogenic variants, including recent advances in MRI imaging [22, 23], emerging biomarkers [24], and the importance of natural history studies. Dr. Talita Conte, from the laboratory of Dr. Bernard Brais (McGill University, CAN) provided a Short Talk entitled "Clinical and genetic characterization of a new dominant herculean myalgic disorder: the Strongman Syndrome."

Session 3B: Recent developments in fundamental muscle biology

Moderated by Dr. Nadine Wiper-Bergeron (uOttawa, CAN), the session opened with Dr. Dawn

Cornelison (University of Missouri, USA) presenting her work on establishment of fiber type in muscle. Dr. Cornelison introduced the concept that motor neurons and the fibers that they innervate may be "matched" as being either slow or fast in part due to interactions of Eph receptors and ephrin ligands [25, 26], and involves a third cell type, terminal Schwann cells, present at the neuromuscular junction (NMJ). Dr. Laurent Schaeffer (Université de Lyon 1, France) presented his work on the role of transcriptional corepressor CtBP1 in muscle gene expression. In extrasynaptic nuclei, expression of myogenin and acetylcholine receptors is repressed due to the action of CtBP1 and the associated repressive chromatin marks on these target genes. Denervation of the muscle causes upregulation of p21-Activated Kinase 1 (PAK1) which phosphorylates CtBP1 causing its export into the cytoplasm, and repressive histone marks are replaced by activating ones, leading to activation of expression of myogenin and likely of other target genes [27].

Dr. Eric Shoubridge (Montreal Neurological Institute, CAN) described the identification and characterization of patient mutations in mitochondrial disorders, which have provided insight into RNA processing in the mitochondria. His presentation included a discussion of GRSF1 (a protein found primarily in granules of RNA biogenesis and which binds specific elements in the 5' UTR of mitochondrial glutathione peroxidase-4 mRNA, thus regulating activity), FASTD2 (involved in mitochondrial ribosome biogenesis) and RMND1 (anchors mitochondrial ribosomes near the sites of mRNA maturation) [28–30]. Dr. Louis Kunkel (Boston Children's Hospital/Harvard Medical School, USA) presented his work with researchers in Brazil, searching for disease modifiers in phenotypic outliers from the Golden Retriever Muscular Dystrophy (GRMD) dog model [31]. Genome wide association studies (GWAS) of an essentially asymptomatic male GRMD dog and a similar descendant identified Jagged1 as a modifier of muscular dystrophy, as this protein was significantly upregulated in the unaffected dogs [32]. Dr. Kunkel postulated that the protein may function in part by inducing alterations in the extracellular matrix such that it provides a better supportive structure for the dystrophic muscle fiber. Dr. Jennifer M. Peterson from the laboratory of Dr. Denis Guttridge (The Ohio State University, USA) provided a Short Talk entitled "NF-kB promotes cardiac dysfunction and impaired calcium handling in a model of Duchenne muscular dystrophy".

SESSION 4: INNOVATIVE DISCOVERIES IN MYOPATHIES

Dr. Monkol Lek (Broad Institute of Harvard and Massachusetts Institute of Technology, USA) expanded on the challenges of molecular diagnosis with NGS presented in Session 1, and addressed alternative approaches to identifying potentially pathogenic variants when exome sequencing fails to detect mutations. For example, RNAseq can pinpoint regions of the genome that are not expressed, when they should be, which could suggest point mutations in promoter regions or that affect gene splicing [33]. Dr. Gisèle Bonne (Institut de Myologie, France) described laminopathy-related disorders, specifically focusing on mutations in *FHL1* (four-and-a-half LIM domains 1) that give rise to Emery-Dreifuss muscular dystrophy (EDMD) [34]. *FHL1* mutations cause several allelic disorders, such as reducing body myopathy (RBM), scapuloperoneal myopathy (SPM) and X-linked myopathy with postural muscle atrophy (XMPMA) [35]. The function of FHL1 protein is unknown.

