for treatments and a cure. The meeting was sponsored by the MGFA in partnership with the NYAS. The leaders of the organizing committee were Drs. Linda Kusner and Ted Burns of the Medical/Scientific Advisory Board of the MGFA. Sue Klinger, acting MGFA Chair, and Nancy Law, MGFA CEO, opened the meeting by emphasizing that the MGFA works to improve the life of people with MG in several ways including support of relevant research. All of the speakers were doctors of medicine (MD), philosophy (PhD), or both.

**DAY 1**

**Session 1: Neuromuscular Junction (NMJ) Structure and Function**

This session was chaired and opened by Clarke Slater from Newcastle University in the UK. He provided an overview of the structure of the neuromuscular junction (NMJ) and emphasized differences in humans compared to other mammals. Humans release very few packets (aka quanta) of the neurotransmitter acetylcholine (ACh) compared to other mammals, so we are more susceptible to disorders of neuromuscular transmission.

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Mark Rich of Wright State Univ. in Ohio talked about the structure and function of the motor nerve terminal that enables ACh release. He described the feedback between the endplate membrane on the muscle fiber and the nerve terminal. This action adjusts the amount of ACh released to accommodate for changes in the sensitivity of the endplate membrane—for example due to changes in the number of ACh receptors (AChR).

Tomasz Prószynski from Poland discussed the complex array and precise arrangement of specific proteins on the postsynaptic membrane. These hold the AChRs and other important components such as sodium channels in place and facilitate the replacement of damaged proteins. Many components do several things including maintaining the structural stability by the ongoing repair of the NMJ.

Markus Ruegg, of Switzerland focused on the roles of key proteins Agrin, MuSK, Dok7, LRP4 and Rapsyn in the insertion and positioning of AChRs on the postsynaptic membrane. Agrin, MuSK, Dok7 and LRP4 are all implicated variants of autoimmune MG in addition to the AChR, which is the most frequent autoimmune target in MG.

Clarke Slater spoke about changes in the NMJ with aging. There are changes that occur with age, but the good news was that the transmission efficiency of the NMJ remains fairly constant.

This session laid groundwork for subsequent sessions dealing with changes in NMJ structure associated with different forms of MG and related diseases.

**Session 2: Congenital Myasthenic Syndromes — chaired by Andrew Engel of Mayo Clinic, MN**

Andrew Engel is the dean of researchers and clinician in the field of congenital forms of MG, which he demonstrated resulted from mutations affecting key proteins involved in ACh release. The enzyme that breaks down ACh called ACh-esterase (AChE), is a component of the postsynaptic membrane that maintains the structural integrity of the endplate. It effects the insertion or replacement of AChRs or mutations of the AChR that alter its function.
Engel discussed two newly recognized forms of congenital MG resulting from mutations in proteins that are critical for the release of ACh. Because ACh is a neurotransmitter in the brain as well as the NMJ, children with these rare disorders had problems with brain function as well as weakness.

Claire Legay of France discussed congenital forms of MG associated with deficiency of AChE. In these disorders prolongation of the action of ACh disrupts the normal communication between the nerve and muscle fiber. In normal conditions the ACh released by the nerve terminal triggers a short duration electrical response from the AChRs, called a depolarization. The AChR induced depolarization triggers the sodium channels at the endplate to generate a large depolarization called an action potential (AP) that travels over the entire length of the muscle fibers. The rapid wave of depolarization triggers muscle fiber contraction. If the action of the ACh is prolonged, repeated APs can be triggered in response to a single episode of nerve terminal release of ACh. In addition, prolonged activation of the AChRs allows too much calcium to enter at the endplate, which causes endplate damage. Calcium is very tightly regulated in cells including skeletal muscle. Calcium is needed for muscle fibers to contract, but too much activates enzymes that cause cell injury.

Hanns Lochmuller from the UK discussed congenital forms of MG associated with weakness affecting control of the face, throat, shoulders and thighs. These conditions were associated with a variety of mutations to endplate proteins including Dok7. David Beeson of the UK discussed how mutations of proteins in the space between the nerve terminal and the endplate membrane disrupted the structure of the endplate including reducing the presence of groups of AChRs.

