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Rethinking the Response to Emerging Microbes: Vaccines and Therapeutics in the Ebola Era—a Conference at Harvard Medical School

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Harvard Medical School convened a meeting of biomedical and clinical experts on 5 March 2015 on the topic of “Rethinking the Response to Emerging Microbes: Vaccines and Therapeutics in the Ebola Era,” with the goals of discussing the lessons from the recent Ebola outbreak and using those lessons as a case study to aid preparations for future emerging infections. The speakers and audience discussed the special challenges in combatting an infectious agent that causes sporadic outbreaks in resource-poor countries. The meeting led to a call for improved basic medical care for all and continued support of basic discovery research to provide the foundation for preparedness for future outbreaks in addition to the targeted emergency response to outbreaks and targeted research programs against Ebola virus and other specific emerging pathogens.

In the first session, the speakers reviewed the outbreak in West Africa and the response to it. Anthony Fauci (NIAID) described the “perfect storm” that led to the recent Ebola outbreak in West Africa, in which the outbreak spread too fast for traditional public health measures to contain it. He summarized the lessons learned, including that treatment outcomes can be improved by interventions such as fluid and electrolyte management, that even the U.S. hospital system was not prepared for the Ebola threat, and that fear must not be allowed to control health policy. He also described the U.S. Government’s support of the development and testing of vaccines and therapeutics.

Jens Kuhn (NIAID) provided an overview of filovirus virology, and he reminded us that the individual filoviruses are indeed very different and that we “know less than we pretend to know about the filoviruses.” He warned against accepting anecdotal evidence provided in both the public media and scientific publications instead of verified and peer-reviewed evidence, and he also warned against interpretation of data in a biased manner. He recommended a more “humble” approach to the state of our knowledge about filoviruses and pointed out that many exciting basic questions remain to be explored. Since the symposium, our lack of knowledge about Ebola virus has been reinforced by the recent evidence that the virus has persisted in the eye of an Ebola patient treated at Emory University Hospital (1). Marshall Lyon (Emory University School of Medicine) described the lessons learned from treating the first two Ebola patients in the United States (2) and said that the key to their survival and recovery was supportive care and the physical structure for biocontainment. He described the importance of the team of individuals working to provide the care, which in total showed that Ebola infection is not a death sentence if intensive care is provided. Paul Farmer (Harvard Medical School and Brigham and Women’s Hospital) described the limitations of the health care infrastructure in West Africa and pointed out the higher survival rate of U.S. patients. He advocated the building of laboratory and medical delivery systems in West Africa so that the survival rate there can equal that in the United States. Dr. Farmer, like Dr. Kuhn, stated that we need to know more about the pathogenesis of filovirus infection. The description of the dedication of the physicians treat-

ing the Ebola patients in both West Africa and the United States was both impressive and inspiring.

In the second session, a series of talks described the tremendous strides in progress that have been made with regard to Ebola vaccines and therapeutics. Erica Ollmann Saphire (Scripps Institute) outlined the work going into optimizing the monoclonal antibody (MAb) cocktails to be used for postexposure prophylaxis. She has organized the Viral Hemorrhagic Fever Immunotherapeutic Consortium to systematically test combinations of MAbs for therapy, as well to build on her work on the structure of antibody binding to Ebola virus to understand why some antibodies work better than others. Kartik Chandran (Albert Einstein School of Medicine) described small-molecule inhibitors of Ebola virus entry that researchers at the Albert Einstein School of Medicine are developing to block the interaction of the virus with its cellular receptor, to prevent the processing of the viral glycoprotein by host cell proteases, or to block the endocytic transport of the virus. Nancy Sullivan (NIAID Vaccine Research Center) reviewed the long-term work on adenovirus vectors as Ebola virus vaccines, starting in the laboratory of Gary Nabel and continuing in her lab. She described how they have defined chimpanzee adenovirus 3 as the best priming immunization for short-term immunity, followed by a poxvirus vector boost for good CD8⁺ T cell long-term memory. Sina Bavari (U.S. Army Medical Research Institute of Infectious Diseases) described a small-molecule inhibitor of Ebola virus replication—an adenosine analog that targets the viral RNA-dependent RNA polymerase and has protected nonhuman primates (NHP) by reducing viral titers. This adeno-

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sine analog also reduces the replication of multiple RNA viruses, a strategy that Dr. Bavari suggests could lead to a broadly active inhibitor. While funding for Ebola virus research is presently strong, we are playing catch-up, and continued broad-based research support was recommended so we can be better prepared for future emerging infections, whatever the agent.

