IMPACT REPORT
SUMMER 2025

Kinji Ohno, MD, PhD, presents on genetic analysis of congenital myasthenic syndromes at the MGFA's 15th International Conference on Myasthenia Gravis and Related Conditions.

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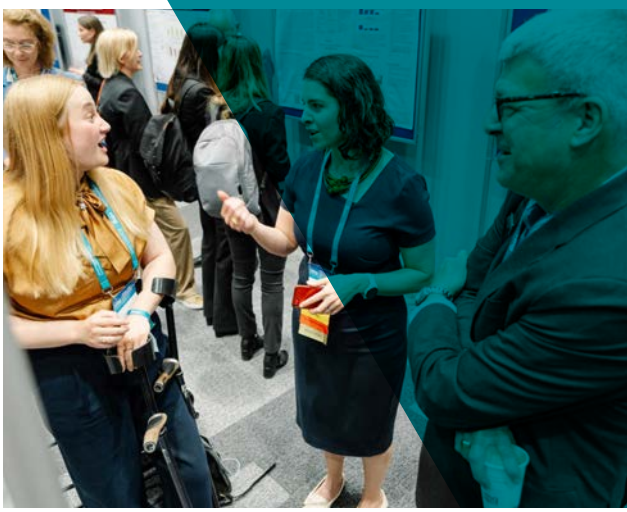


I. OUR EXCEPTIONAL LEADERSHIP

MGFA's History of Research Funding & Strategic Priorities

Since our inception in 1952, the MGFA has led the charge to support the most promising scientific endeavors—funding research, engaging young scientists and clinicians, and spearheading a comprehensive patient registry. At our national conference and international symposiums, we bring together the brightest minds in the field of myasthenia gravis and related disorders.

Research has led to significant improvements in diagnostic techniques, treatments and therapies, and improved disease management.

Despite advances, today's treatment options still come with significant side effects and only partially address life-altering symptoms of MG. Some people with MG do not respond to any of the treatment options currently available.

Our charge is clear: more work in this area is necessary to better understand MG, expand treatment options, and ultimately, find a cure.

Biomarkers

Facilitate early diagnosis, predict clinical outcomes and immunosuppressive therapy response, and utilize in clinical trials.

Disease Mechanisms

Understand basic mechanisms and self-tolerance loss throughout course of disease.

Targeted Therapies

Develop new therapeutic targets, prevent widespread immunosuppression and off-target side effects, optimize treatment strategies with existing therapies.

Patient Outcomes

Understand the full impact of disease on daily living and patient treatment priorities, understand collateral effects of disease-related medical conditions, side effects and financial impact.

Pediatric Treatment

Identify strategies, safety concerns, and long-term outcomes.

MGFA's Research Investment: $3.5M in the past five years

II. OUR GRANT PROGRAM

Active Grant Funding Award Types

Nancy Law Impact Award
The Nancy Law Impact Award supports high-impact clinical research or scientific investigations.

Post-Doctoral Fellowship Award
This award ensures a promising researcher (MD, PhD, or equivalent) can study meaningful, translational research related to myasthenia gravis.

Global MG Registry Publication Award
Through this grant, the MGFA is funding highly meritorious projects that enable academic investigators to use patient-reported data in the MG Patient Registry.

High Impact Pilot Project Award
This award supports promising, results-oriented research projects. Our pilot grants focus on improving the lives of those living with MG now and in the future. All pilot grant applications must coincide with one of our five broad research priorities: biomarkers, disease mechanisms, targeted therapies, patient outcomes, or pediatric treatments.

Active Grant-Funded Research Projects

Myasthenia Gravis Disease Subsets

Project Funded: Defining new autoimmune mechanisms in seronegative MG

Researcher: Kevin C. O'Connor, PhD, Yale School of Medicine

Myasthenia gravis is characterized by the presence of immune system proteins called autoantibodies that are found in most patients. MG autoantibodies cause disease by disrupting normal communication between nerves and muscles.

Seronegative MG (SNMG) is a disease subset of MG characterized by the absence of detectable autoantibodies. Little is known about SNMG, and it has not been well studied.

Several new therapeutics have become available for treating autoantibody-positive MG, many of which are very beneficial. Patients with SNMG are often excluded from certain therapeutic treatments and clinical trials that are open to autoantibody-positive patients. The reason for this is that logical treatment approaches for SNMG are uncertain due to our lack of understanding the disease mechanisms.

