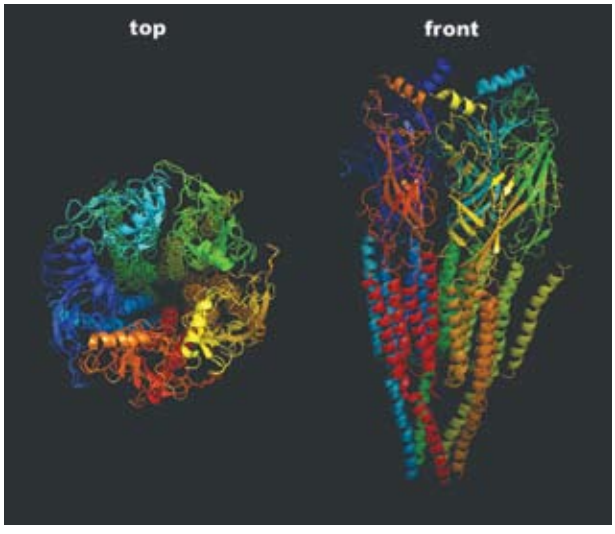
HOPE FOR MG SUFFERERS?

Monarsen: An Orphan Drug In Need of a Sponsor

by Marjorie Mazel Hecht

Officially, Monarsen is an "orphan drug," looking for an investor to fund phase II clinical trials. But for the thousands of sufferers of myasthenia gravis, Monarsen, which performed extremely well in its first clinical trials, is a lifeline to better functioning and a better future.

Myasthenia gravis (MG) is a debilitating auto-immune disease affecting neuromuscular transmission, and causing specific and progressive muscle weakness and exhaustion. MG afflicts 70,000 or more Americans (the conservative estimate of the Myasthenia Gravis Foundation of America), and 400,000 people worldwide, another conservative estimate. The disease is undercounted because MG is difficult to diagnose: The symptoms wax and wane, and vary in each case, often mimicking those of other ailments.



Top and front view of a 3-D model of the muscle-type nicotinic acetylcholine receptor. In myasthenia gravis, the body's immune system attacks the acetylcholine receptor that transmits the signal to the muscle.

The disease tends to strike women in their 20s and 30s, and men after 50, in all ethnic groups. The eye and facial muscles are commonly affected (drooping eyelids and difficulty swallowing), often arms and legs, and in the most serious cases, the pulmonary muscles.

MG is usually not fatal, just disabling. Many patients can achieve remission and lessened symptoms, but can also relapse. Although the initial cause of the disease is not known, the mechanism responsible for the weakness in the voluntary muscles (the muscles that we can control) has been identified as a disconnect between the nerve and the muscle: The receptor for the chemical acetylcholine, which is necessary for transmission of the neutral signal, is attacked at the neuromuscular junction by antibodies produced by the body's own immune system.

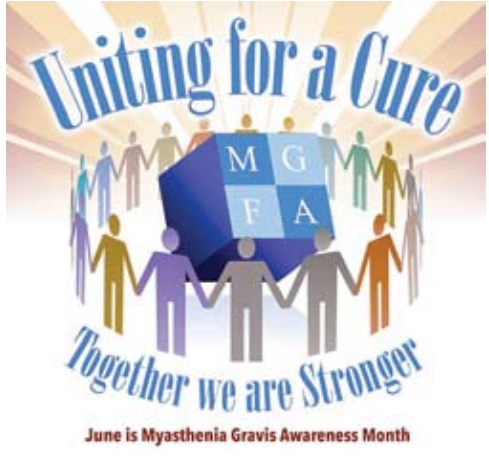
These antibodies disrupt the neurotransmission, and the muscle fails to contract. Current approved pharmaceutical treatments for symptoms include the drug Mestinon (pyridostigmine), which inhibits the cholinesterase enzyme that normally breaks down excess acetylcholine, thus increasing the amount and duration of acetylcholine available; and immune suppressant drugs like Prednisone, Cyclosporine, and Azathioprine. All of these drugs have long-term side-effects, however. And some MG patients become resistant to pyridostigmine.

Living with MG

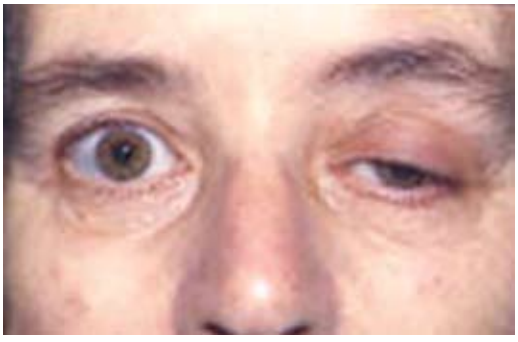
Myasthenia gravis is found around the world, and in all ethnic groups, but tends to occur more among younger women and older men.