Dr. Stephen Greenberg (Brigham and Women's Hospital, USA) presented his work on gene expression analysis in patients affected with myositis, and how this has led to both screening for novel small molecule therapies and the development of a new assay for screening patients [36]. Microarray of samples from dermatomyositis patients revealed enhanced expression of type I interferon-dependent cytokines, which has resulted in a clinical trial with sifalimumab, an anti-IFN-α monoclonal antibody, for dermatomyositis and polymyositis [37]. Similarly, microarray of samples from patients with inclusion body myositis (IBM) showed an upregulation of immunoglobulin genes, caused by an infiltration of plasma cells [38]. Subsequent studies demonstrated that ∼70% of IBM patients develop disease in part due to autoantibodies against cytosolic 5'nucleotidase 1A [39], and a dot blot assay has been developed for patient screening purposes. Dr. Carsten Bönnemann (National Institutes of Health, USA) presented an update on congenital myopathies, and highlighted the interplay between NGS and molecular and phenotypic heterogeneity and how this impacts accurate diagnosis. Use of NGS to identify causative genes for patients with a novel phenotype enables more rapid diagnosis in all subsequent patients presenting with a similar phenotype [40]. Dr. Dwi Kemaladewi from the laboratory of Dr. Ron Cohn (University of Toronto, CAN) provided a Short Talk on "Elucidating

the role of polyamine in laminin-deficient congenital muscular dystrophy". The session was moderated by Dr. Jocelyn Côté (uOttawa, CAN).

AN EVENING AT THE CANADIAN MUSEUM OF HISTORY

A dinner session was convened at the Canadian Museum of History (Gatineau, Canada), which featured two special presentations. Dr. Lawrence Korngut (University of Calgary, CAN) is the National Principal Investigator of the Canadian Neuromuscular Disease Registry (CNDR) and the Canadian Neuromuscular Disease Network (CAN-NMD). Both of these initiatives are designed to unite and enhance NMD research and patient care across Canada. CNDR is a Canada-wide registry of medical information from patients diagnosed with NMD, with the goal of improving the surveillance of these diseases, assist with current clinical management and accelerate the development of new therapies. CAN-NMD is jointly funded by MDC and the Canadian Institutes of Health Research, and is mandated to create a national network of stakeholders in NMD to establish Canada as a world-class leader in clinical patient care, basic and clinical research, and education and training for clinicians, scientists and trainees in the fields of neuromuscular and rare diseases.

Conferences delegates were then treated to an inspirational, educational and entertaining talk by Dr. Danielle Peers (Concordia University, CAN). Dr. Peers is currently a Postdoctoral Fellow in Communication Studies, and studies disability sport and social justice movements in Canada. In her former career as a wheelchair basketball athlete, Dr. Peers won several Canadian national and world titles, a Paralympic Bronze-medal, and was voted World's Most Valuable Player in Wheelchair Basketball in 2006, and was nominated as a finalist for International Sportswoman of the Year in 2007. Dr. Peers discussed her journey to diagnosis with NMD, life as an athlete and her desire to live life to its fullest. We, as NMD researchers and clinicians, were tasked with helping to ensure as high a quality of life as possible for all people affected with NMD.

SESSION 5: RECENT ADVANCES IN MYOTONIC DISORDERS

Dr. Robert Korneluk (CHEORI, CAN) acted as session moderator. Dr. Maurice Swanson (University of Florida College of Medicine, USA) discussed NMDs that arise through proteins binding RNA, including hnRNP21, TDP43, FUS, hdRNPH and MBNL. Dr. Swanson spoke of his work showing that MBNL binds to the expanded CUG repeats in DMPK found in DM1 using the HITS-CLIP/CLIPseq approach [41]. This approach can also be used to identify mRNAs that MBNL normally binds, which would likely be misregulated when MBNL is sequestered in DM1 patients, and as a more generalized approach to identify RNA bound by other RNA-binding proteins. Dr. Bernard Jasmin (uOttawa, CAN) discussed his work on Staufen1, a RNA-binding protein involved in localizing or stabilizing specific mRNAs in the region of the NMJ. Staufen1 levels are increased in skeletal muscle from DM1 mouse models and patients, and overexpression of Staufen1 can rescue the export of CUG-expanded mRNA from the nucleus, thereby counteracting their sequestration and allowing protein expression [42]. However, Staufen1 seems to have conflicting roles in muscle [43], as a global survey of genes showed that Staufen 1 may also function to upregulate expression of atrogenes, and its upregulation in rhabdomyosarcoma may contribute to the inability of these cells to follow a normal differentiation pathway.