Accordingly, Dr. O'Connor's research project is designed to better understand the abnormal immune system functions contributing to SNMG. He and researchers in his lab will investigate whether SNMG shares immunologic features with other subtypes of MG or has features that are unique. Defining these immunologic features is fundamental to guiding treatment decisions for SNMG, as many therapies function only in certain disease subtypes that are defined by the immune system pathology.

We anticipate that this work will answer fundamental questions related to the immunopathological features of SNMG. This will allow clinicians to treat the disease more effectively and guide researchers toward developing new targeted treatments.

Project Funded: Preclinical models and biomarkers for predicting MuSK CAART clinical outcomes

Researcher: Aimee Payne, MD, PhD, University of Pennsylvania

MuSK MG is caused by MuSK autoantibodies that lead to life-threatening muscle weakness, so the ideal therapy would be to eliminate autoantibody-producing B-cells while preserving healthy B-cells. CART cells in the body are currently being re-programmed to eradicate B-cell cancers, prompting researchers to explore whether this precision medicine can be used for other diseases like myasthenia gravis. The project researchers are testing a novel autoantibody receptor T-cell therapy designed to re-program MG patient T-cells to selectively kill anti-MuSK B-cells that cause MuSK MG. The research is designed to test the working hypothesis in hopes of leading to a safe and lasting disease response and develop protocols for the detection and characterization of MuSK-CAART to validate novel biomarkers. Dr. Payne presented her ongoing work in this area during the 2022 AANEM MGFA Scientific Session and the MGFA's 15th International Conference in May 2025.

Project Funded: Novel mechanistic insights into the MuSK-specific autoantibody repertoire

Researcher: Gianvito Masi, MD, Yale School of Medicine

A subset of patients with MG has antibodies that target a protein known as muscle-specific tyrosine kinase (MuSK). In MuSK MG, muscle weakness is typically severe, with most patients having trouble breathing, swallowing, and talking. Despite recent advances in MuSK MG research, many aspects of the immune mechanisms underpinning the disease remain unknown, including the initiation of MuSK autoimmunity and how antibodies secreted by different B cells contribute to muscle pathology.

Dr. Masi and his colleagues are conducting a comprehensive investigation of the antibody response against MuSK to study (1) how newly generated B cells recognize MuSK, and (2) the functional impact of different MuSK antibodies on the neuromuscular synapse. Through focused examination of the MuSK-specific autoantibody repertoire, the investigators anticipate that findings from this research will enhance our understanding of MuSK MG and facilitate the development of targeted treatments for this disease.

Dr. Masi presented insights into his findings at the MGFA's 15th International Conference in May 2025.

Project Funded: AAV-mediated gene therapy for congenital myasthenia caused by recessive synaptotagmin 2 mutations

Researcher: Ricardo Maselli, MD, University of California, Davis

The recessive variant of congenital myasthenia linked to the synaptotagmin 2 gene is a newly recognized disorder usually affecting children of consanguineous families. The disease manifests itself at birth with profound weakness, muscle atrophy, and respiratory failure, often requiring mechanical ventilation and gastric tube feeding. Currently available medications are not effective.

This condition results from mutations in the synaptotagmin 2 gene (SYT2), which encodes a protein that is fundamental for the calcium-regulated release of the neurotransmitter acetylcholine at the neuromuscular junction. The genetic transmission of this disorder is recessive, so parents are non-affected carriers, while the disease only expresses in 25% of their offspring. The aim of this project is to develop and obtain FDA approval for a gene therapy based on the delivery of the normal SYT2 gene through an adeno-associated virus vector. After the AAV vector is delivered to the central nervous system, the spinal motor neurons are transduced with the normal SYT2 gene and start translating a normal synaptotagmin 2 protein, which, in turn, is transported through the nerve axoplasmic flow to the neuromuscular junction. This results in the re-establishment of normal neuromuscular transmission and potential cure of the disease.