Particularly exciting was Jacqueline Palace’s presentation on treatment strategies for people with congenital forms of MG. Palace is part of an excellent group of researchers and clinicians in the UK that includes David Beeson and Angela Vincent. By knowing the mutation responsible for the congenital MG, it was possible to develop rational and effective treatment strategies. The useful classifications were: 1) disorders of ACh release, 2) AChE deficiency, 3) deficiency of AChR, 4) altered function of AChRs, and 5) disruption of the endplate structure. Here’s a list of some examples of treatments based upon specific mutations. Drugs used to treat asthma, ephedrine, albuterol, and salbutamol, are useful for mutations of Dok7. Albuterol/salbutamol is also helpful for mutations of agrin and LRP4 (a protein associated with AChR clustering). Ephedrine helps people with AChE deficiency. Ephedrine or albuterol help patients with AChR deficiency syndromes, whereas pyridostigmine (mestinon) does not help. Pyridostigmine or ephedrine help with specific AChR mutations, whereas quinidine or fluoxetine help people with different types of AChR mutations. Disorders of Dok7 can be worsened by pyridostigmine or 3,4DAP.
Session 3: Thymus in Myasthenia Gravis — chaired by Rozen Le Panse from France

The thymus is critical to the development of T-type lymphocytes (“T” refers to thymus). Le Panse spoke about a key difference between the thymus glands of people with MG associated with AChR-antibodies vs. people without MG. MG-associated thymus tissue produces an excessive amount of chemicals that promote inflammation. Perhaps this is why the T-cells from people with MG promote inflammation. Her work helps explain why removing the thymus tissue may reduce the severity of MG. Alex Marx of Germany presented his initial findings on the microscopic appearance of MG thymus tissue. This study was part of the international clinical trial evaluating the benefit of thymectomy in people with MG. The MGFA funded Dr. Marx’s work. The thymus gland normally atrophies as people age and is replaced by fatty tissue. Marx found that MG thymus glands had less fat and had more active immune cells than non-MG thymus tissue from age matched controls. Additionally the people who showed the most benefit from thymectomy were those who had the most active thymuses. The role of T-lymphocytes in MG is to induce B-lymphocytes to make antibodies.

Paola Cavalcante from Italy discussed the presence of chemicals in the MG-thymus glands associated with activation of B-cells. Several different types of chemicals that activate B-cells were present in MG-thymus glands. The inflammatory state of MG-thymus tissues may be the result of prior virus infections such as Ebstein-Barr virus (EBV) or a genetic predisposition to an exaggerated immune state. EBV is a herpes virus that has been implicated in the genesis of several cancers. It is also the most frequent cause of mononucleosis (“mono” or kissing disease), consequently an appreciable portion of people have been exposed to EBV. EBV is also being considered as a possible trigger for multiple sclerosis (MS).

Session 4: Serological Phenotypes and Unique Treatment Responses — chaired by the eminent Angela Vincent from England

Session 4 was chaired by the eminent Angela Vincent from England, who has devoted her life to MG research. She is a past Chair of the Medical/Scientific Advisory Board of the MGFA. Serological classification is the recognition of different markers in a person’s blood, such as antibodies to AChR or other endplate proteins that identify a person as having a disease such as MG. Vincent reviewed the recognition of antibodies against the AChR in 1975-6. About 20% of people with clinical MG do not have detectable AChR antibodies. About 6-10% of people with MG have antibodies against MuSK. Other antigens associated with MG include endplate proteins LRP4 and agrin. Vincent also showed that the form of the AChR may change its ability to bind pathogenic antibodies. Her laboratory showed that the antibodies from some patients will only recognize human AChR that are present in clusters, the state that the AChRs exist in at the endplate.

“Amelia Evoli …pointed out some of the clinical differences between AChR-MG and MuSK-MG including that people with MuSK MG more commonly have symmetric eye muscle weakness and ptosis, more frequently have throat weakness and respond better to immunosuppressant treatment and plasmapheresis compared with IVIG.”

