COLD SPRING HARBOR MEETING

NEW ROUTES TO MORE EFFECTIVE VACCINES

COLD SPRING HARBOR, N.Y.—Participants at this year's Cold Spring Harbor Laboratory meeting, "Modern Approaches to New Vaccines, Including Prevention of AIDS," were exposed to a variety of novel strategies for enhancing the efficacy of vaccines produced through recombinant DNA technologies.

Hepatitis core antigen. Presenting subunit or peptide antigens in the context of a highly immunogenic particle, like the hepatitis B surface antigen, has been an attractive although unsuccessful strategy for increasing potency—unsuccessful until now. Berwyn Clarke (Wellcome Biotechnology, Ltd., Beckenham, Kent, U.K.) has added nucleotides encoding a peptide immunogen to the 5′ end of the gene for hepatitis B core (HBc) antigen. HBc, like the the surface protein, self-assembles into discrete particles. Particles formed by the fusion protein, Clarke said, are up to 1000-fold more immunogenic than the uncoupled peptide. When the HBc antigen is joined at its N-terminus with a foot-and-mouth disease virus (FMDV) peptide, as little as two micrograms of the purified hybrid particle (formulated in an oil emulsion) elicts levels of FMDV neutralizing antibodies in guinea pigs comparable to those obtained with an equivalent number of inactivated virus particles. This is two to three orders of magnitude higher than can be induced by the synthetic peptide alone.

T-cell determinants. In addition to an enhanced ability to stimulate a primary B-cell response, peptide vaccines will need to contain domains that interact with T-lymphocytes and Ia antigens—to provide cell-mediated immunity and allow natural boosting—before they can realize their full potential. Michael Francis (Wellcome Biotechnology) has taken a significant step towards designing such peptides. He and his colleagues were able to overcome a genetically controlled unresponsiveness to a synthetic peptide simply by adding defined T-cell sites from ovalbumin or sperm whale myoglobin to the FMDV peptide, 140-160 VP1. Such molecules induced high levels of antibodies in a mouse haplotype that does not give any response to the unmodified molecule.

Covalent modification. Richard Lerner (Scripps Clinic, La Jolla, CA) described another approach to making peptides better immunogens. He and his colleagues, in collaboration with Victor Nussenzweig's group at New York University Medical Center, introduced a covalent modification into the immunodominant tetrapeptide repeat (NANP) of the circumsporozoite antigen of the malaria parasite, *Plasmodium falciparum*. Their hope was to stabilize a conformation that might be more efficiently recognized by the immune system. Molecular modeling of the peptide suggested that hydrogen bonds formed by the asparagines across proline could be mimicked and fixed in space by ethylene bridges. When dodecapeptides containing such bonds were synthesized, they proved to be potent antigens, inducing high-titer antibodies that reacted with authentic circumsporozite protein more avidly than antibodies raised by the corresponding unshaped peptide.

Multiple-determinant supergenes. Although circumsporozoite antibodies may be protective, most researchers feel that ultimately an effective malaria vaccine will need to contain critical antigens from all stages of the parasite's life-cycle. Chris Langford (The Walter and Eliza Hall Insitute of Medical Research, Victoria, Australia) described the first steps towards such a vaccine. He and his co-workers have engineered a vaccinia virus vector to encode a hybrid protein consisting of five different repeating epitopes from four different malarial antigens (see diagram). Animals infected with this vaccinia virus synthesize moderate amounts of antibodies to all of the component epitopes.

A fowlpox vector. As attractive as vaccinia-based vectors continue to be they suffer from a number of potential problems related to the fact that the virus productively infects most animal hosts. To overcome these difficulties, Jill Taylor and her colleagues at the New York State Department of Health (Albany, NY) and Rhone Merieux (Lyons, France) have begun to adapt a fowlpox virus for use as a vaccine-vector. Like vaccinia, fowlpox virus has a large double-stranded DNA genome and replicates in the cytoplasm of infected cells. But unlike vaccinia, it is highly restricted as to the cell types in which it can multiply. In particular, it cannot grow in mammalian cells at all.

Nonetheless, mammalian cells infected with the virus do synthesize considerable amounts of messenger RNA, and it can therefore serve as a kind of transient expression vector. As a first instance, the researchers constructed a fowlpox virus containing a gene for a rabies glycoprotein and used it to infect rabbits, mice, cattle, cats, and dogs. All the animals developed significant levels of neutralizing antibodies, but in no case was any new virus produced. Further, given a sufficient inoculum, mice could be protected from a massive challenge with virulent rabies virus.

IL-2 as an adjuvant. While all these approaches have focused on recombinant products as vaccines, Jack Nunberg (Cetus Corp., Emeryville, CA) reported using a recombinant protein as an adjuvant. In experiments undertaken with Gary Anderson (University of Nebraska, Lincoln) and Charles York (BioTrends International, Winters, CA), the Cetus group used the immunomodulator interleukin-2 (IL-2) to greatly increase the potency of an inactivated rabies vaccine in a standard mouse-challenge assay. Under conditions where the challenge was lethal in 100 percent of the mice receiving vaccine alone, there were no deaths in the group that received vaccine plus IL-2.

—Harvey Bialy

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The construction of a vaccinia-vector "supergene" designed to deliver multiple immunogens. In this case the vector has been engineered to contain five distinct epitopes from four different malarial antigens.