This article was occasioned by the plight of one young woman, the mother of three children under six, and her difficulties coping with the symptoms of her recently diagnosed MG. How does she explain to her youngsters that she can't do the things she used to—pick them up, play with them, take care of them? How does she keep from being depressed about the fact that her symptoms may worsen, and that there is as yet no cure for MG?

Because she has had difficulty with allergic reactions to certain drugs, for her—and for many others—Monarsen holds out much hope. As one British MG patient commented on the promise of Monarsen, "If I had 20 million dollars, I would give them to Prof. Soreq straight away [for the clinical trial]. A good medicine for myasthenia gravis is definitely overdue."



Poster of the Myasthenia Gravis Foundation of America.



MG often affects the eye and facial muscles. The drooping eyelid of this MG patient is typical.

In life-threatening cases, such as an MG patient who is unable to breathe, blood cleaning (plasmapheresis) is a short-term treatment, as is treatment with intravenous immunoglobulins. Most radical (and controversial) is the surgical removal of the thymus gland, which is believed to be involved with MG.

An 'Antisense' Approach

Monarsen (previously known as EN 101), operates entirely differently from these conventional treatments. It is an "antisense" drug, which works by inactivating acetylcholinesterase, the protein that breaks down acetylcholine, *before* the protein is synthesized. This allows more of the acetylcholine to react with the receptors on the surface of the muscle cells.

It is called "antisense," because it makes use of the opposite sequence, or "sense," of the RNA messenger gene associated with acetylcholinesterase. (See interview.)

Monarsen is based on the innovative research work of Prof. Hermona Soreq at Hebrew University, who pioneered antisense technology and acetylcholinesterase biology. After animal studies showed that Monarsen successfully alleviated MG symptoms in rats that were engineered to have MG symptoms, human trials were initiated in 2002, to assess its safety and efficacy.

The results of a small clinical trial carried out in Israel and the U.K., showed a range of 27.8 to 53.4 percent symptom improvement—far better results than those of the current first-line MG treatment with Mestinon. Mestinon (pyridostigmine) targets the finished protein, thus stimulating the body to produce more acetylcholinesterase, which "triggers a battle between the drug and the nervous system," as the Monarsen developer describes it. In contrast, Monarsen inhibits the synthesis of acetylcholinesterase and "doesn't cause this vicious cycle."

In addition, Monarsen can be taken orally only once a day, instead of several times daily for pyridostigmine; it has a far lower dose; and it has no significant side effects. These advantages could make a difference in returning MG sufferers to their former lifestyle and employment.

This was the "first demonstration of the safe and effective use of an orally administered antisense therapy for a neurological disease," according to the now defunct Ester Neuroscience, Ltd., the Israeli pharmaceutical firm that conducted the trial.

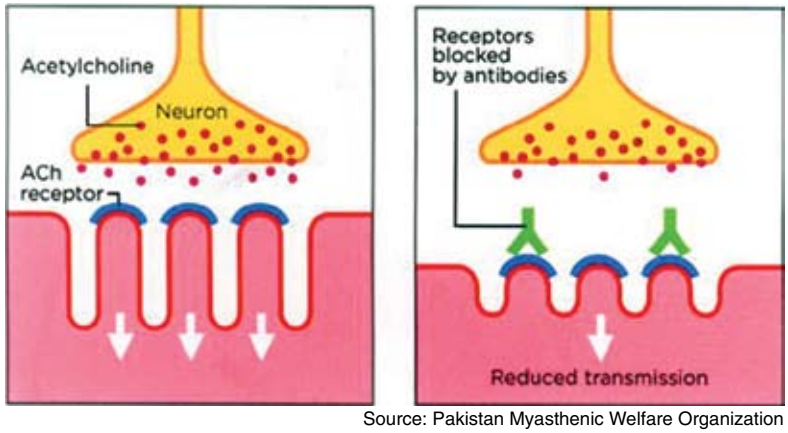
An 'Orphan' Orphaned Again

Ester Neurosciences secured "orphan drug" status for Monarsen from the Food and Drug Administration the next year, 2003. This designation is given to potentially beneficial treatments for severe illnesses that affect 200,000 or fewer people, and conveys to the developer tax incentives, a reduction from certain fees for marketing approval, and marketing exclusivity in the United States for seven years after approval. Ester also received "orphan" status for Monarsen in Europe.

But as the next clinical trial was being organized, in 2007, Ester Neurosciences was sold to the small U.K. pharmaceutical firm Amarin, which had initially agreed to develop Monarsen. Sadly, the company changed its strategy, and dropped Monarsen, leaving the orphan drug without a sponsor. However, as of 2011, the development rights are back in the hands of Hebrew University's technology transfer company, Yissum, which is again actively looking for an investor.