Isabel Illa from Spain described antibodies to cortactin in people with MG. Cortactin is present at the endplate, but cortactin is present only inside muscle cells. It does not appear on the surface, so how does the immune system recognize the presence of cortactin to produce antibodies? One possibility is that cortactin antibodies develop only after endplates have been damaged and cortactin is exposed to the extracellular space so the immune system can react to cortactin. Consequently, cortactin antibodies may not be associated with the genesis of MG, but still be a marker for MG. Almost 20% of people with clinical MG who do not have AChR antibodies (seronegative MG or SNMG) have cortactin antibodies.
Amelia Evoli from Italy found that about 8% of SNMG patients have antibodies against MuSK. She pointed out some of the clinical differences between AChR-MG and MuSK-MG including the finding that people with MuSK MG more commonly have symmetric eye muscle weakness and ptosis, more frequently have throat weakness and respond better to immunosuppressant treatment and plasmapheresis compared with IVIG. The antibodies against MuSK differ from AChR antibodies in that the MuSK antibodies do not fix complement, whereas complement is responsible for much of the endplate damage in AChR-MG. Hence treatments that suppress complement may be useful in AChR-MG, but not MuSK-MG. Jeannine Heckmann described MG in South Africa. Arthur Melms from Germany described agrin antibodies in MG. Agrin antibodies may be similar to cortactin antibodies, markers of MG, but not initiating MG.

**DAY 2**

The second day of the conference began with a panel of MG clinical researchers discussing the unmet needs of patients with MG. The panelists were James Howard, Univ. of North Carolina, Richard Nowak, Yale Univ. and Gil Wolfe, State Univ. of New York at Buffalo. This was a unique discussion where clinicians suggested research directions with basic researchers in order to direct future research programs to explore issues that are important to patients with MG and the clinicians who care for them.

**Session 5: Mechanisms of Autoimmunity (basic, including diseases other than Myasthenia Gravis) — chaired by Sonia Berrih-Aknin from France.**

This session began with an overview of the immune system by Berrih-Aknin. Overall autoimmunity is complex with a plethora of cells and chemicals that regulate the immune system. The immune system needs an appropriate number/amount of agents to prevent tipping into a pro-inflammatory state. The keynote address,

“The late onset of MG in men may relate in part to lower testosterone levels with aging.”

“Pathogenic and Regulatory T-cells in Central Nervous System Autoimmunity” was delivered by Vijay Kuchroo of Harvard. Interleukin IL-23 induces T-cells into a pro-inflammatory state. Endogenous production of saturated fatty acids, which occurs in obesity, upregulates IL-23. The observations suggested that being in a pro-inflammatory state may contribute to obesity and that obesity may lead to a pro-inflammatory state. Claudia Mauri from UK discussed Regulatory B cells in Health and Disease. B-lymphocytes not only produce antibodies, these immune cells also produce chemicals that regulate the activities of T-lymphocytes and other B-cells. Women, particularly prior to menopause, are more likely to develop autoimmune disorders.

Nadine Dragin from France discussed the role of a chemical in the thymus called AIRE that regulates the process of copying information from DNA to produce proteins, a process called transcription. Low levels of AIRE produce an autoimmune state and AIRE is decreased by estrogen and increased by testosterone. The late onset of MG in men may relate in part to lower testosterone levels with aging. Maartje Huijbers of the Netherlands discussed IG4 autoimmune disorders. Specifically, the antibodies associated with MuSK-MG are immunoglobulin class 4, which do not activate complement. The antibodies in MuSK-MG act by disrupting the function of MuSK, an essential protein involved in maintaining the high density of AChRs in the endplate membrane. There is a normal turnover of AChRs and disrupting the process of replacing AChRs results in a lower density of AChRs, which impairs neuromuscular transmission.
Session 6: Mechanisms of Myasthenia Gravis Autoimmunity — chaired by Kevin O’Connor from Yale Univ.

Kevin O’Connor discussed ways to control production of pathogenic antibodies in MuSK-MG. One strategy is to deplete a class of lymphocytes called CD20+ B cells, which is how Rituximab works. John Yi from Duke discussed a recent strategy to treat metastatic cancers that rev up the immune system by inhibiting a class of chemicals made by the body called Immune Checkpoint Regulators, which create a hyper-active immune system that attacks cancers. Unwanted side effects of inhibiting Immune Checkpoint Regulators include that patients can develop autoimmune disorders such as MG. Biomarkers are something that can be used to determine the presence or future activity of a disease. AChR antibodies levels are biomarkers for the presence of MG, but are not useful for determining how well a treatment is influencing the course of MG. Anna Rostedt Punga from Sweden discussed circulating microRNAs, small pieces of RNA found in blood, as potential biomarkers for MG. The pattern of microRNAs may indicate disease presence for people who do not have detectable antibody levels or tell whether a treatment will improve the status of someone weeks before the improvement would be obvious to the person with MG.

