

## Understanding... Treating ... Curing...

**M**ultiple sclerosis is an autoimmune disease in which the immune system targets the myelin sheaths that surround nerve fibers.

Myelin sheaths work like the insulation surrounding an electrical wire, allowing the nerve fibers to transmit information throughout the body. When the immune system attacks the myelin sheath it damages small areas of tissue. These damaged areas, called "lesions", are gaps over which signals cannot be transmitted, resulting in a wide range of neurological symptoms including loss of sensation and mobility, loss of vision, interference with mental processes, and, in extreme cases, death. At the Multiple Sclerosis National Research Institute, ongoing research includes studies to understand the causes of MS, the development of treatments for MS, and the design of novel strategies for the development of vaccines against MS.

### Understanding MS

Why does the immune system attack and destroy the myelin sheath? Under a grant

Dr. Eli Sercarz discovered that EAE, an MS-like disease in mice, can be induced by a specific group of immune cells, or T cells, that "drive" the disease. Dr. Sercarz is now investigating these "driver" immune cells in detail, hoping to find the reason that these specific cells induce inflammation and have such a detrimental effect on the brain and spinal cord. Dr. Vipin Kumar is exploring the mechanisms that the immune system uses to turn off the immune attack, by using mice that have the capability of spontaneously recovering from EAE (the mouse model for MS).

### Treating MS

The most common form of MS, called Relapsing-Remitting MS ("RR-MS"), affects approximately 85% of patients. There are currently five FDA-approved treatments for RR-MS, one of which is Copaxone®. Copaxone® is at least as efficacious as the other treatments, with a low side effects profile. Drs. Richard Houghten and Clemencia Pinilla began this project by accessing the Institute's "combinatorial libraries" – millions to trillions of



Dr. Richard Houghten

Dr. Vipin Kumar

Dr. Clemencia Pinilla

Dr. Eli Sercarz

Dr. Darcy Wilson

compounds organized in a mixture format. Next, they used the Institute's patented methods for screening these libraries. Using the resulting information, they designed a "custom library". Within this custom library they discovered new potential drug candidates which are as effective as Copaxone® in preliminary studies using the mouse model for MS. In collaboration with Dr. Roland Martin at the National Institutes of Health, Pinilla and Houghten are guiding these new drug candidates as they move toward further testing in early stage clinical trials using human donors.

### Curing MS

Vaccines may hold the promise of a cure for MS. The Institute's scientists are working to test a variety of strategies for designing a vaccine against MS.

Dr. Eli Sercarz' work, described earlier, is focused on understanding MS by studying the "driver" T cells which he discovered to be responsible for inducing inflammation in EAE. Using a strategy that is similar to that used to develop vaccines against viruses, Dr. Sercarz's group is testing the possibility that immunizing mice that are susceptible to EAE with the "driver" clones might stimulate immune cells that will prevent the action of the "driver" cells, and thereby arrive at a new vaccine strategy for MS.

Dr. Vipin Kumar has a similar dual goal. He hopes to advance the understanding of MS by discovering how a natural immune response to EAE allows mice to spontaneously recover from EAE. By investigating the specifics of this mechanism, and uncovering a way to stimulate the production of the body's own regulatory cells, he hopes to find answers which are instrumental in designing more effective vaccines against MS.

Another of the Institute's approaches to finding vaccines begins with the use of the Institute's "combinatorial libraries" –

similar to those used to identify the "Copaxone®-mimic" described earlier. Using the Institute's patented libraries and screening methods, Dr. Darcy Wilson is looking through the libraries for peptide compounds which show a wide range of biological activity against a T cell clone known to cause EAE. The important finding thus far is that some of these library-defined peptides activate the T cell clone to cause disease, while others are very effective at blocking this disease-causing activity. By identifying active compounds that prevent the development of disease, or that modify ongoing disease, Wilson hopes to use these compounds for the development of vaccines to down-regulate the underlying autoimmune process in MS.

### Investing in the Future

Drs. Richard Houghten and Adel Nefzi direct projects focusing on the development of novel small molecule and macrocyclic combinatorial libraries. These new chemical diversities are being generated with the goal of enabling their screening in a wide variety of assays, including those used in T cell based systems for the discovery of treatments for MS, as well as those used for discovering potential new treatments, such as the "Copaxone®-mimic" described earlier. That particular compound, now in clinical trials, was discovered using variations on the combinatorial libraries designed 15 years ago. Likewise, both the old and newly developed combinatorial libraries are being used in MS vaccine design research, and in new projects that are designed to understand the cause of MS. The development of new combinatorial libraries today is an investment in tomorrow's MS research. Whether tested at our Institute or by a collaborator on the other side of the globe, combinatorial libraries are being utilized in a variety of methods directed towards understanding the cause of, finding a treatment for, or designing a vaccine against MS. ❖



**Multiple Sclerosis  
National Research Institute**  
3550 General Atomics Court  
San Diego, California 92121 USA  
(866) 676-7400  
www.ms-research.org



## Multiple Sclerosis National Research Institute

### **About Us**

The Multiple Sclerosis National Research Institute is a division of Torrey Pines Institute for Molecular Studies, a 501(c)(3) not-for-profit basic research center dedicated to conducting basic research to advance the understanding of human disease and the improvement of human health. Scientists at Torrey Pines Institute conduct research in fields associated with a wide variety of major medical conditions, including multiple sclerosis, cancer, heart disease, Types I and II diabetes, AIDS and other infectious diseases, Alzheimer's disease, pain, inflammation, transplantation rejection and rheumatoid arthritis.

At the MS Institute, scientists work on a variety of approaches to understand MS, including its causes, how its various forms

progress, treatments of its symptoms, and the design of vaccines and other approaches that could someday lead to the prevention or cure of MS. Our research is supported in part by grants from the National Institutes of Health ("NIH") and by public donations.

Donations are used in many ways to support our important MS programs. For example, some grants do not fully support the entire cost of a given research project, requiring that we find another funding source willing to "match" a portion of such grants. Public donations are used to purchase equipment needed by these laboratories. Donations provide our scientists with increased opportunities to participate in international scientific

conferences. Finally, we can now fund research that is not supported by other grant mechanisms, including novel approaches that have not received external funding due to a lack of early experimental data. Using donations as "seed money", we are able to support both new scientists starting in the field as well as established scientists who wish to try a new approach to an old question.

We believe that by combining resources and scientific knowledge with others throughout the world, we can all work more effectively towards the common goal of understanding multiple sclerosis. ❖