Dr. Lubov Timchenko (Cincinnati Children's Hospital Medical Centre, USA) discussed her work on the use of GSK3β inhibitors to treat mouse models of DM1. Dr. Timchenko's work showed that GSK3β is upregulated in DM1 tissue, and that administration of GSK3β inhibitors resulted in a restoration of cyclin D3 levels, phosphorylation of CUGBP1, and thus release of CUGBP1-sequestered mRNA [44]. Encouragingly, treatment of DM1 mice with a GSK3β inhibitor for 6 weeks at 1 month of age resulted in phenotypic correction for 1 year. Dr. Giovanni Meola (University of Milan, Italy) discussed the differences in DM1 and DM2, the relative impact of RNA-binding proteins involved in these diseases (i.e. MBNL, CUGBP1), and the impact of modifier genes. For example, Dr. Meola described 2 patients with DM2 that had additional heterozygous mutations in *CLCN1,* which caused an unusually young juvenile-onset myotonia [45]. In an adult patient with DM2, an additional mutation in *SCN4A* increased the severity of myotonia [46]. Dr. Mani Mahadevan (University of Virginia School of Medicine, USA) gave a Short Talk entitled "A new inducible/reversible mouse model of RNA toxicity and RAN translation in DM1".

SESSION 6: PHENOTYPIC AND MOLECULAR INSIGHTS INTO SPINAL MUSCULAR ATROPHY

The session devoted to SMA was moderated by Dr. Rashmi Kothary (OHRI, CAN). Dr. Chris Lorson described his efforts to develop an antisense oligonucleotide (ASO)-based therapy to promote favorable splicing events in mRNA derived from the survival of motor neuron 2 (*SNM2*) gene. Administration of ASO directed towards splicing Element 1, located upstream of exon 7 of *SMN2*, extended life in a severe mouse model of SMA from 13 to 65 days, and improved other measures such as righting time and NMJ structure [47]. Dr. Frédéric Charbonnier (Université Paris Descartes, France) showed that exercise can lead to enhanced expression of SMN through both increased gene expression of *SMN2* and favorable splicing of mRNA derived from this gene to include exon 7, with a subsequent increase in lifespan in a mouse model of SMA [48]. Dr. Charbonnier further demonstrated that insulin growth factor receptor (IGFR) is upregulated in SMA-like mice, but is downregulated by exercise, which in turn can activate a number of signaling pathways in the cell, including MEK/ERK, PI3K/AKT and JAK/STAT, which ultimately impact upon SMN expression and splicing [49].

Dr. Charlotte Sumner (Johns Hopkins University, USA) presented her work characterizing a long non-coding RNA (lncRNA) that forms a natural antisense transcript (NAT) expressed from exon 1 of the SMN gene. Interestingly, expression of this lncRNA increases postnatally which correlates with the decline in SMN expression over time. Using ASO technology, Dr. Sumner showed that knockdown of the lncRNA resulted in enhanced expression of SMN protein. NAT may function through its ability to recruit the polycomb repressive complex 2 (PRC2) to the SMN promoter. Dr. Alex MacKenzie (CHEORI, CAN) described exciting therapeutic discoveries achieved through repurposing existing, approved drugs for treatment of genetic disease. For example, publically available databases showed that activation of the p38 kinase pathway leads to upregulation of SMN protein expression. Celecoxib activates the p38 pathway, and can modestly extend lifespan in SMA mice [50]. A similar approach identified mexiletine as a symptomatic therapy for myotonic dystrophy [51]. The enormous potential of screening approved drug libraries for therapeutic efficacy is being expanded upon as part of the Care for Rare initiative described above (Session 1). Dr. Melissa Bowerman, from the laboratory of Dr. Matthew Wood (University of Oxford, UK) closed the session with a Short Talk entitled "Development of a cell penetrating peptide that crosses the adult blood-brain barrier for spinal muscular atrophy therapy".

SESSION 7: CONCURRENT CLINICAL AND BASIC SESSIONS IN NMD

Session 7A: Advances in clinical neuromuscular disease

The second session devoted to clinical advances in NMD was moderated by Dr. Pierre Bourque (TOH, CAN). Dr. Amelia Evoli (Institute of Neurology, Catholic University, Italy) provided an in-depth review of the underlying pathophysiological mechanisms and treatment options in myasthenia gravis (MG). Dr. Evoli outlined the antibody testing algorithm, including first acetylcholine receptor antibodies (Abs), then muscle-specific tyrosine kinase receptor (MuSK) Abs (especially in young adult women with bulbar and neck weakness), and then the more recently described low-density lipoprotein receptor-related protein 4 Abs. Dr. Evoli explained that most MuSK-MG patients are unresponsive to acetylcholinesterase inhibitors and may benefit from 3,4-diaminopyridine and albuterol [52]. Rituximab may also be effective in MG, especially in MuSK-MG [53].

