

AUGUST 05, 2002

## Immune System Abnormality Foils Lyme Disease Vaccine

A subtle abnormality in the immune system may prevent certain people from responding favorably to a vaccine for Lyme disease, report researchers from the Howard Hughes Medical Institute at Yale University School of Medicine.

The discovery of the immune system abnormality, which otherwise exerts no ill effect on people who have it, underscores the importance of the multiple protective pathways that the immune system uses in fending off microorganisms. The studies also suggest several routes for improving the Lyme disease vaccine.

The researchers, led by Erol Fikrig and Howard Hughes Medical Institute investigators [Richard A. Flavell](#) and [Ruslan Medzhitov](#), all of whom are at the Yale University School of Medicine, published their findings in the August 2002, issue of *Nature Medicine*. Other co-authors are from SmithKline Beecham Biologicals in Belgium and the University of North Carolina at Charlotte.

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- **Richard A. Flavell**

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The Lyme disease vaccine, which was approved by the Food and Drug Administration in 1998, generated a protective immune response in 95 percent of people who used the vaccine. However, the vaccine's manufacturer GlaxoSmithKline, PLC, withdrew the vaccine LYMERix from the market in February 2002, citing poor sales.

During phase III clinical trials of LYMERix at Yale University School of Medicine, researchers noted that seven of 492 people generated no immune

response to the vaccine. Flavell and his colleagues found it intriguing that such a small group would show no response, so they set about the task of trying to find out why.

While numerically there were very few of these people, they were significant because it tells us that in the human population there is a low frequency of a variant gene that prevented their response to this vaccine protein, and therefore presumably to some infectious agents, said Flavell.

The Lyme disease vaccine relies on a cell surface protein from the causative bacterium, *Borrelia burgdorferi*, to generate an immune response in humans. That protein, called outer-surface protein A (OspA), is among the most abundant immune-reactive antigens found on the surface of the Lyme bacteria.

According to Medzhitov, the scientists suspected that low immune response to the vaccine might be due to a defect in one of a family of receptors on the surface of immune cells called macrophages. When these receptors, called Toll-like receptors (TLRs), detect distinctive molecules on the surface of bacteria, they help activate the immune system to fend off the bacteria.

Because the immune systems of non-responders (to the vaccine) behaved as if they couldn't recognize OspA, our hypothesis was that they had a defect in the innate immune system, and therefore, most likely in Toll-like receptors, said Medzhitov. The receptor TLR2 was known to be instrumental in recognizing microbial lipoproteins (a class of bacterial products which includes OspA), and TLR2 was known to functionally cooperate and to form heterodimers with TLR1, although the ligand for the TLR2/TLR1 pair was unknown, he said. Based on this information, the scientists decided to search for defects in TLR receptors in the seven people who did not respond to the vaccine.

In studying macrophages isolated from this group of people, Medzhitov and his colleagues observed that the macrophages generated a low immune response to OspA. So, that suggested immediately that something was wrong with the recognition system in these people, which most likely involved these Toll-like receptors, said Medzhitov.

Additional studies of the macrophages revealed that the components of their immune-system machinery that depended on TLR2 were normal. And in analyzing the TLR genes in the macrophages, the researchers found no abnormalities in the *TLR2* gene or its protein. However, while they found no defects in the TLR1 gene itself, they did find lower-than-normal expression of the TLR1 protein on the surface of the macrophages.

In a parallel set of experiments, Flavell and his colleagues developed mutant mice that lacked the TLR1 gene. Mice lacking the *TLR2* gene were obtained from another group of researchers. In studying both types of mutant mice, the

scientists found that, like the humans in the Yale clinical trial, the animals also lacked responsiveness to the OspA protein, although their other immune responses appeared normal.

In additional tests, the researchers found that *TLR2*-deficient mice generated lower antibody levels against OspA alone when compared to wild-type mice. However, when the scientists added an adjuvant that boosted immune response, the TLR2-deficient mice responded similarly to wild-type mice.

According to Flavell, finding that faulty TLR1 expression is involved in generating a poor response to the Lyme vaccine suggests that altering components of the vaccine might enhance its efficacy. For example, he said, a different adjuvant might improve the immune response by involving an alternate immune system pathway that circumvents the TLR1-dependent pathway.

This problem is broader, however, in that there are other vaccines in which we have non-responders and in which the mechanisms are not well understood, said Flavell. And there may be equivalent situations with these vaccines, in which different formulations are necessary to overcome low response.

Medzhitov emphasized the significance of the single defect in the immune systems of low-responding people. It's very important to note that non-responders exhibited a very specific defect in TLR1, he said. If the defect had been more general, these people would not have survived to adulthood. However, they were only unresponsive to a narrow set of pathogens, and to this particular type of vaccination.

According to Medzhitov, pinpointing the specific defect in low-responders to the vaccine could greatly improve understanding of how TLR genes are expressed and how their receptors travel to the surface of macrophages.