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Live Recombinant Vaccine Protects Against Fungal Disease

ScienceDaily (Dec. 1, 2000) — For the first time, scientists have used recombinant DNA technology to create a live vaccine that protects against a fungal infection in mice. This new vaccine is safer than live vaccines made without recombinant technology and more effective than "killed" vaccines. Many fungal diseases are on the rise in the United States, and this recombinant live vaccine approach could be used to protect against them.

Mycologist Bruce Klein, M.D., and colleagues at the University of Wisconsin-Madison report their results in the December 1 issue of the Journal of Clinical Investigation. The effort was supported by a grant from the National Institute of Allergy and Infectious Diseases (NIAID).

"This work achieves what many would have thought highly unlikely, if not impossible," comments Dennis M. Dixon, Ph.D., chief of the bacteriology and mycology branch at NIAID. "It validates the concept of a vaccine approach for disease-causing fungi." Developing an anti-fungal vaccine is extremely difficult because fungi are complex organisms with large numbers of genes. The immune system must respond to a fungal infection with an equally complex set of defenses.

A live vaccine is the best way to achieve this response for blastomycosis thus far, experts say, but rendering a pathogenic fungus harmless so that it can be used as a live vaccine is no easy task. To do so, scientists must find and inactivate a "virulence" gene -- one that allows an organism to cause disease. To give an idea of the relative difficulty of this search, the fungus used in this study has a genome of 25 million base pairs of DNA; a bacterium such as Escherichia coli has only 4.6 million base pairs, and HIV has under 10,000.

Klein and his team worked with a fungus called Blastomyces dermatiditis, which causes a sometimes fatal lung infection, blastomycosis, even in people with healthy immune systems. The researchers identified a particular virulence gene, WI-1. When they knocked out the WI-1 gene with recombinant DNA technology, they found that the altered B. dermatiditis strain could no longer cause disease in laboratory mice. Furthermore, they discovered that exposure to the harmless engineered strain induced a T-cell response that fully immunized the mice against all strains tested of the lethal, naturally occurring fungus.

"The WI-1 gene codes for a surface protein molecule that allows the fungus to stick and stay in the lung," explains Dr. Klein. In addition, the WI-1 protein actively interferes with the immune response by disrupting the balance of defensive molecules called cytokines produced by the

immune system. The WI-1 protein is probably the major reason B. dermatiditis is so potent -- a mere 10 to 100 cells of the organism are enough to cause fatal infection in healthy mice.

A previous live vaccine, for the fungus Coccidioides immitis, used a variant form of the organism that did not cause disease. However, there is always a chance that such variants will spontaneously revert to the disease-causing form, Dr. Klein explains, a risk that is eliminated by using recombinant DNA technology to irreversibly knock out a virulence gene.

Blastomycosis is not common in humans. Various studies report anywhere from one to 40 cases per 100,000 people in areas where B. dermatiditis commonly lives: the South Eastern, South Central and upper Midwestern United Sates. Like many fungi, this one lives in the soil, especially around waterways, and can cause pneumonia when people inhale its spores into their lungs. Current treatments with anti-fungal drugs usually take six months to be effective.

However, other diseases-causing fungi similar to B. dermatiditis are much more common, and Dr. Dixon hopes the new recombinant live vaccine might encourage researchers to develop vaccines against other fungi. For example, Coccidioides immitis caused an epidemic of San Joaquin Valley Fever in the California area in 1992. And Histoplasma capsulatum, which can cause the lung infection histoplasmosis, is endemic to the Ohio and Mississippi River Valley, where it infects most of the population by age 20. The majority of these infections are benign, but in about 10 percent of individuals the infection can produce life-threatening symptoms such as inflammation of the membranes around the heart. Researchers are working to develop vaccines against these organisms as well.

In addition, so-called "opportunistic" fungal infections, caused by organisms such as Aspergillus and Candida, are on the rise. This increase is caused in part by the growing number of people with impaired immune systems due to AIDS, chemotherapy, bone marrow transplants or surgical procedures.

The B. dermatiditis vaccine may have a more immediate use as a veterinary vaccine, because blastomycosis affects a large number of dogs. Dr. Klein is studying how the vaccine works in dogs, and this work should help him further refine his vaccine method.

NIAID is a component of the National Institutes of Health (NIH). NIAID supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, tuberculosis, malaria, autoimmune disorders, asthma and allergies.

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Reference: M Wüthrich, et al. Mutation of the WI-1 gene yields an attenuated Blastomyces dermatiditis strain that induces host resistance. Journal of Clinical Investigation 106(11):1381-89 (2000).

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