Session 7: Short Talks

Session 7 was a collection of short talks selected from abstracts submitted for posters.

José Adolfo Villegas Vazquez spoke about the role of Interleukin-23 to increase inflammation in the thymus glands of people with MG. The initial trigger for enhanced activity of IL-23 may be a viral infection. Michael Hehir presented initial findings from a 10 site trial of Rituximab treatment for MuSK-MG.

How many of you take probiotics – yogurt, kefir, kambucha etc.? These foods contain bacteria that aid in digestion and may restore the normal composition of gut flora. A new area of research considers how the microbial community in your GI tract, the gut biome, influences the immune system. Elena Rinaldi from Italy presented data showing that giving rats two common strains of probiotic bacteria, Lactobacilli and Bifidobacteria, prevented the development of experimental autoimmune MG. The bacteria acted in part by reducing the amount of circulating pro-inflammatory chemicals and reducing the activity of B-cells.

Session 8: Clinical Trials Update — chaired by Henry Kaminski from George Washington University

Kaminski reviewed prior International Symposia and pointed out that prior meetings up through 2007 had only one, or a few, treatment studies involving patients. This symposium had 18 phase one or two trials – a truly dramatic increase. Chip Howard from University of North Carolina presented initial data from a multicenter trial demonstrating that Eculizumab (a monoclonal antibody treatment that targets the complement system) improved muscle strength and the ability of people to perform activities of daily living (shopping, cleaning house, preparing meals, etc.). Gil Wolfe, Univ. of Buffalo, led the international MG Thymectomy trial (MGTX). He noted three people who were instrumental in initiating the study, Fred Jaretzki, a surgeon from Columbia Univ.; Claudio Mazia the lead physician for South
America, and John Newsom-Davis, the initial study director, who died in a car crash while recruiting a site in Europe. The initial report was published in the New England Journal of Medicine in 2016. Thymectomy was clearly beneficial in improving the clinical state and lowering the dose of prednisone needed for people with MG.

Rudy Mercelis from Belgium presented initial findings of a Phase 1b Clinical Trial of CV-MG01, a preparation of AChR mimetic peptides. This work is based upon work done by Blalock over 1 year involving 24 patients from 6 countries. There were no adverse side effects other than local injection site reactions. The study needs to be completed.

Session 9: Clinical Trials 2 — chaired by Jeffrey Guptill, Duke University

One trial suggested by Guptill was to compare the effectiveness of different medications to reduce the dose of prednisone in MG. Richard Nowak from Yale presented data on a Phase 2 Trial of Rituximab (a monoclonal antibody treatment that targets B-cells involved in MG). The treatment was well tolerated. Effectiveness data is still being analyzed. Initial findings were published in JAMA Neurol 2017 74(1) pages 60-66. Jon Lindstrom from Univ. of PA presented animal data on AChR-Specific Immunosuppressive Therapy for experimental MG. The treatment was successful in both reducing the severity of established MG and in rendering rats resistant to developing MG. Michael Benatar from Univ. of Miami (FL) discussed difficulties in constructing clinical trials.

The day ended with a ceremony honoring the MGFA Philanthropist of the Year, Mona Roth, who generously donated $50,000 to research in honor of her late husband, Sidney Roth.

Session 10: Acetylcholine Receptor Animal Models of MG — chaired by Linda Kusner, George Washington University

Linda Kusner discussed the role of complement. She is a leader on the role of complement in several different animal models. Her work, supported by MGFA with a 2010 High Impact Pilot Grant, was the foundation for using antibodies against C5 (ECULIZIMAB) for MG. Pilar Martinez-Martinez from the Netherlands discussed the role of molecules associated with AChR clustering and insertion in the endplate membrane, such as MuSK (muscle specific kinase, a kinase adds a phosphate group to a protein) and Dok-7 (sometimes these names are random and often scientists don’t understand how they arose). In AChR-MG, the presence of these molecules enables the endplate to recover from injury and to continue to replace AChRs. Some forms of MG are associated with antibodies against MuSK or Dok-7. If the levels of MuSK or Dok-7 are reduced, MG becomes more severe. Conversely, enhancing the levels of Dok-7 reduces severity of experimental MG.

