

Local Scientist Dr. Douglas Feinstein Discusses Current Research on Possible New Therapy to Help Restore Function in People with Multiple Sclerosis



Dr. Douglas Feinstein

Last October, funds from the Illinois State Lottery helped launch eight innovative local MS research projects which range from investigating the reduction of disease development and stimulation of myelin repair to original rehabilitation and physical exercise techniques. To get a better understanding of the research happening statewide, Greater Illinois Chapter marketing staff interviewed the lead researcher overseeing each pilot project.

Dr. Douglas Feinstein is one of the National MS Society's grant recipients for 2013. Dr. Feinstein received his BS from MIT, his Ph.D. in cell biology from the Johns Hopkins University, and then did post-doctoral training at the Scripps Clinic in San Diego, the University of Uppsala in Sweden, and the University of Lausanne in Switzerland. He was a faculty member at the Cornell University Medical College in New York for several years before moving to Chicago. Currently, Dr. Feinstein is at the University of Illinois at Chicago and holds a position at the

Jesse Brown VA Medical Center. He is investigating a possible new therapy to slow nerve damage and enhance nerve growth and myelin repair in individuals with multiple sclerosis.

Q: *First, tell me a little about yourself. How did you come to be interested in MS research?*

A: Currently I'm a professor in the Department of Anesthesiology here at University of Illinois at Chicago. I do some anesthesiology-related research, as it concerns effects of anesthetics on the nervous system and trying to find methods to prevent any damage that might be caused. However, my primary research interests are MS and Alzheimer's disease. One of the reasons I first became interested in MS research was my desire to get training in the area of neuro-immunology, and after receiving my Ph.D., I applied for and received a postdoctoral fellowship from the National MS Society in 1990 to study with Dr. Robert Milner at the Scripps Clinic, and I've been with the NMSS ever since. As the years have progressed I've become very much involved in all aspects of MS research – basic research, clinical research, serving for the National MS Society on study sections, and other related work.

Q: *Do you have a personal connection to MS?*

A: Personally, within my family there is no one who has been diagnosed with MS, so that was not a key factor to get into this research. However, since doing research I've been interacting more and more with patients, occasionally giving low-key informal seminars to explain what we do. Several years ago we started doing clinical research in which I got to meet with patients one-on-one and talk to them and find out about their experiences. It's been very rewarding.

Q: *What is MS and what aspect of the disease does your research focus on?*

A: My work is mainly with the animal models of MS. I'm not a clinician and I'm not a physician, so I never diagnose patients or prescribe any treatments. But basically, in a healthy individual there are cells in the central nervous system called oligodendrocytes which produce large amounts of lipids and fats that are incorporated into a substance called myelin. The myelin forms concentric circles that wrap around the axonal projections of neurons. A main purpose of the myelin is referred to as 'saltatory conduction,' which basically provides insulation of the electrical signals and allows the nerve impulses to travel quickly and safely.

MS is considered by most people to be an auto-immune disease. For some reason the body develops a type of immune response, very often, but not always, directed to the oligodendrocytes in the CNS. Antibodies bind to proteins that are present on the oligodendrocytes, which eventually cause damage and causes weaknesses to occur in the myelin wrapping which results in less rapid neuronal transmission. Not only does transmission become slower, but ultimately the loss of myelin can lead to actual damage to the neuronal processes. This may be due to the fact that areas of the processes are now being exposed to substances that are present in the surrounding tissue that they usually don't encounter, for example high amounts of glutamate or other neurotransmitters, or could be due to some proteins becoming exposed on the neuron's axon, which other antibodies normally don't see but can now react with these exposed regions and cause further damage.

Q: *Why aren't nerves in the peripheral nervous system attacked?*

A: In the case of MS, antibodies are mostly directed against proteins that are present on the oligodendrocytes, and some other cells, that are only present in the central nervous system. For example, there may be an antibody response directed against proteolipid protein, a protein that is only expressed on oligodendrocytes, and although schwann cells -- cells responsible for making myelin in the peripheral nervous system -- express a related protein called P0, it is different enough that those antibodies do not cross-react.

Q: *You were recently awarded funding from the Illinois State Lottery to pursue a new research project. Can you describe what you and your research team are investigating?*

A: First, we're very happy that we got this award and want to thank the Illinois State Lottery for making these types of funds available for basic and clinical research. One of the goals of our project is to look for interventions that would provide support or increase survival of the neurons and the axons in individuals with MS. The title of our project is called "The effects of LKE in demyelinating disease." LKE stands for Lanthionine Ketimine Ester, a semi-synthetic drug, which was developed by a colleague of mine, Ken Hensley, a neurochemist at the University of Toledo, Ohio. He synthesized and treated cells with LKE and he found that it was very effective in reducing neuronal damage and inflammation in ALS, a mouse model of amyotrophic lateral sclerosis, and also found that LKE promotes axonal growth. Part of the process of axon growth is to add a protein called tubulin to the extending process. He found that LKE interacts with a protein called CRMP2 that facilitates the movement of tubulin to the growing end of a nerve's axon. By binding to the CRMP2 protein, LKE appears to stimulate the axon growth process.