Race and Inequalities + Myasthenia Gravis

Project Funded: Influence of race/ethnicity on clinical features of MG and inequalities in clinical care

Researcher: Richard Nowak, MD, MS, Yale School of Medicine

Various studies have reported differences in MG disease characteristics and outcomes based on race/ethnic groups, yet no studies have confirmed these results on a large nationwide dataset. Dr. Nowak's research group's recent analysis of the physician-reported registry (EXPLORE-MG, based at the Yale MG Clinic) showed significant differences in clinical features between races, such as age of symptom onset, thymectomy usage, and hospitalization rates. The team is using the MG Patient Registry to further validate their findings. This study is comparing disease characteristics between White, African American, Asian, and Hispanic patients while simultaneously identifying racial groups more likely to experience hospitalization for MG. Ultimately, the results of this study will provide clinicians and the community with a better understanding of racial differences in MG, allow them to mitigate these differences in terms of clinical care, and identify areas of improvement in MG patient care.

Project Funded: The role of race and income in management of myasthenia gravis

Researcher: Yaacov Anziska, MD, State University of New York Downstate Medical Center

This study is investigating whether certain patients with myasthenia gravis, either non-White or with lower incomes, have worse disease outcomes compared to their fellow patients.

Exercise + Myasthenia Gravis

Project Funded: Physical activity and factors associated with exercise participation among patients with myasthenia

Researcher: Amanda Guidon, MD and Zoe Sheitman, PT, DPT, Massachusetts General Hospital

Few studies have been performed regarding physical activity and factors associated with exercise participation among individuals with myasthenia gravis (MG). This is a critical gap for clinical and research programs. Clinicians and MG patients require improved guidance regarding exercise participation. Additionally, physical activity and exercise may be a critical outcome measure and/or confounder needing to be measured in future clinical trials. This project aims to address these knowledge gaps through analysis of data from adult patients in the US with MG enrolled in the MG Patient Registry. The primary outcomes the researchers are examining are participation in any physical activity and achievement of recommended thresholds for exercise. This study will examine the association of patient and disease demographics on these outcomes. We aim to use this information in future studies, specifically those involving the use of structured physical therapy and digital outcomes/wearables to promote physical activity and improved quality of life in patients with MG.

MGFA 15th International Conference on Myasthenia and Related Disorders, May 13 – 15, 2025

Biomarkers + Myasthenia Gravis

Project Funded: Measuring AChR autoantibody effector functions in myasthenia gravis patients

Researcher: Fatemeh Khani, PhD, Yale School of Medicine

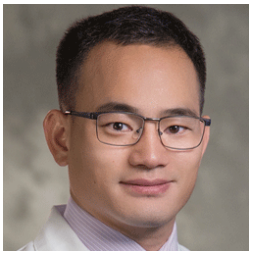
The project investigation is focused on providing the framework for the development of MG biomarkers that can directly help patients by predicting treatment efficacy and disease progression. Dr. Khani seeks to understand immune mechanisms underlying MG that are anticipated to more precisely define this heterogeneous disease. These collective studies will provide a set of well-characterized biomarkers which will serve as tools for the community to more accurately model AChR in vitro. In addition, the work will provide a framework for understanding the association between autoantibody binding properties and effector functions in MG and identify candidate biomarkers that may proactively predict response to therapeutic complement treatment and avoid severe side effects from unnecessary interventions.

What is a **biomarker**? A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

In addition to gaining a deeper understanding of MG immunopathology, the work will generate forward-looking deliverables that are relevant to MG patient care in terms of prognosis and personalized/tailored therapies. This project's proposed outcome may provide a deeper understanding of the mechanisms underlying the production of autoantibodies – a highly important determination for both the patient and clinician.

Project Funded: Deciphering Immunological Biomarkers in Myasthenia Gravis by Using Multiomics

Researcher: Yingkai "Kevin" Li, PhD, Duke University



Development of new treatments for diseases often relies on the identification of biomarkers, which are measurable indicators and must have the potential to predict responsiveness to therapy. Biomarkers can also assist clinicians in tailoring a treatment strategy that is most effective based on the patients' biomarker profile. Consequently, biomarkers can help in limiting over-medication or unnecessary medication, maximizing disease control while minimizing side effects.

Unfortunately, the lack of effective biomarkers in MG has greatly affected the pace of development for novel therapeutics. Considering these facts, the need for a reliable biomarker in the treatment of MG is critical and urgent. The current project aims to (1) identify and characterize the changes of immune cell networks and pro-inflammatory cytokine networks in MG patients by using Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq) and Olink proteomic platform, respectively, and (2) then to validate the identified biomarkers in predicting the responses in MG patients with mycophenolate mofetil treatments.

