

In Search of the Holy Grail for Treating Myasthenia Gravis

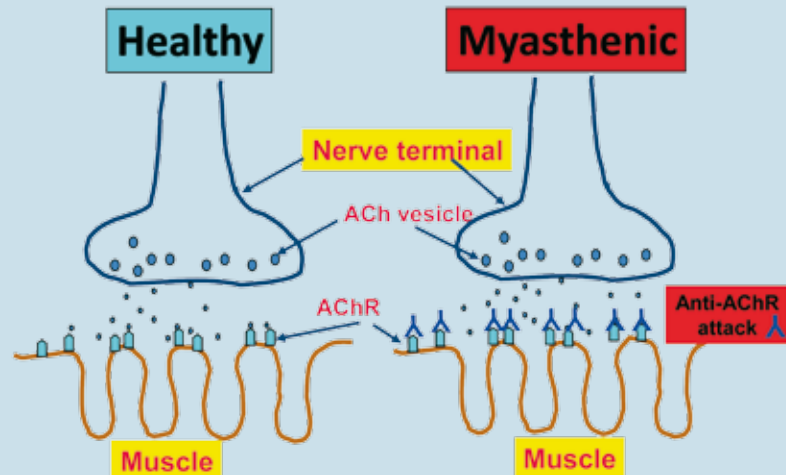
Prof. Miry Constantini-Souroujon, former Head of the Research Authority and Professor in the Department of Natural Sciences at the Open University, is searching for the "holy grail." Not as King Arthur and Lancelot who were looking for a spiritual elevation of mankind, but rather in the sense of a decades-old quest for answers to issues that could markedly elevate mankind, medically.

Prof. Souroujon has dedicated some three decades of her life to the study of myasthenia gravis (MG), an autoimmune neuromuscular disease. The hallmark of myasthenia gravis is muscle weakness that increases during periods of activity and improves after periods of rest. Certain muscles, such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing, are often, but not always, involved in the disorder. The muscles that control breathing and neck and limb movements may also be affected.

While a largely chronic, rather than fatal illness, MG can in fact result in death, as in the case of the Greek shipping tycoon, Aristotle Onassis.

MG is a rare disease affecting only one out of 10,000 individuals. In Israel there are 'only' 600-700 known cases. So why study it, if it is neither fatal nor extremely prevalent?

Impaired neuromuscular transmission in myasthenia gravis due to an autoimmune attack on a muscle component (AChR; acetylcholine receptor)



All Out War vs. Tactical Approach

"MG is considered to be a model disease. There are good experimental models existing in animals, an important tool in the pre-clinical stages, and more important results emerging from MG as a model disease could serve or be applied to other autoimmune and neurological diseases," explains Prof. Miry Souroujon.

Now, with a European Commission grant of six million Euros to an international consortium of 12 teams of which Prof. Souroujon, Dr. Sonia Berrie-Aknin, the coordinator of the consortium, from the Technion and the French Institute of Health (INSERM) and Prof. Socrates Tzartos from the Hellenic Pasteur Institute in Greece, the consortium will be spending the next four years looking to resolve one of the key issues regarding the treatment of MG specifically, and autoimmune diseases in general. Prof. Souroujon's specialty, one of three that lie at the heart of the international research project, is in novel therapies.

To fully understand the extraordinary direction that Prof. Souroujon's research efforts are taking, one must examine current treatments for autoimmune diseases in general. Then, it will also be possible to understand why researchers and the medical community are so interested in locating and grabbing that "holy grail."

An autoimmune disease means that the body has lost the ability to discriminate between self and non-self – i.e. exactly what belongs to the body vs. a foreign entity. So, what happens is the body begins to identify its blood, muscles, plasma or nerves, for example, as foreign elements or transplanted enemies. The body's antibodies, which are generally released to fight foreign invaders, turn against the body itself.