Dr. Jean Marc Léger (Centre de référence maladies neuromusculaires rares, France) described the spectrum of immune-mediated neuropathies, which broadly encompasses an acute subtype, Guillain-Barré syndrome (GBS), as well as 3 chronic subtypes, including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and distal acquired demyelinating symmetric neuropathy associated with IgM anti-myelin-associated glycoprotein (MAG) (anti-MAG neuropathy). Dr. Léger provided a comprehensive review of the clinical trials favoring therapies for GBS [Plasma exchange (PLEX) and intravenous immunoglobulin (IVIG)], CIDP (Corticosteroids, PLEX, and IVIG) MMN (IVIG), and anti-MAG neuropathy (possibly Rituximab) [54, 55].

Dr. Michael Geraghty (CHEO, CAN) discussed established and recently described mitochondrial disorders caused by defects in mitochondrial protein translation. Dr. Geraghty reviewed the heterogeneous

clinical presentations and approach to diagnostic investigations of mitochondrial syndromes, including mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), and tRNA nucleotidyl transferase TRNT1-related disorder [56]. Dr. Craig Campbell (Children's Hospital, London Health Sciences Centre, CAN) provided an informative review of the clinical trial era of Duchenne muscular dystrophy. Dr. Campbell comprehensively described the underlying pathology in DMD and the mechanism of ASO-mediated exon skipping to restore the disrupted dystrophin reading frame. The rationale of these approaches were outlined with a detailed overview of challenges and opportunities when implementing current clinical trials for DMD. Dr. Lawrence Korngut (University of Calgary, CAN) gave a Short Talk overviewing ALS Clinical Trials in Canada, and provided an inclusive summary of potential new therapies in ALS on the horizon.

Session 7B: Advances in muscle stem cell biology

The second session devoted to basic NMD research focused on muscle stem cells, and was moderated by Dr. Alexander Blais (uOttawa, CAN). Dr. Emanuela Gussoni (Boston Children's Hospital/Harvard Medical School, USA) spoke on her research dedicated to improving cell-based therapies for NMD. Dr. Gussoni's studies showed that muscle cells that are double-positive for the cell surface markers CD82 and MCAM show an enhanced ability to engraft when used in transplantations studies, compared to cells either positive for only one of the markers or double-negative. Interestingly, to gain some insight into its normal function, Dr. Gussoni showed that CD82 forms a complex with α7 integrin and α-sarcoglycan in normal muscle, but this complex did not form in tissue from DMD patients or those with α-sarcoglycanopathy. Dr. Fabio Rossi (University of British Columbia, CAN) presented his work on the interplay between fibro-adipogenic progenitors (FAP) and macrophages, and their role in the formation of fibrosis and adipose tissue in dystrophic muscle. During normal regeneration, FAP have a promyogenic effect on satellite cells [57], but the FAP disappear late during regeneration through apoptosis caused by TNFα released from infiltrating M1 macrophages. During chronic inflammation, as is observed in dystrophic muscle, macrophages release both TNFα and TGFβ, causing a decreased induction of apoptosis of the FAP, leading to enhanced fibrosis. Dr. Rossi implicated the p38 kinase signaling pathway and NF-kB in mediating this effect, and showed that administration of nilotinib, a tyrosine kinase inhibitor, restored the ability of *mdx* macrophages to kill FAP, thereby reducing fibrosis and adipose deposition in dystrophic muscle [58].

Dr. Jeffrey Dilworth (OHRI, CAN) presented his studies on cell fate transitions in muscle cells, focusing on the histone demethylase UTX. Knockout or inhibition of UTX results in a poor ability of muscle to regenerate, which appeared to be due to the ability of UTX to demethylate histones present in the promoter regions of crucial genes such as myogenin [59]. UTX appears to be recruited to enhancers through its ability to bind the Six4 transcription factor. Dr. Dilworth also presented evidence that sequential inhibition of UTX and its antagonizer Ezh2 can perhaps be used to expand the pool of muscle progenitor cells and, ultimately, enhance muscle regeneration. Dr. Bradley Olwin (University of Colorado, USA) studied the function of satellite cells in normal muscle homeostasis. Satellite cells are believed to exist in a "quiescent" state until stimulated to divide following muscle damage. However, Dr. Olwin showed that over a two week period, approximately 10% of the satellite cells in an undamaged muscle undergo division, which suggests that low level replenishment of the muscle myonuclei, through activation and fusion of satellite cells into fibers, may be a normal part of muscle maintenance. Ms. Wenxuan Liu from the laboratory of Dr. Joe Chakkalakal (University of Rochester, USA) presented a Short Talk entitled "Inducible depletion of Pax7+ satellite cells impairs the regeneration of adult neuromuscular synapses".

