Researchers vet vaccines for MS in the lab and early trials

Our image of vaccines is a powerful one—after all, vaccines eradicated polio. Conventional vaccines are usually killed or altered infectious agents that boost the ability of the body's immune system to fight the infection. "Vaccines" under research for MS, however, focus on disarming or neutralizing the misdirected immune attack on the brain and spinal cord. It's a tricky business, considering that the trigger for this attack is still not known, but researchers funded by the National MS Society and others are bringing this strategy into early clinical studies.

Developing DNA vaccines

Lawrence Steinman, MD (Stanford University, CA), former winner of the Society and American Academy of Neurology's John Dystel Prize for outstanding contributions to MS research, has played a key role in bringing one vaccination strategy to clinical trials in people with MS. His team designed customized DNA vaccines containing the genetic material that instructs several myelin proteins, in order to induce maximal immune system tolerance. Myelin is the substance that insulates nerve fibers, and is a target of the immune attack in MS. The vaccines succeeded in reducing relapse rates in mice. **Nature Biotechnology** 2003;21:1033–1039

Dr. Steinman co-founded Bayhill Therapeutics, Inc., a company that then licensed the compounds from the Stanford team. Bayhill funded a phase II study of BHT-3009 vs. inactive placebo in 289 people with relapsing-remitting MS. The study did not show statistically significant differences in the primary endpoint for the rate of new, active lesions, but showed a significant effect on a number of secondary endpoints including a reduction in the rate of active MRI lesions between those on therapy and those on placebo from weeks 8 to 48 of the study. Immunological data in a preselected subgroup of patients showed that immune tolerance was achieved, with a reduction in antibodies to components of myelin. **Annals of Neurology** 2008;63:611–20 Plans for a phase III trial are underway.

Taking on T cells

Several groups worldwide are developing vaccines using pieces of myelin proteins, or peptides—which are targets for immune T cells—to induce immunity to the MS attack by these cells.

One of these teams is a true success story for the National MS Society's research programs. David Wraith, PhD, began his career in MS research with a postdoctoral fellowship from the Society. He then developed a novel vaccination strategy and founded **Apitope International NV** to develop this strategy further. Apitope has developed synthetic peptides that might be able to train immune cells to ignore target tissues and thus suppress an attack. The lead product is ATX-MS-1467, an equal parts mixture of four peptides, which increases the activity of regulatory T cells.

Apitope recently announced that the drug was safe and well tolerated with promising early evidence of potential efficacy in a pilot clinical trial in 6 people with secondary-progressive MS. Now, Apitope has received $1 million in funding for a clinical trial from Fast Forward, LLC, a nonprofit organization established by the Society to accelerate the development of MS treatments. In partnership with Merck-Serono, Apitope is conducting a larger study to determine safety and effectiveness in 40 people with relapsing forms of MS (relapsing-remitting, and secondary-progressive with relapses).

Opexa Therapeutics sponsored a one-year, multi-center

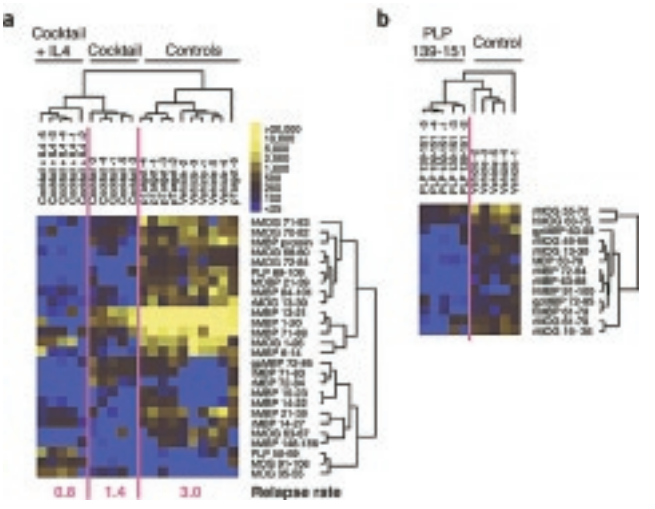
trial of Tovaxin, a T cell vaccine, in 2008. The placebo-controlled study involved 140 patients with relapsing-remitting MS and 10 patients who had experienced a neurological episode that put them at possible risk for MS. Those on treatment received five monthly subcutaneous injections of their own deactivated immune T cells and were followed for one year. The treatment was found to be safe, but did not achieve statistical significance in the primary endpoint, which was the reduction of disease activity on MRI in those on active therapy versus those on placebo. **World Congress of MS 2008**, Abstract #56

Additional data reported this year, however, show significant clinical benefit, and the vaccine succeeded in increasing the levels of regulatory T cells, which may help to suppress the immune response. **American Academy of Neurology 2010**, Abstract #P04.211 In a June 7 letter to shareholders, Opexa says it plans to meet with the FDA to discuss future studies.

According to a research progress report from the University of Hamburg, Germany, Roland Martin, MD, and colleagues recently began a study called "ETIMS", or Establish Tolerance in MS. The team selected seven peptides of myelin proteins to which T cells have shown high reactivity in MS. They coupled these peptides to antigen-presenting cells (APCs). Although T cells are main players in the attack that destroys myelin, they get clues about what to attack from APCs. The team is currently testing safety in a phase I study in 6 patients, and will soon begin a phase IIa trial in 12 people with early relapsing-remitting MS to determine whether treatment reduces brain inflammation on MRI. The work is based on preclinical work by Stephen D. Miller, PhD (Northwestern University), a longtime grantee of the Society.

With funding from the Society and others, Arthur Vandenbark, PhD, Halina Offner, Dr. Med., and colleagues at Oregon Health & Science University developed molecules called recombinant TCR ligands (RTLs), which are designed to inhibit the ability of specific T cells to initiate damage to myelin. Artielle ImmunoTherapeutics, Inc., is developing one of these molecules, RTL1000, as a potential treatment for MS. In a small safety study in 34 people with relapsing-remitting or secondary-progressive MS, doses of 2 mg to 60 mg were safe and well tolerated, with higher doses producing moderate side effects (hypotension and diarrhea). The clinical efficacy of RTL1000 will be evaluated in larger Phase II studies. **American Academy of Neurology**, Abstract #S21.003

Vaccinations for MS are making real progress through the MS pipeline. Although more studies are underway to bring this therapeutic strategy to the clinic, the progress to date indicates some new avenues for stopping MS in its tracks.



This microarray from Dr. Steinman's early work in MS-like disease in mice shows the variety of myelin proteins responding to BHT-3009.