In each type of autoimmune disease – Multiple Sclerosis (MS), Diabetes II, Lupus – a different organ is attacked. The traditional treatment for autoimmune diseases has largely been

Research

based on an all-out war effort on the autoimmune system, where often the patient pays a high price.

In recent years, researchers have been focusing on searching for a targeted treatment, an antigen-specific therapy or one that shuts off the undesirable autoimmune attack without affecting the entire immune system. This is where Prof. Souroujon and her colleague, Prof. Sara Fuchs from the Weizmann Institute, are beginning to prove their mettle.

Myasthenia Gravis – An Interrupted Transmission

Myasthenia gravis is, in effect, a communication disorder occurring at the junction where nerve cells connect with the muscles they control. Normally, the nerve endings release a neurotransmitter substance called acetylcholine. Acetylcholine travels to the neuromuscular junction, binds to receptors which, in turn, are activated and generate a muscle contraction. In myasthenia gravis, the body's antibodies attack the receptors of acetylcholine at the neuromuscular junction which prevents the muscle contraction from occurring.

Visualize this: with MG, one tells the body to bend the right arm, which the body may do, but one may not be able to then straighten the same arm because the receptors are no longer functioning at full capacity, or have been destroyed altogether.

A number of years ago, Prof. Souroujon and Prof. Sara Fuchs received a patent for a novel therapy that proved effective in rats. "We thought" Prof. Souroujon relates, "that if we administered a derivative of the acetylcholine receptor, this derivative would act as a kind

of decoy and draw the autoimmune disease away from the neuromuscular junction." As such, Prof. Souroujon and her team prepared a recombinant fragment, which they fed to MG infected rats and saw that they could significantly suppress MG.

However, what Prof. Souroujon and her team also saw was that "in severely-affected animals it was difficult to reverse the disease symptoms and achieve suppression. This then led us onto another track. We understand that autoimmune responses depend on a kind of seesaw balance between effector and regulatory T cells (Treg cells).

Our most recent work is based on the use of Treg cells. In autoimmune diseases, you want to up the response of the Treg cells, because these are the cells that suppress the autoimmune system."

In MG patients, there are fewer Treg cells, and many of them are impaired. The team's first experiment was to extract Treg cells from healthy animals and administer them to MG-induced animals. The results: MG was suppressed.

In order to apply this approach in humans one would have to avoid the transplantation of Treg cells from healthy individuals into MG patients. Ideally, the patient's own Treg cells should be used.

Now, the quest is to extract the Treg cells from a body with MG (they will be working with "humanized" mice), manipulate the cells ex vivo (i.e. in the lab) and re-administer them to the sick MG body. They are also examining how best to generate large numbers of healthy cells to re-inject them into the original body – so that, in effect,

the body will be reproducing its own healthy Treg cells.

A Life-Long Love Affair

This work is exacting, time consuming and mostly, for Prof. Souroujon, a continuation of a life-long quest of trying to find a cure for MG, creating novel therapies for other autoimmune diseases, and working at the Open University.

While doing her Ph.D. at the Weizmann Institute, Prof. Souroujon was a tutor for biochemistry and life sciences courses at the Open University. "It was then" she claims "that I fell in love with the Open University. I loved the interaction with students who are actually eager to study, and I loved the idea of a second opportunity. I identified with the calling of the University, so when I started to think what I would like to do in my life, I decided I wanted to combine the two: research and serving as a faculty member with the understanding that half of my time, I'm dedicating to research."

One day during Prof. Souroujon's post-doctorate studies at Tuft's University in Boston she invited her children to come and visit her in the lab. They observed the mice and rats in their cages, and asked their mother what she was doing with so many rodents. She explained that she was looking for cures. One of her children responded, "If you cure all the mice in the world will you be happy?"

Perhaps Prof. Miry Souroujon's response would be that she would be happy if she could find a targeted treatment for MG sufferers and novel therapies for other autoimmune diseases. This would make the Open University and millions of sufferers around the world happy.