



Testimony
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Subcommittee on Energy Policy, Natural
Resources, and Regulatory Affairs
United States House of Representatives

NIH's Biomedical Research
Response to West Nile Virus

Statement of

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Mr. Chairman and members of the Committee, thank you for the opportunity to appear before you today to discuss research conducted by the National Institute of Allergy and Infectious Diseases (NIAID) on West Nile virus. Today I will briefly outline what we know about the basic biology of West Nile virus and summarize our research programs for the development of new vaccines, which will help to limit the number of West Nile cases, and new treatments, which will reduce the human cost the virus exacts from infected people and their loved ones.

West Nile virus is a relatively new threat in this country. As such, it joins the ranks of the many other emerging and re-emerging infectious disease threats we currently face. These include HIV, multi-drug resistant tuberculosis, influenza, and SARS, just to name a few. To these naturally emerging infections, we must now add threats from “deliberately emerging” diseases such as anthrax, smallpox, and plague—diseases that would not pose significant hazards to our society were it not for the possibility that they might be used in a deliberate biological attack. Unpredictable new threats from infectious diseases, whether emerging, re-emerging, or deliberately-emerging, will be with us indefinitely.

The NIAID research portfolio for West Nile virus, therefore, is best understood in the broader context of our comprehensive emerging infectious diseases program. The effort to cope with new and emerging infectious diseases is one of the most important missions of NIAID, and encompasses a significant portion of the

research carried out by NIAID. It involves comprehensive and closely coordinated efforts to identify new threats as they emerge, and to develop the vaccines, treatments, and diagnostic tools that are necessary to confront these new threats.

Basic Research

West Nile virus is a member of the flavivirus family of viruses, which also includes the viruses that cause yellow fever, dengue, and St. Louis encephalitis. It can infect many species of mammals and birds, and even reptiles (e.g., alligators). The virus is transmitted to humans by mosquitoes that have first fed on an infected animal, typically a bird; more than 40 species of mosquitoes are capable of transmitting the virus. About 80 percent of infected people clear the virus before experiencing any symptoms at all. For those who do become ill, mild symptoms begin three days to two weeks after infection, and include fever, malaise, headache, and muscle aches, sometimes accompanied by swollen glands and a mild rash. If the virus enters the central nervous system, it can cause serious illness or death. People with compromised immune systems and people over the age of 50 are at highest risk for such severe outcomes. Recovery from severe illness can be very slow, and cognitive and functional disabilities can linger for months or years after the acute phase; some of the neurological effects—such as paralysis—may be permanent.

When West Nile virus appeared on the East Coast of the United States in 1999, NIAID immediately initiated a program to develop specific countermeasures. Fortunately, we already had in place an active basic research program on flaviviruses that served as a solid foundation for the West Nile virus research effort, and that allowed us to move forward far more rapidly than we could have otherwise. Research funding on West Nile virus has increased approximately ten fold since the virus first appeared in North America. With this infusion of resources, scientific progress over the past five years has been swift.

The development of specific countermeasures to any disease depends on painstaking and detailed basic scientific investigation. To this end, NIAD grantees and intramural investigators are in the process of determining the mechanisms by which West Nile virus causes disease, and are working to understand precisely how viral proteins interact with the human host. They are also studying the genetic and ecological factors that allowed the virus to establish itself in North America, and unraveling the complex interactions between the mosquito vector that spreads the virus and the animal reservoirs that maintain it.

Two recent published studies by NIAID-supported investigators help to illustrate current progress in basic research. In one study, published last year in *Science*, researchers used advanced electron microscopy and image reconstruction techniques to determine the physical structure of the West Nile virus strain that

has spread throughout the United States; this structural information will be of great value in the development of antiviral drugs and vaccines. Another group of researchers carried out a detailed study of the spread of West Nile virus in California since it first appeared there last year; this study has shed light on the mechanisms by which the virus propagates and is maintained in a new environment.

Vaccines

The goal of any vaccine is to prime the immune system to respond quickly and effectively should the vaccinated person ever be exposed to the pathogen against which the vaccine is designed to defend. NIAID scientists are pursuing several strategies to develop a West Nile virus vaccine, one of which already is being tested in humans.