Project Funded: Validating diagnostic and prognostic serum biomarkers for AChR antibody seropositive MG

Researcher: Anna Punga, MD, PhD, Uppsala University, Sweden

A major concern in the MG field today is that we do not have disease-specific biomarkers, which results in the absence of personalized treatments for specific MG subgroups or reliable tests to predict how the disease will progress or see if treatments are working. This research project aims to address these challenges by confirming biomarkers in the blood that could predict MG development and treatment effectiveness. Specifically, we will study small RNA molecules and inflammatory proteins in the blood of MG patients with and without antibodies against the acetylcholine receptor (AChR). Previous and preliminary data from our research suggest that certain biomarkers can distinguish MG patients from healthy individuals and identify different MG subgroups, enabling personalized treatment approaches.

The project will validate these biomarkers in MG patients with acetylcholine receptor antibodies and explore their role in patients without detectable antibodies. Additionally, control groups (healthy and with other neuroimmunological conditions) will be included to establish the accuracy of these biomarkers. This research could lead to the discovery of blood-based biomarkers for MG, potentially improving personalized treatment for MG patients in the future.

Dr. Punga presented her work on biomarkers to date at the MGFA's 15th International Conference in May 2025.

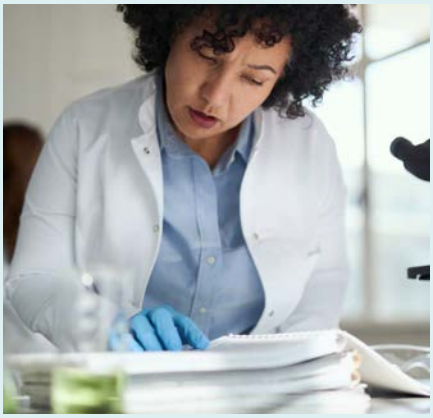
Project Funded: Purification of the acetylcholine receptor toward atomic-scale mechanisms underlying MG

Researcher: Ryan Hibbs, PhD, University of California, San Diego

Most patients with myasthenia gravis have autoimmune antibodies that attack the connections between their brain and their muscles. The most common target of these antibodies is the protein that sits on the surface of muscles and binds the neurotransmitter acetylcholine. This protein is known as the acetylcholine receptor. When acetylcholine binds the receptor, it opens a hole in the cell membrane that allows ions to permeate the cell. This movement of ions is the event that triggers muscle contraction. Antibodies binding to the receptor interferes with this process, causing progressive muscle weakness. Our ability to treat patients with myasthenia gravis is limited by our knowledge of the receptors and how antibodies attack it. The research team's goal was to discover, for the first time, the 3-dimensional architecture of the receptor, and how antibodies from patients bind to it. The first major step in this research goal was to purify enough of the muscle acetylcholine receptor, which was the focus of the ambitious pilot proposal funded by the MGFA. Dr. Hibbs, alongside colleagues in his lab, has made major progress in their quest to successfully model the AChR receptor. Relevant work has been published in Nature (July 2024) and Cell (May 2025). Having this new information can show, at the level of atomic detail, how antibodies from patients with myasthenia gravis interfere with nerve-muscle signaling. The ultimate goal is to use these discoveries to generate more specific therapies to help patients with myasthenia gravis.

MGFA 15th International Conference on Myasthenia and Related Disorders, May 13 – 15, 2025

III. PUBLICATIONS FROM MGFA-FUNDED RESEARCH



What is the importance of publications in research?

Publications in the field of research demonstrate validity, disseminate knowledge, and encourage intellectual exchange. In an academic setting, institutions may use the publications as a way to identify progress in research, secure additional funding to continue research, and as a tool for researcher career growth. By publishing research, the science is peer-reviewed and therefore scrutinized to ensure the highest standards are being met. **Publications are the best way to demonstrate impact and movement in the research field.**

Recent Publications

Autoimmune mechanisms elucidated through muscle acetylcholine receptor structures

Publication in *Cell* by Huanhuan Li, Minh C. Pham, Jinfeng Teng, Kevin C. O'Connor, Colleen M. Noviello, Ryan E. Hibbs (May 1, 2025)

Progress in understanding the molecular basis of MG has been limited by the absence of structures of intact human muscle AChRs. In this publication, study authors shared high-resolution cryoelectron microscopy structures of the human adult AChR in different functional states.