SESSION 8: NEW INSIGHTS AND SMALL MOLECULE THERAPIES FOR DYSTROPHINOPATHIES AND OTHER MYOPATHIES

The final session of the conference was moderated by Dr. Tuan Bui (uOttawa, CAN), and opened with Dr. Kevin Campbell (University of Iowa, USA) speaking about his work on dystroglycanopathies. Dystroglycan is extensively glycosylated, which involves at least 18 different genes, mutations in which can result in dystroglycanopathy. In most of these disorders, the dystrophin glycoprotein complex (DGC) forms correctly, but failure to properly glycosylate dystroglycan prevents attachment of the complex to the extracellular matrix (ECM). Dr.

Campbell also discussed his efforts to identify small molecules that upregulate LARGE, a glycosyltransferase, which can enhance glycosylation of DGC proteins, thereby strengthening the connection between muscle fibre and the ECM [60]. Dr. Michael Rudnicki (OHRI, CAN) presented his work on the role of dystrophin in establishing polarity in satellite cells [61]. *mdx* mice, which lack dystrophin, show a 5-fold reduction in satellite cell asymmetric divisions (i.e. cell division giving rise to daughter cells in which one is a satellite cell and the other is a committed muscle progenitor cell). Dr. Rudnicki's team showed that dystrophin expression is normally polarized to the basal surface in satellite cells where it recruits Par1b, a member of the Par polarity complex. In satellite cells from mdx mice, Par1b does not localize correctly, and the cells show an aberrantly high number of centrosomes which results in apoptosis and a loss of satellite cells, thus contributing to the dystrophic pathology [62].

Dr. Jeff Chamberlain (University of Washington, USA) presented an update on his efforts to develop a gene therapy strategy to treat Duchenne muscular dystrophy. Systemic delivery of an adeno-associated virus (AAV) vector encoding a micro-dystrophin gene can lead to efficient, body-wide transduction (depending on the AAV serotype). However, this AAV transduction can "rescue" muscles (i.e. the diaphragm), but does not completely prevent contraction-induced injury, suggesting that delivery of micro-dystrophin genes may never lead to a complete recovery of muscle function [63, 64]. Dr. Chamberlain discussed recent work on using Crispr/Cas9 genome editing technology to correct dystrophin mutations in *mdx* mice. Dr. Elizabeth McNally (Northwestern University, USA) described her efforts to develop an exon-skipping strategy to treat LGMD caused by γ-sarcoglycan (γ-SG) deficiency [65]. Exon-skipping was first used extensively by several groups for treatment of DMD, as dystrophin protein has an internal repeating rod domain structure that can vary significantly in length yet still provide proper function; therefore, "skipping" of regions in the rod domain that contain nonsense mutations can lead to partially functional protein. Although γ-SG does not have a protein structure similar to dystrophin, Dr. McNally showed that an engineered mini γ-SG gene which lacked exons 3-8 produced a protein that in a fruit fly model of γ-SG-deficiency localized correctly, interacted with normal cellular partners, and restored muscle function to normal levels. Similar results were observed in γ-SG-deficient mice transgenic for the mini-gene. Finally, in patient fibroblasts converted to muscle cells, administration of ASO could induce exon skipping of the γ-SG mRNA. Based on the mutations found in patients, this novel approach may be applicable to approximately half of all patients with γ-SG-deficiency. Dr. Hansell Stedman (University of Pennsylvania, USA) provided an eclectic Short Talk entitled "Prevention of histological signs of muscular dystrophy by AAV vector encoding a nonimmunogenic protein based on the evolution of utrophin and dystrophin." Closing remarks were provided by Dr. Robin Parks (OHRI, CAN) who, on behalf of the organizers, thanked the attendees, speakers and sponsors.

CONCLUDING REMARKS

By all accounts, the Ottawa NMD 2015 conference was a great success. The Ottawa NMD 2015 conference accomplished its goals of providing educational and thoughtful talks that could engage and inspire all 300 attendees, regardless of their level or specific field of expertise, trainees, scientists and clinicians alike. We hope that the conference provided a venue that could foster new collaborations, or re-establish old ones, lead to new understandings of biology and disease mechanisms, and enhance diagnosis and treatment options for patients affected by NMDs. Enhanced collaborations and interactions among world-leaders in NMD is of the utmost importance as it will greatly facilitate major breakthroughs ultimately benefitting NMD patients, their care-givers and communities.

Planning is already underway for the next Ottawa NMD conference. The 4th Ottawa International Conference on Neuromuscular Disease and Biology (Ottawa NMD 2017) will take place on September 7–9, 2017. Mark your calendars! Once again, we look forward to exciting and dynamic updates from leading basic and clinical researchers in NMD here in our National Capital.

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