Since there is axonal damage in MS and in animal models of MS, and since this drug seems to promote axonal growth, it made sense to test this in at least one mouse model of MS. And that is what this project is primarily about. Because the CRMP2 protein has never been studied in the context of MS, the first aim of this project is to characterize what's happening to this protein in normal mice and in mice that have been immunized to develop a kind of MS disease. The second part of this project is to study the effects of LKE in the mice with the MS like disease, to look at the expression and levels of the enzymes that are responsible for making this chemical, and in particular to test if the LKE reduces the axonal damage that is known to occur.

Q: *What have you accomplished so far in the time since receiving the grant?*

A: The grant started in October 2012 and since that time we've collected a lot of samples to start characterizing the CRMP2 protein pathways and the LKE enzymes. This has already shown us that some of these proteins are reduced during the course of the mouse disease, suggesting to us that a deficit in these pathways might be contributing to the axonal damage. We have also begun to test the effect of LKE in the mice that show the MS symptoms, a disease called EAE, or experimental auto-immune encephalomyelitis. In the first study we will treat the EAE mice with LKE, both before they get sick as a preventative treatment, and more importantly once the mice are sick with this as a therapeutic treatment. We hope to see that the controls, e.g. the group not given LKE, would continue to get sick while the group treated with LKE would either stabilize or actually show recovery.

Q: *If this were to work in the mice models, is your hope to start conducting human trials?*

A: Yes, definitely. Although LKE itself has not yet been tested in humans, some related compounds have been that appear to be safe. Once LKE is shown to be safe in healthy humans it will be easier to start testing it in patients with MS. The first step would be to do a safety study, where we might do a study of 20 MS patients and 20 controls with one dose of this drug and monitor it for up to six months to make sure there are no adverse effects. We would then move on to look at actual clinical symptoms and measure how well the drug is actually working.

Q: *Many people with MS want to know – why is there still no cure? What is your answer to that?*

A: There are several answers. One is, more funding needs to be put into basic and clinical research for MS. This can be done by using sources like the Illinois State Lottery and other means. For example, in New Jersey and likely other states, some of the money that is collected from parking and driving violations goes toward funding spinal cord injury research. The National MS Society has many donors who are truly gracious and generous, but the need for more funding is true for most diseases. Secondly, MS is a very complex disease. There are different stages, there are various changes occurring in your brain and your spinal cord, in your immune system, diet is becoming more and more important regarding risk for development and progression of MS, and vitamin D has recently been shown to be a risk factor as well. All of these aspects are being studied, and all have to be considered when developing therapeutic treatments and interventions, all of which take more time than we would like.

Q: There are so many stories about promising studies being done in mice models. Why does it take so long to shift from animal studies to human studies to the final product of an FDA-approved drug?

A: Many drugs get tested in rodents, and many times in other animals. Sometimes if the drug has already been shown to be safe in humans, and shows strong effects in the animal studies, you can move it into healthy human patients fairly quickly. In the case of MS, out of the hundreds of drugs that have shown some benefit in rodent models, only a handful have shown similar efficacy in patients. And all together it's a very long process. Even after you get approval to test your drug in humans, you need to go through various phases, starting from a phase I trial which can be very small numbers, a phase II trial which can be several hundred people, and a phase III trial which can be several hundred to several thousand patients before attempting to get FDA approval. The cost of this process is usually beyond that of most individual researchers; and even more than societies like the National MS Society can manage. The NIH funds clinical trials up to and sometimes beyond phase III, but to bring a drug all the way through testing to production and treatment is often beyond what NIH can fund. It then becomes necessary to establish collaborations with a biopharmaceutical company, who understands the time and cost involved, and who is willing to take those risks.

Q: Are there other ways for a drug to become FDA-approved?

A: There's been a resurgence of interest in what's called repurposing of drugs. There are hundreds, or more likely thousands of drugs which have been brought very far through the approval process for let's say, cancer, or Alzheimer's disease, and for some reason these drugs either did not get final approval or the company decided to drop them for some other reason. Both NIH and several private societies now want to go back in and say "let's re-evaluate this drug, but in the context of MS." I think this might open up a number of good, possible therapies.

Q: What other MS research projects are you pursuing?

A: I have this grant from the Illinois State Lottery to pursue the LKE project and I also currently have another grant from the National MS Society that focuses on the roles of a neurotransmitter called noradrenaline in MS and EAE. Noradrenaline is important to have at the right levels in your brain and spinal cord, not just for what it does to behavior, but also because this neurotransmitter has very potent anti-inflammatory and neuro-protective effects. We found, and published these results last year in the journal *Brain*, that levels of noradrenaline and the neurons that make noradrenaline are reduced in both the EAE mouse model and in MS patients. So we're now looking at ways to either protect those neurons or to treat patients with drugs that should raise noradrenaline levels. A second project we are working on is one that by serendipity, we came across a family where five of five children, who are now adults, all have been diagnosed with MS. We are hoping to carry out some DNA sequence analysis to try to identify a novel risk factor that might be causing MS in this family.