Using six MG patient-derived monoclonal antibodies, they mapped distinct epitopes involved in diverse pathogenic mechanisms, including receptor blockade, internalization, and complement activation. Electrophysiological and binding assays revealed how these autoantibodies directly inhibit AChR channel activation.

These findings provide critical insights into MG immunopathogenesis, uncovering unrecognized antibody epitope diversity and modes of receptor inhibition, and provide a framework for developing personalized therapies targeting antibody-mediated autoimmune disorders.

Composition and function of AChR chimeric autoantibody receptor T cells for antigen-specific B cell depletion in myasthenia gravis

Publication in *Science Advances* by Sangwook Oh, Fatemeh Khani-Habibabadi, Kevin C. O'Connor, and Aimee S. Payne (February 28, 2025)

This publication, whose co-authors include three MGFA grant recipients, reports on the design of a chimeric autoantibody receptor (CAAR) that could function as part of a future treatment for AChR-MG. This study demonstrates the importance of a specific transmembrane domain (the CD28 TMD) for CAAR stability and in vivo function, laying the groundwork for future development of precision cellular immunotherapy for AChR-MG.

IV. 15TH INTERNATIONAL CONFERENCE ON MYASTHENIA AND RELATED DISORDERS

Convening Top Minds from Around the World

This May, the MGFA brought together leading and emerging scientific investigators for the 15th MGFA International Conference on Myasthenia and Related Disorders.

Hosted by the MGFA since 1954, this influential gathering is a prominent opportunity for neuromuscular researchers and medical professionals to present their work and hear from accomplished peers.

Nearly 700 attendees convened in The Netherlands. The conference was held outside of the United States for the first time in recognition of the important research taking place around the world.

The event was curated as a three-day journey to the future of MG. Each day featured a renowned plenary keynote speaker followed by a variety of sessions, talks, panels, roundtable discussions, and interactive debates.

Topics included congenital myasthenic syndromes, novel treatments, debates addressing hot topics in the field, non-pharmaceutical interventions, new models to study MG, and the etiology of MG.

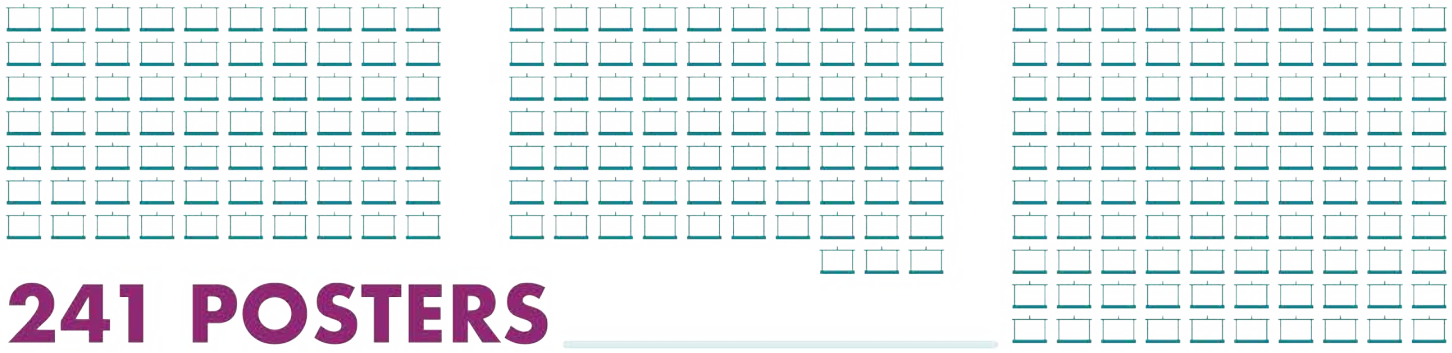
Research presented at the International Conference is published after the event to facilitate knowledge sharing. Sessions are also available in their entirety on the MGFA YouTube channel.

> **“The conference had just the right combination of clinicians, researchers, and patients. It was especially good to see people with lived experience for whom researchers and clinicians are working so hard to improve their quality of life.”**
>
> **—2025 International Conference Attendee**

660 ATTENDEES

39 COUNTRIES

73 PRESENTATIONS



241 POSTERS

Explore research from the 15th International Conference

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