The third session examined the challenges in developing and stockpiling vaccines and therapeutics for an agent like Ebola virus where outbreaks are sporadic and limited in their scope. The location of most of these outbreaks in resource-poor countries has also limited the interest of pharmaceutical companies in developing treatments for these agents. Peter Jahrling (NIAID) outlined the challenges in developing medical countermeasures for Ebola virus by using NHP. Although Ebola disease is thought to be best recapitulated in NHP, the basic studies on pathogenesis are more difficult and costly than studies with small-animal models. As a result, a number of studies remain to be done to define the optimal species of NHP, the virus strain, the dose and route of inoculation, and correlates of protection, for example. Protection against lethal infection has correlated best with reduction of viremia, but immunological correlates have been difficult to define. Gary Nabel (Sanofi) reiterated that effective treatments of outbreaks like Ebola require long-term commitment and coordination of efforts to move vaccines and medicines from laboratories to clinical practice. He described the long history of Ebola vaccine research in his laboratory, which has needed long-term NIH commitment for the program. He described the Ebola Response Coordination team organized by the transindustry PhRMA group and emphasized that industry-wide collaboration with governmental agencies is needed to respond to international public health crises. Barney Graham (NIAID Vaccine Research Center) pointed out the unprecedented response from multiple parties to the Ebola outbreak in West Africa and credited the enormous effort by all stakeholders. This showed that it is possible to compress the timeline for responses, but he emphasized that this is possible for other agents only if there is extensive prior preparation. Dr. Graham felt that this could be achieved for other pathogens if global surveillance were effective in identifying emerging and reemerging pathogens, our knowledge of all pathogens were expanded, and platform technologies and vaccine strategies for all virus families were established. Phil Krause (U.S. FDA) described the ways that the FDA is expediting the development of Ebola-related products. Regulatory mechanisms have been established for expedited approval of the use of products demonstrated to be safe, including “traditional approval” based on disease endpoints, “accelerated approval,” and the “animal rule.” There would be a requirement for follow-up studies on effectiveness, but expedited mechanisms are being made available for products to be used in an outbreak.

The final session examined how we can best prepare for future emerging infections. Richard Whitley (University of Alabama—Birmingham) described the challenges of developing therapeutics from an academic institution. He was optimistic that good communication and partnerships could lead to the emergence of therapeutics from academic labs if governmental and industry relationships were formed. Because traditional placebo-controlled studies will not be feasible under outbreak conditions, novel trial designs, in particular, adaptive trial designs, need to be considered. Don Ganem (Novartis) pointed out that a different “perfect storm” has hit infectious disease therapeutics research. Cuts in governmental funding for basic research, as well as industrial dis-

covery research, have combined to threaten the future of basic infectious disease research. He used antibiotics as an example, where there are many challenges for the pharmaceutical industry to invest in their development, and he emphasized the need for governmental support of basic research on microbes, as well as funding of the later stages of clinical drug development. He is optimistic about the future in that some companies are reentering the infectious disease space, two companies have created stand-alone institutes for developing products for neglected diseases, and numerous public-private partnerships have sprung up. Dylan George (Office of Science and Technology Policy, The White House) described the extensive response of the U.S. Government to the Ebola outbreak in West Africa and cited the commitment of the United States to Ebola vaccine research, which was documented in President Obama’s recognition of Nancy Sullivan and NIH’s long-term commitment to basic Ebola vaccine research. This led to some discussion from the participants that broad-based discovery research, as well as targeted translational research, is needed.

The importance of basic research, not just for defining targets for antivirals and vaccines but also as the foundation for basic clinical care, was emphasized repeatedly. The causative agent of the next outbreak cannot be predicted, so it is important to have a foundation of knowledge of all infectious agents. When Bernie Fields wrote in an important commentary in 1994 (3) that it was “time to turn to basic science” in the AIDS field, he did not mean that it was time to return to the basic science of HIV only. He postulated that advances would come from “unrelated areas of research,” and he recommended that an increased emphasis be placed on basic research in a broadened view of AIDS-related research. A similar sentiment was echoed by Harvard Magazine, which summarized the symposium (4) as a call for “back to basics,” which they described as both basic research and basic clinical care.

The lessons from the Ebola outbreak, as discussed at the conference, were severalfold. (i) Basic supportive health care is essential for Ebola treatment. (ii) A high-quality health care infrastructure around the world is necessary to combat not only Ebola but also any infectious disease outbreak. (iii) Broad-based basic science is necessary not only to combat Ebola but also other potential outbreaks. Because we cannot predict what the next agent will be, broad research in virology, infectious disease, and immunology is needed to lay the foundation for preparedness. Similarly, it is impossible to predict where the next basic breakthrough in our knowledge will come from—hence the need for continued broad-based basic discovery research. (iv) Public-private partnerships and international collaboration among academic scientists and clinicians, government researchers and agencies, and industry are needed to prepare for future Ebola and other infectious disease outbreaks. The Ebola response can serve as a model for future responses. (v) Preparedness involves both preparation for known infectious agents and broad-based knowledge of infectious agents and immune responses to them. (vi) A strong educational enterprise is needed to maintain and strengthen the community of scientists, clinicians, and veterinarians in the area of infectious disease, pharmacology, and medicinal chemistry.

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