One very promising approach is to create a so-called “chimeric vaccine,” based on research that NIAID pioneered more than a decade ago. Just as the chimera of Greek myth was a blend of different animals, a chimeric vaccine is a combination of more than one virus. In the early 1990s, NIAID scientists were the first to show that chimeras can be made from closely related flaviviruses. They then went on to replace genes for the surface proteins of one flavivirus with genes for the surface proteins from another flavivirus, and showed that the resulting engineered chimera could be used as a vaccine. In 2000, NIAID

entered into a fast-track development agreement with the vaccine manufacturer Acambis to develop a chimeric West Nile virus vaccine based on this approach, using a licensed live, attenuated Yellow Fever virus as the starting platform. Testing of the chimeric West Nile virus vaccine candidate in mice, hamsters, horses, and non-human primates indicated that it could protect these animals against West Nile virus infection. Phase I safety and immunogenicity testing in humans is currently under way, with promising preliminary results. If this work proceeds as expected and no adverse side effects are uncovered, this West Nile virus chimeric vaccine could be on the market within the next two to three years. NIAID intramural researchers have also created another chimeric West Nile virus vaccine based on a dengue virus platform, which has been tested successfully in animal models; initial safety and immunogenicity testing in healthy volunteers is awaiting FDA approval.

Another promising vaccine strategy for West Nile virus, called a DNA vaccine, is currently being developed under a Cooperative Research and Development Agreement between the NIAID Vaccine Research Center and Vical, Inc. A DNA vaccine is unique in that it contains no protein or whole virus, but only certain genes from the virus encoded in short sequences of DNA. When these DNA sequences are injected, cells in the host take up the genes, translate them into proteins, and display them on their outer surfaces; circulating immune cells bind to the displayed foreign proteins, and sensitize the host immune system so that it

can mount a fast protective response should the host ever encounter the live virus. Research data suggest that a DNA vaccine containing two West Nile virus genes protects mice against West Nile virus infection. Initial human studies are planned for early 2005, pending FDA approval.

Treatment

Currently, doctors can only offer supportive care for West Nile virus infection; no specific therapy is available. NIAID is pursuing several lines of research to increase the treatment options for the most severe cases of West Nile disease.

One treatment strategy is called passive immunization, in which human antibodies that can bind to West Nile virus particles are injected directly into a patient's bloodstream. A randomized, double-blind clinical trial currently is under way to evaluate whether a mixture of purified human antibodies manufactured by an Israeli pharmaceutical company can reverse or prevent life-threatening cases of West Nile infection. Because this preparation is derived from blood plasma donated by people living in a region where West Nile virus has been endemic for many decades, it contains a significant amount of antibodies specific for West Nile virus. In this study, patients who already have been diagnosed with West Nile neurologic illness, or who are infected and at high risk for developing neurologic illness, are given either the Israeli preparation, a different immunoglobulin preparation that does not contain West Nile antibodies, or a

placebo. Patients in the trial also are being studied in great detail to better understand and delineate the medical course of severe West Nile disease. This ongoing trial began in 2003 at 35 sites, and recently was expanded to more than 60 sites in the United States and Canada with an enrollment goal of 100 patients.

Antiviral drugs are another treatment opportunity, and NIAID is conducting a vigorous program to find promising drug candidates. The program is referred to as the NIAID Preclinical Antiviral Screening Program and is carried out by our Collaborative Antiviral Testing Group. This program screens large numbers of compounds, including drugs already licensed for other uses, for their ability to prevent viral growth in cell culture. Promising candidates are then subjected to further testing in animal models and, if appropriate, human volunteers. To date this program has screened more than 1000 compounds, and has identified 12 candidates that showed significant activity against West Nile virus; these are now being evaluated further in animal models. In addition, several interferons, which are small, antiviral proteins produced by cells when they come under viral attack, and interferon inducers have been identified as possible drug candidates.

Although animal testing so far has shown that in order to be effective these interferons must be given before exposure to the virus, further work on these compounds is continuing.

Conclusion

NIAID will continue to pursue its research agenda to combat West Nile virus, and we are hopeful that both an effective vaccine and specific treatments for use in severe cases will be available in the not-too-distant future. It is unquestionably true that the research program on West Nile and other flaviviruses that we had pursued before the virus appeared in the United States was of major benefit; had we been obliged to start the program *de novo*, we would not be nearly as close to our goals as we are today. It is also important to bear in mind that West Nile virus is only one of many emerging, re-emerging, and deliberately emerging infectious disease threats to confront us, and it certainly will not be the last. NIAID's past successes and current strengths make us ready to meet new infectious disease threats that we will inevitably face in the future.

Thank you for the opportunity to appear before you today. I would be pleased to answer any questions that you may have.