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

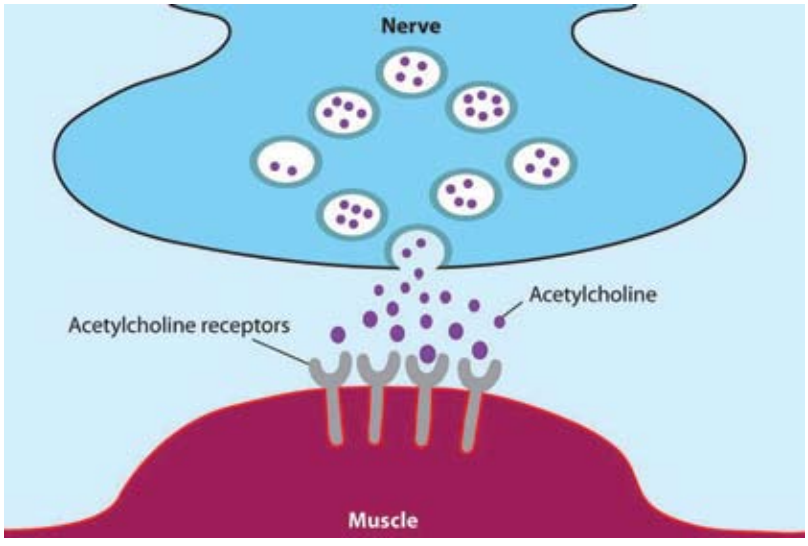
Hermona Soreq, Ph.D., is a Professor of Molecular Neurobiology at Hebrew University's Edmond and Lily Safra Center for Brain Sciences. She has published more than 250 peer-reviewed articles and seven books, especially in the field of brain-to-body communication. The past president of the Israeli Society 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-



NORMAL ACETYLCHOLINE RECEPTORS ON MUSCLE
In myasthenia gravis, the body's immune system disrupts the acetylcholine receptors (proteins) on the muscle, which normally receive the signals from nerves telling the muscles to contract. This causes muscle weakness and fatigue.
Source: Muscular Dystrophy Organization

fully aware of the shortcomings of the small molecule inhibitors of acetylcholinesterase (AChE) that are available for therapeutic indications in general, and for the treatment of myasthenia gravis in particular: First, there are many variant AChE proteins with different biological properties and functions, but the small molecule agents block all of them non-selectively.

Second, exposure to these agents induces rapid overproduction of AChE, which should be avoided. Third, the small molecule agents are needed in relatively large doses and display short duration of activity. Since I have cloned the human AChE gene, I thought that targetting the mRNA transcript could overcome these limitations—be variant-selective, act in low dose and for a longer duration, and limit the side effects. All of this came true.

Question: Monarsen makes use of a fairly new concept—antisense technology. Can you say something about how antisense works?

Soreq: Antisense sequences are inversely oriented compared to their mRNA targets; they can bind their target tightly by forming hybridization bonds, like the two DNA strands; and they can both block the translation of their targets into protein and induce the degradation of these targets. We protect our antisense agent by introducing methyl groups, which stabilize the molecule and prolong the duration of its effect.

Question: How is Monarsen different from the current therapies for MG?

Soreq: You may think of gene expression as a pyramid: one copy of the gene (DNA), several hundred mRNA molecules per cell, and many thousands of protein product molecules. The current therapies, like most of the medications we know, are targetted to block the active site of the protein product. This is economically unwise because you need many more drug molecules to reach an effective dose; but we did not know enough about mRNA until lately, so that this traditional approach was the best that was available.

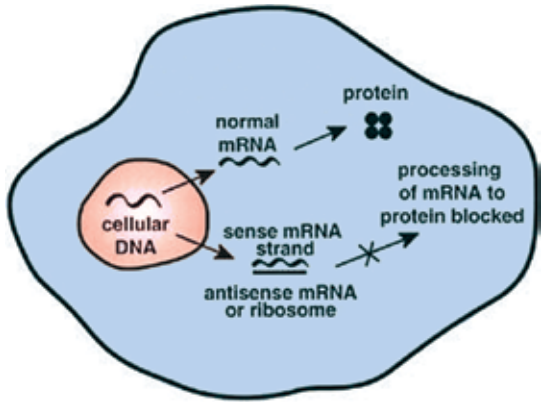
Furthermore, many different proteins share some structural features of their active site, which causes side effects due to the interaction of protein blockers with other targets. But today, with the Human Genome project being completed, we know the mRNA sequences for all of the human genes so we can design antisense chains. Their interaction is far more specific, avoiding side effects; they need to block far fewer molecules, which can reduce the effective dose by several orders of magnitude, limit the side effects even further, and achieve better specificity.

Last, but not least, they can block only the targetted mRNA transcript, avoiding undesirable effects.

Question: How did Monarsen perform in the clinical trials?

Soreq: Very well indeed: It improved the myasthenia symptoms of progressive muscle fatigue at least as effectively as the currently employed small molecule drug, but at 1,000-fold lower dose and

ANTISENSE SEQUENCE BLOCKS THE PRODUCTION ACETYLCHOLINESTERASE
Monarsen inactivates acetylcholinesterase, the protein that breaks down acetylcholine, before the protein is synthesized. The diagram illustrates in general how antisense mRNA works.
Source: Global Library of Women's Medicine, DOI 10.3843/GLOWM.10274, 2008



Hebrew University

Prof. Soreq (left) speaking at a recent conference.

for far longer period (24 hours, unlike the multiple daily doses needed with the current drug). There were practically no significant side effects, and the patients seemed very happy. (One of them wrote me that he never felt that well ever since he was diagnosed, 29 years before. . . .)

Question: Since Monarsen appears to be more effective in helping MG patients, and does not have side-effects, what is holding up further trials and commercialization? What are the chances for speeding up this process?

Soreq: I am a university professor, not a pharmaceutical company. Patent applications on this invention were submitted to the authorities by the technology transfer company of the Hebrew University, Yissum, which holds the rights to this invention. The rights to develop this project were then licensed to a U.S.-Israel venture capital fund, Medica, which established a start-up company, Ester Neuroscience, to develop this invention.

Ester Neuroscience completed toxicity tests and phase I and phase IIa clinical trials, obtained an Orphan Drug approval for the use of Monarsen, and was then sold to Amarin, a U.K./Irish start-up pharmaceutical company which planned to proceed with phase III trials, but then went through managerial changes and refocussed its efforts on cardiovascular drugs.

Consequently, Yissum requested—and received—the rights to develop this project, which happened very recently. At present, Yissum seeks strategic partners to complete the development of this new drug.

Question: Is this the first drug you have worked on using this concept? Has Ester been involved in producing similar drugs for other diseases?

Soreq: This was not the first antisense agent I used for research, but the first one which reached clinical trials from my laboratory, and the only one to be developed by Ester. Because it is targetted against AChE, which is involved in several other diseases, there may be other diseases where patients can benefit from its use.

There are many more oligonucleotide agents undergoing clinical trials at present, for different diseases; and a joint international academia-industry society, Oligonucleotides Therapeutics Society (OTS) was established to develop this direction, of which I am one of the founding members. The current president is Prof Gunther Hartmann of Bonn University, Germany.

Question: Have you looked into what causes MG? Could there be bacteria involved?

Soreq: Myasthenia gravis is an autoimmune disease, where antibodies are erroneously formed against the muscle receptor for acetylcholine, which is the neurotransmitter activating our muscles. It is yet unclear whether the initiation of this disease is triggered by bacterial or viral infection, but this is a possibility.