Rozen Le Panse from France spoke about molecules called Toll-like Receptor (TLR) that regulate the activity of collections of lymphocytes in the thymus. Further work in this area may lead to therapeutic alternatives to thymectomy.

Jaap Plomp from the Netherlands talked about the electrical changes at the endplate relative to MG. Many forms of autoimmune MG are associated with loss of AChR and sodium channels due to endplate membrane damage. For nerve terminal stimulation to induce muscle contraction, the endplate potential has to be large enough to trigger APs at the endplate that travel across the muscle membrane to the ends of the fiber.

Mark Rich from Wayne State Univ. spoke about the feedback mechanism that increases the amount of ACh released to accommodate for diminished
responsiveness of the endplate to ACh. The feedback mechanism operates in AChR-MG, but is disrupted in MuSK-MG and other forms of MG associated with antibodies directed against endplate proteins associated with AChR insertion and packing at the endplate.

Session 11: Other Animal Models in Myasthenia Gravis — Chaired by William Phillips from Australia

Phillips continued the discussion about feedback regulation of ACh release showing that MuSK and Rapsyn are involved with the feedback. Jan Verschuuren from the Netherlands spoke about the ability of the IgG4 class of antibodies directed against MuSK to induce MG in animals. The pathology is not associated with complement destruction of endplate membrane, rather with disruption of the normal process of replacing and clustering AChRs in the endplate membrane. Angela Vincent from the UK discussed seronegative MG (SNMG). Some people with SNMG have AChR antibodies that only react with clustered AChRs. Stephen Meriney of Univ. of Pittsburgh spoke about animal models of Lambert–Eaton Myasthenic Syndrome (LEMS). Lin Mei of Augusta Univ. spoke about Lrp4 and agrin antibodies in MG. He showed that Lrp4 is involved with the feedback mechanism regulating ACh release.

This session ended with a remembrance of Claudio Mazia, a key member of the Thymectomy Trial, who passed away before the Thymectomy Trial results were released. His family attended the program.

Session 12: Hot Topic Short Talks (Selected from Submitted Abstracts)

Emanuela Bartoccioni from Italy discussed how Rituximab reduces the activity of T-cells due to reduced B-cell activation of T-cells. Ricardo Maselli from Univ of CA, Davis campus described a newly recognized form of congenital MG. An Vanhaesebrouck, from Oxford, UK presented data on the ability of an agent used in asthma, salbutamol, to improve fatigue and enhance the effectiveness of pyridostigmine in an animal model of MG. Salbutamol appears to aid the AChR replacement mechanism and increases ACh release. Saif Huda, also from Oxford, discussed SHP2, a protein that regulates MuSK action at the endplate. Inhibiting SHP2 reversed some damage seen in an animal model of MuSK-MG. Mario Losen from the Netherlands described a novel treatment strategy for MuSK-MG which employs injecting an altered form of IgG4 antibodies that appear to tie up the pathogenic MuSK-MG antibodies.

Session 13: Treatment Guidelines from Around the World — chaired by Donald Sanders from Duke University

Sanders spoke about the International Consensus Guidance Statements for Myasthenia Gravis Treatment that were supported by the MGFA and published in 2016. These guidelines are important to patients with MG because they provide treatment justifications for insurance providers. Hiroyuki Murai from Japan spoke about treatment guidelines for MG in Japan. Jon Sussman described the MG Guidelines of the Association of British Neurologists. The British and Japanese guidelines complemented the International Guidelines by making a statement that directly applies to specific nations’ healthcare systems. Valeria L. Salutto from Argentina discussed unique MG treatment challenges in South America. The session ended with a panel discussion, that included the above mentioned speakers as well as Gil Wolfe from Buffalo and Henry Kaminski from George Washington University. The participants compared and contrasted MG treatment strategies from around the World. It was clear that MG health care givers are working together to improve MG treatments and find cures for different forms of MG.