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REPORTER

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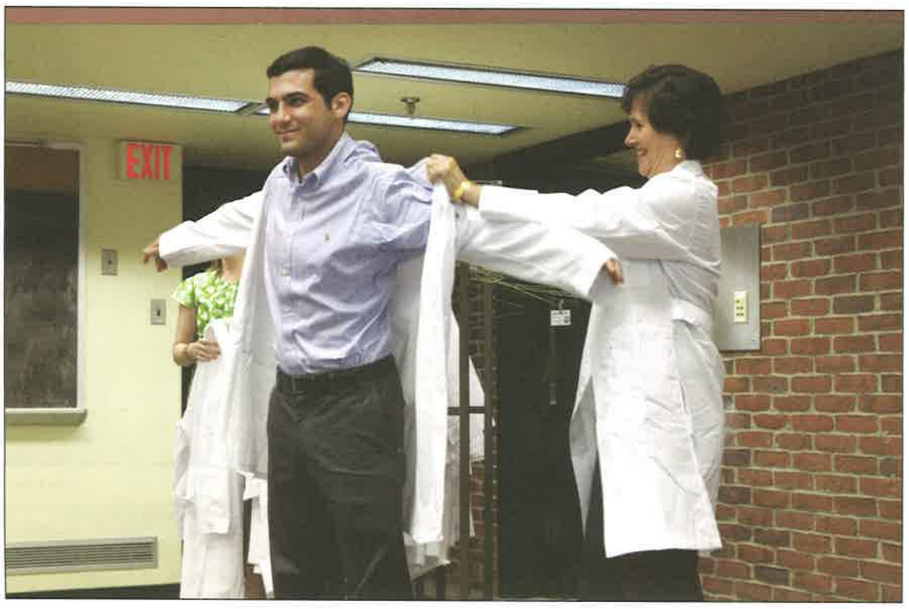

Anne Rayner

Controversial info release aids VUMC bird flu research

by Carole Bartoo

Vanderbilt University Medical Center research has produced reassuring results that addresses some fears about the pandemic power of avian influenza viruses created in research labs.

H5N1 avian influenza virus essentially does not yet seem to transmit from person to person in nature, only directly from birds to people. However, in 2010, scientists in the Netherlands and at the University of Wisconsin found that when H5N1 avian influenza was passaged intentionally in the laboratory from ferret to ferret, the deadly virus could acquire aerosol transmissibility.

The work stirred fears in the scientific community of potential use of this information for bioterrorist purposes and led to the unusual step of journals

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temporarily withholding publication of the research. The sequences of the transmissible viruses eventually were published in the journals *Science* and *Nature*.

Now, the Vanderbilt work, published online Sept. 3 in the *Journal of Clinical Investigation*, shows that human antibodies to the natural strain of H5N1, induced in volunteers during experimental H5N1 vaccine testing, are able to kill the potentially more dangerous, laboratory-created, strain of the avian flu.

"The work we did was only made possible by the publication of the controversial sequences. The publications identified the mutations, and we were then able to go back and engineer them into our recombinant protein to determine if our antibodies might be effective against such aerosol transmissible viruses," said Natalie J. Thornburg, Ph.D., a scientist in the Vanderbilt laboratory of James E. Crowe, M.D., Ann Scott Carell Professor, professor of Pediatrics, Professor of Pathology, Microbiology and Immunology and first author of the publication.

The team did not use the viruses themselves; they used a noninfectious synthetic protein and added the controversial viral mutation sequences to the surface of the protein. This allowed the Crowe laboratory to study the effect of the mutations in viral structures safely through finely tuned experiments.

Crowe

Then, because Vanderbilt is home to a National Institutes of Health (NIH)-funded Vaccine and Treatment and Evaluation Unit (VTEU), housed within Vanderbilt Vaccine Research Program, Crowe's team was able to ask participants previously involved in an H5N1 vaccine trial to return and supply blood cells to the laboratory for isolation of antibodies they had produced in response to the vaccine.

"Fortunately, we discovered the antibodies we isolated from subjects immunized with the existing vaccine also would neutralize strains that had these specific new mutations," Thornburg said.

Senior author James E. Crowe Jr., M.D., director of the Vanderbilt Vaccine Center and professor of Pediatrics Pathology, Microbiology and Immunology, said the combination of the release of critical information from the 2010 research, and the use of highly developed biotechnology used in his laboratory shows this type of work can continue to inform vaccine and treatment development, even for pandemics that do not yet exist.

"Our images show that the antibodies are able to reach down into a protected area of the virus to bind to and neutralize it, despite the changes made in its structure of the virus that are in an adjacent area. These findings provide important information about immunity to these new viruses, and in this case the information is also reassuring," Crowe said.

Some of the new computer-driven, virtual test models used in this study provide virus/antibody interaction snapshots that may be quicker and easier to capture than the classical method of crystallography of natural protein complexes.

Crowe calls it a "hybrid approach" to describing viral/antibody interactions, and his team, in collaboration with David Nannemann, Ph.D., a postdoctoral student in the Department of Chemistry, and Jens Meiler, Ph.D., associate professor of Chemistry and Pharmacology, in the Center for Structural Biology, have shown the models have a high degree of accuracy so far. However he pointed out that it will be useful to compare the Vanderbilt results with traditional crystallography as the field progresses, which the team is pursuing with Ben Spiller, Ph.D., assistant professor of Pharmacology, and his team. ❑

John Russell

David Nannemann, Ph.D., left, and Natalie Thornburg, Ph.D., are investigating the human antibody response to H5N1 bird flu.