U.S. FOOD & DRUG ADMINISTRATION

Determining the Safety and Efficacy of Vaccines to Protect Against Viruses that Infect the Central Nervous System

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General Overview

FDA regulators at CBER are now reviewing several live, attenuated (weakened versions of viruses) vaccines that are derived from neurotropic wild-type viruses (viruses that infect the central nervous system).

There are as yet no reliable markers (biological evidence) that can be used to determine whether such viruses have been successfully attenuated--other than the failure of the vaccine to produce obvious symptoms of disease in recipients. This problem is based on the lack of knowledge of 1) virus virulence factors (molecules that help viruses infect cells and cause disease); 2) characteristics of cells targeted by such viruses; and 3) how these viruses spread in the host. In addition, for many of these vaccines there are as yet no known markers of efficacy (measurable responses of the body that accurately signify that the vaccine is working effectively). This lack of markers of efficacy, such as a specific level of antibody, makes it difficult to interpret immune response data collected during clinical trials of these vaccines.

Our laboratory uses the mumps virus as a model to identify markers of successful virus attenuation as well as to identify markers in the blood that signify that the vaccine is providing significant protection. The present lack of sufficient knowledge in areas of mumps vaccine safety and efficacy is highlighted by the licensure of some mumps vaccines that have caused a complication called aseptic meningitis (inflammation of the membranes covering the brain and spinal cord) and the occurrence of mumps outbreaks in highly-vaccinated populations.

Problems with vaccine safety can be linked to an inadequate understanding of the infection process. Therefore, our research efforts are focused on identifying 1) cells that the virus naturally infects; and 2) mechanisms the virus uses to facilitate its spread in the infected host.

To help identify markers of vaccine efficacy, our laboratory is studying the ability of vaccine-induced antibodies to inactivate a broad range of variations of the virus obtained from different patients. Our goal is to determine the level of antibody that signifies that the immune response to the vaccine is providing protection against the virus.

We chose mumps virus as the model to study because, for the first time in over 40 years, new live attenuated mumps vaccines are being submitted to FDA for approval. Therefore, FDA regulators must understand what to test for in vaccines based on attenuated mumps virus to demonstrate that they are safe and effective. In response to these challenges, we are trying to learn more about mumps virus vaccine safety and efficacy and to apply this to other viral vaccines.

Scientific Overview

Identification of markers of virus neuroattenuation

Understanding viral pathogenesis is key to successful development of attenuated virus vaccines. In these studies we are trying to identify cell types infected following a natural route of inoculation (intranasal or intra-tracheal) in an animal model and follow the subsequent dissemination of the virus to other sites in the body, including the central nervous system. We inoculate animals via the respiratory route with recombinant mumps viruses expressing enhanced green fluorescent protein (eGFP). The viruses used for these studies include a highly attenuated mumps virus strain, a highly neurovirulent mump virus strain, and chimeric viruses consisting of mixtures of genes from these two viruses.

Disease-relevant host cells identified from the animal studies will then be used for in vitro testing to identify functional differences in the gene products (proteins) of both virulent and attenuated viruses. Our goal is to identify biomarkers of mumps virus neurovirulence, e.g., specific cellular targets of infection or functional properties of specific viral proteins, and to apply this knowledge to efforts at attenuating other neurotropic viruses, in order to facilitate the development and use of safer vaccines.

Examination of vaccine-induced protective efficacy

Over the past decade numerous mumps outbreaks have been reported in highly vaccinated populations in several countries. Widespread use of only one of the two recommended doses of vaccine was believed to be largely responsible. In 2006 the US experienced its largest mumps outbreak in 20 years. Multiple independently performed outbreak investigations found that between 70% and 99% of cases had received the recommended 2 doses of mumps-containing vaccine, indicating lower vaccine efficacy than previously estimated. While mumps was historically a disease of childhood, now mumps primarily occurs among young adults. The most likely explanations of this epidemiological change are (1) the ability of certain mumps virus strains to escape vaccine-induced immune responses, or (2) waning immunity.

To address the virus escape mutant theory, serum samples from recent vaccinees will be assessed for neutralizing antibody titer against a panel of phylogenetically distinct mumps virus strains, including an isolate from the 2006 US mumps outbreaks. The ability of serum to effectively neutralize all virus strains would argue against the virus escape mutant theory.

To address the waning theory, serum samples from individuals at 1 month to 15 years post vaccination will be assessed for neutralizing antibody titer against the vaccine virus itself as well as an isolate from the 2006 US mumps outbreaks. The anti-viral activity in serum will be assessed as a function of time post vaccination.

Finally, to identify a protective titer of mumps antibody, serum samples acquired via the CDC from a Red Cross blood drive at a university prior to a mumps outbreak will be assessed for pre-exposure mumps virus neutralizing antibody titer. The pre-exposure mumps virus neutralizing antibody titer in subjects who later developed or did not develop mumps during the outbreak will inform us of non-protective and protective levels of antibody.

Note from InformedChoiceWA:

Former Merck Scientists Sue Merck Alleging MMR Vaccine Efficacy Fraud

"Stephen A. Krahling and Joan A. Wlochowski, former Merck virologists blew the whistle by filing a *qui tam* action lawsuit in August 2010. The scientists allege that the efficacy tests for the measles, mumps, rubella vaccine (MMR) were faked. The document was unsealed in June, 2012."

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