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Scientists target future pandemic strains of H5N1 avian influenza

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Preparing vaccines and therapeutics that target a future mutant strain of H5N1 influenza virus sounds like science fiction, but it may be possible, according to a team of scientists at the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), and a collaborator at Emory University School of Medicine. Success hinges on anticipating and predicting the crucial mutations that would help the virus spread easily from person to person.

Led by Gary Nabel, M.D., Ph.D., director of the NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC), the team is reporting in the August 10, 2007 issue of the journal *Science* that they have developed a strategy to generate vaccines and therapeutic antibodies that could target predicted H5N1 mutants before these viruses evolve naturally. This advance was made possible by creating mutations in the region of the H5N1 hemagglutinin (HA) protein that directs the virus to bird or human cells and eliciting antibodies to it.

"What Dr. Nabel and his colleagues have discovered will help to prepare for a future threat," says NIH Director Elias A. Zerhouni, M.D. "While nobody knows if and when H5N1 will jump from birds to humans, they have come up with a way to anticipate how that jump might occur and ways to respond to it."

"Now we can begin, preemptively, to consider the design of potential new vaccines and therapeutic antibodies to treat people who may someday be infected with future emerging avian influenza virus

mutants," says NIAID Director Anthony S. Fauci, M.D. "This research could possibly help to contain a pandemic early on."

Making a vaccine against an existing strain of H5N1 or any other type of influenza virus is relatively routine. Typically, samples of existing influenza virus strains are isolated and then grown inside eggs or in cell cultures. The virus is then collected, inactivated, purified and added to the other components of the vaccine.

A flu shot prompts a person's immune system to detect pieces of the inactivated virus present in the vaccine and make neutralizing antibodies against them. Later, if that same person is naturally exposed to a flu virus, these same antibodies should help fight the infection.

Influenza viruses constantly mutate, however, and vaccines are most effective against the highly specific strains that they are made from. This makes it difficult to predict how effective a vaccine made today will be against a virus that emerges tomorrow.

Dr. Nabel and his colleagues started their project by focusing narrowly on mutations that render H5N1 viruses better able to recognize and enter human cells. Bird-adapted H5N1 binds bird cell surface receptors. But these receptors differ slightly from the receptors on human cells, which in part explains why bird-adapted H5N1 can infect but not spread easily between humans.

About a year ago, the research team began asking what mutations help the virus shift its adaptability. They compared the structural proteins on the surface of bird-adapted H5N1 influenza virus with those on the surface of the human-adapted strain that caused the 1918 pandemic. They focused specifically on genetic changes to one portion of the H5 protein--a portion called the receptor binding domain. They showed that as few as two mutations to this receptor binding domain could enhance

the ability of H5N1 to recognize human cells.

Additional mutations would likely need to accumulate for H5N1 to spread more easily from person to person, says Dr. Nabel. The few mutations he and his colleagues identified are likely just a subset of those, he emphasizes.

Moreover, they found that these mutations change how the immune system recognizes the virus. Mouse antibodies that target H5N1 were up to tenfold less potent against the mutants. Dr. Nabel and his colleagues used their knowledge of receptor specificity to create vaccines and isolate new antibodies that might be used therapeutically against human-adapted mutants.

They vaccinated mice with the material from viruses they altered to contain the mutant receptors, and they discovered one broadly reactive antibody that could neutralize both the bird- and human-adapted forms of an H5N1 virus.

According to Dr. Nabel, their findings should contribute to better surveillance of naturally occurring avian flu outbreaks by making it easier to recognize dangerous mutants and identify vaccine candidates that might provide greater efficacy against such a virus before it emerges.

“Our findings build on elegant studies of the influenza HA protein by structural biologists,” notes Dr. Nabel. “Insight into the structure of the avian flu virus has enabled us to target a critical region of HA that directs its specificity. Such a structure-based vaccine design may allow us to respond to this future threat in advance of an actual outbreak.”

Source: National Institute of Allergy and Infectious Diseases