

INDIVIDUALLY TAILORED MULTIPLE SCLEROSIS VACCINES: PROTEOMICS MEETS AUTOIMMUNITY

In multiple sclerosis (MS), an unknown trigger causes the immune system to attack the myelin sheath that insulates nerve fibers in the central nervous system. Antibodies against the various components of myelin are produced, contributing to an out-of-control autoimmune response that leaves damaged neurons in its wake, along with brain lesions and inflammation.

The resulting disease is notoriously unpredictable in its course, sometimes causing progressive loss of motor control, sometimes abating suddenly for no evident reason, but then sometimes recurring. The best-studied mouse model of MS, called EAE (experimental autoimmune encephalopathy), doesn't fully replicate the human disease, but it does show a similarly idiosyncratic progression.

Despite this confusing clinical picture, Bill Robinson and his colleagues at Stanford University Medical School reported in the September *Nature Biotechnology* that the severity of EAE is predictable for individual animals. By using custom-designed protein arrays to analyze the autoimmune antibodies from specific mice, Robinson's group found that they could identify telltale serological patterns associated with the animals' ultimate disease severity. More intriguing still, their same proteomic approach may also be used in designing individualized vaccines for MS—vaccines that won't just prevent but will actually reverse the autoimmune disease after it is established.

The key, coauthor Claude Genain (UC San Francisco) observes, is looking beyond the presence of single autoantibody species by using the arrays to evaluate the larger pattern of autoimmune responses. By studying these patterns, one can "tailor the vaccines for individuals, depending on their serologic profiles," Genain claims.

Same Genes, Different Disease

A remarkable finding of the current study is that the antibody profiles can vary, even between the genetically identical mice treated identically. "There's a genetic and environmental component that determines which T cells emerge, but it is very poorly understood," Robinson points out. "There could [also] be stochastic or random elements in how they select their [B and T] lymphocyte repertoires that predispose [animals or humans to disease]." But whatever the basis of the variability, the antibody profiles that

Robinson's group defined correlate with the animal's risk of progressing to severe EAE.

The researchers developed a protein chip carrying a variety of known antigenic regions from such myelin sheath proteins as the myelin basic protein (MBP) and the myelin oligodendrocyte glycoprotein (MOG). Using this chip, they tested mouse sera for their ability to bind the various epitopes. In various model systems, EAE is provoked by injecting one or another of these myelin proteins into an animal. As Robinson's group found, the way that the autoimmune response "spreads" to epitopes other than the one used as an immunogen—particularly spreading to certain epitopes of MOG—provides the best predictor of disease severity.

Inducing Tolerance with DNA Vaccines

Beyond identifying the epitopes in myelin that the auto-antibodies target, the researchers used the serological data to construct DNA vaccines carrying four key epitopes in an attempt to induce immune tolerance and reverse the disease in mice. The animals did improve, and to come full circle, the researchers used their array to monitor disease progress and found that the most improved animals showed the greatest reduction in autoreactive B-cell epitope spreading.

The DNA vaccine approach is well suited to the experimental system, Robinson says, because it allows researchers to provide tolerizing epitopes to the animal in any combination and thereby, perhaps, fine-tune the autoimmune response. Whether the same approach will work in humans is less clear. DNA vaccines have been used in a number of clinical studies, most notably against cancer, and, as Rob-

inson acknowledges, "they have basically failed in human trials.... In rodents and monkeys you get a very robust response, and in humans you don't."

Questions about the applicability of the mouse research to human MS also arise because of the lingering doubts about the EAE model. "Mice have less demyelination and more inflammation," explains Genain. Robinson, too, recognizes that the EAE model is imperfect. "Ultimately, it is going to be human trials that determine whether such a therapeutic approach will have efficacy in humans.... There are clearly [therapies] that have worked in EAE that made human MS worse," he adds.

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An Ounce of Cure Worth a Pound of Prevention

Still, Robinson remains optimistic that tolerization against customized sets of autoimmune epitopes can work for MS patients. He notes that currently available drugs such as Betaseron[®] and Copaxone[®], which have proved helpful in humans, were originally validated in mouse EAE models. Moreover, he says, their group's current findings indicate that vaccination is not just a means to block the autoimmune response early on—it can also work in the more clinically relevant setting of existing disease, altering the course of EAE, rather than preventing the disease. “We’re starting treatment a week after they have been paralyzed and [we show] that we can affect the disease process. When you [apply that standard], there is a much higher level of con-

cordance [between efficacy in EAE and in human MS] than when you just look at prevention,” Robinson argues.

More generally, the researchers are enthusiastic about the applicability of arrays for predicting which patients will have aggressive disease and thus be good candidates for early treatment. Because many individuals who initially present with MS-like symptoms never progress to the more serious phases of the disease, doctors often hesitate to administer the existing drugs, which are inconvenient and expensive and have potentially serious side effects. “A serologic marker of disease... [one or more antibodies that predict] a more severe course, may enable us to determine which patient to put on those therapies early,” says Genain.

—Mignon Fogarty