And so, Monarsen's fate depends on the whims of a "market" that invests its money where it can make the most profit, without regard to the human consequences of not developing this improved palliative treatment.

What about non-profit backing? The MG Foundation of America has ruled out support for clinical trials. When asked about Monarsen, foundation chief executive Tor Holtan, told me that the Monarsen alternative was not "100 percent proven yet" in terms of efficacy—a curious response, given the less than optimal state of the currently used treatments for MG. Mr. Holtan also said that the foundation



Source: Pakistan Myasthenic Welfare Organization

DIAGRAM OF NEUROMUSCULAR JUNCTION

In a normal neuromuscular junction, acetylcholine transmits a signal from the nerve to the muscle to contract. In a myasthenia gravis patient, the immune system produces antibodies that attach to the receptors for acetylcholine on the muscle cells and reduce signal transmission; muscles then fail to contract, causing weakness and fatigue.

The current treatment of choice, the drug pyridostigmine, inhibits the enzyme acetylcholinesterase which normally breaks down excess acetylcholine. In contrast, Monarsen works by interfering with the synthesis of acetylcholinesterase, thus allowing more acetylcholine to function.

did not support drug development, only basic research, and that the foundation had very little funding available in general, because MG is a "small disease."

The National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health, which oversees research on MG, along with hundreds of other neurological disorders, last year invested $11 million into MG research, and now has two active clinical trials. NINDS program director, Dr. John Porter, told me:

"It is NIH policy to not offer public opinions on the potential for specific therapies that are under development, so I cannot comment on any strengths/weaknesses of the existing data or on the rationale for Monarsen as a putative therapeutic for myasthenia gravis."

"Many putative therapies do fail in development," Dr. Porter said, "so it is important that they be tested rigorously. NINDS has several mechanisms to support preclinical and clinical therapy development efforts in rare diseases, such as myasthenia gravis.... Like any candidate therapeutic, the later stage development costs of Monarsen may exceed NIH resources (NINDS alone is responsible for 400-600 neurological disorders) and the developers would also have to attract partners (venture capital, Pharma) to the effort."

At this time, NIH is funding two clinical trials for MG: one to determine whether thymectomy benefits MG patients who are receiving Prednisone, and another to test a drug that increases skeletal muscle activation.

A fanciful 1624 drawing depicting John Smith taking King Opechancanough (1554?-1646) prisoner. Opechancanough was a tribal chief of the Powhatan Confederacy in what is now Virginia. A description of his ailment included the drooping eyelid characteristic of MG.

From Captain John Smith's General History*, 1624.*

The Larger Picture

The short history of this orphan drug, points to the sad state of the U.S. health system. A promising drug languishes for want of a sponsor's capital, while thousands of MG victims (not to mention those yet to be diagnosed) continue to suffer with treatments that are less than optimal and at the same time far more costly in human and monetary terms than the few million dollars it will take to conduct the next phase of trials for Monarsen. In addition, indications are that Monarsen might also have benefits for other diseases, including Alzheimer's and ALS.

In the larger picture, MG is still a disease without a cure, and without a known cause. The mechanics of the symptomatic muscle weakness are now increasingly well characterized; science researchers continue to probe these mechanics in finer and finer detail, as medical research and imaging techniques advance.

In fact, MG is "the best understood autoimmune disorder, serving as a model for understanding not only autoimmunity, but also synaptic function," according to Henry J. Kaminski, M.D., a prominent MG expert. Such a "model" serves to highlight what's missing: For a disease whose symptoms were noted in the 1600s (including the famous case of the American Indian Chief Opechancanough, who died in 1644), shouldn't we have come further in learning what initiates MG, and being able to prevent it?

INTERVIEW: DR. HERMONA SOREQ

The Development of Monarsen for MG

Chryssa Panoussiadou

Hermona Soreq, Ph.D., is a Professor of Molecular Neurobiology at Hebrew University's Edmond and Lily Safra Center for Brain Sciences. She has published more than 250 peer-reviewed articles and seven books, especially in the field of brain-to-body communication. The past president of the Israeli Society of Biochemistry and Molecular Biology (2000-2002) and the first elected woman dean of the Hebrew University's Faculty of Science (2005-2008), Soreq collaborates with top scientists worldwide, is a member of the European Community's advisory committee on health-related issues, and a consultant to the Israeli Ministers of Health, Commerce, and Science.

She has also received many honorary Ph.D. degrees and prizes for her work. With 12 patents, two recombinant proteins, and one DNA-based drug at different stages of clinical trials, Soreq is also an Adjunct Research Professor at the Arizona State University BioDesign Institute.

She was interviewed in February 2011 by Marjorie Mazel Hecht.

Question: How did the idea for Monarsen come about?

Soreq: Most of my research efforts during my academic career were aimed at the cholinergic system, and I was pain-