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Institute of Medicine Panel Discussion

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Chairman Stobo and members of the committee, thank you for allowing me the opportunity to speak about the scientific need for chimpanzees in research. I am a physiology researcher at the University of Iowa, but I am here today in my capacity as chair of the Federation of American Societies for Experimental Biology's Committee on Animals in Research and Education. FASEB is the nation's largest coalition of biomedical researchers, representing 23 scientific societies and over 100,000 researchers from around the world. FASEB's mission is to advance health and welfare by promoting progress and education in biological and biomedical sciences.

Research involving chimpanzees has been, and we believe continues to be, important for biomedical and behavioral research that will be needed for the advancement of the public's health. Chimpanzees are an invaluable resource because they are the only animals susceptible to many diseases that afflict humans and share many of the same physiological characteristics as humans.

This panel has been asked to evaluate the scientific need for chimps in research. Therefore, I will provide my perspective—as a scientist with a strong commitment to the humane treatment of animals—on how chimpanzees have, and continue to be, critical for the development of vaccines and treatments for viral infections, how they are used in the development and safety testing of monoclonal antibodies, their role in developing countermeasures against bioterrorism, and the importance of chimp research for sustaining wild chimp populations. Because you will hear extensive, detailed testimony later this summer from experts in related scientific fields, I will merely provide an introduction now.

It is well-documented that research on chimps led to the development of diagnostic tests for hepatitis A, B, and C and vaccines for both A and B. As a result of these diagnostic tests, the spread of these diseases through blood transfusions has virtually been eliminated. Because of the vaccine, Hepatitis B is now nearly unknown in children born in the United States, and hepatitis A rates in the U.S. have declined by 92% since the vaccine was introduced in 1995. According to a 1997 National Academy of Sciences report: "Because chimpanzees are the only nonhuman primates susceptible to infection with hepatitis B, they were critical to the development of a vaccine by providing a source of virus and viral antigens and by making it possible to evaluate the safety and the effectiveness of candidate vaccines."

Despite these successes, a vaccine to combat hepatitis C has yet to be developed. Importantly, the cloning of hepatitis C in 1989 from the plasma of chimpanzees provided insights into the most significant aspects of hepatitis C infection and pathogenesis.

Current work in chimpanzees continues to teach us a great deal about the immediate antiviral immune responses following hepatitis C infection. These events can be studied in a way that is not possible in acutely infected humans, since human subjects remain asymptomatic directly following exposure to the

virus. In addition, some chimpanzees that were infected with the B and C virus 30 years or more ago have developed cirrhosis and liver cancer similar to that seen in chronically infected humans. This shows that chimps are also invaluable models for the study of chronic hepatitis C.

One of the most important breakthroughs in finding a cure for hepatitis C has been the development of new antiviral therapies. Almost 200 million people suffer from chronic hepatitis C infection and are at risk for liver failure and liver cancer. Many of the drugs currently in human clinical trials were tested in chimpanzees for safety and efficacy prior to their use in man. The long awaited therapeutic validation of antisense technology came from a novel therapy for hepatitis C first tested in chimps. This same technology can now be applied to many other diseases, including cancer.

According to the CDC, approximately 17,000 Americans are infected with the hepatitis C virus each year, and liver cancer due to chronic hepatitis C infection is now the most rapidly increasing cause of cancer death in the U.S. Current predictions suggest this will increase by four-fold over the next 10-20 years. According to the 2010 Institute of Medicine report on 'Hepatitis and Liver Cancer', studies to develop a vaccine to prevent chronic hepatitis C virus infections should continue. Chimpanzee research will be essential in moving this work forward.

Many attempts have been made to identify alternative methods to study hepatitis C infection and lifecycle; however, the chimpanzee continues to be the best model available to study all aspects of hepatitis C: infection, viral lifecycle, immune response and vaccine development. Hepatitis C infection has only been possible in one human liver cancer cell line, Huh7. The problem with this in vitro cell culture technique is that the Huh7 cell line is transformed, only slightly mimics the state of liver cells in vivo, and can only produce infectious particles of one viral isolate. This severely limits our ability to understand how the virus interacts with and induces changes in liver cells in vivo to produce clinically observed hepatitis C-associated liver disease.

Mouse models have also been developed to help better understand the hepatitis C virus. For example, uPA/SCID mice, which have their endogenous liver cells removed and then repopulated with human liver cells, can be useful for some aspects of antiviral drug development. There are significant downsides to this model, however. For instance, this mouse's immune system is completely non-existent, making studies on the immunology and immunopathology of the virus impossible. The evaluation of new vaccines is also not feasible with this model. In addition, while humanized mouse models containing human-derived liver cells and immune system components show promise, they are difficult to generate. Moreover, they do not contain all components of the human immune system. Each of these approaches have substantial limitations—well-documented in the scientific literature—that limit their usefulness in comparison with chimps.

The scientific justification for continued use of chimps is not limited to their value in hepatitis C research and vaccine development. Chimpanzees are also needed for the study of other viruses—such as respiratory syncytial virus, HIV, and dengue fever; however, time does not permit in-depth discussion of these diseases.

In addition to vaccine development, chimpanzees are of great importance in developing and testing monoclonal antibody therapies for autoimmune diseases and cancers such as non-Hodgkin's lymphoma. Chimps are the only species useful for developing and testing these biologics because of the closeness of their receptors and their cytokine profiles to humans. These similarities make chimpanzees especially important for testing the safety of monoclonal antibodies. Dr. Stuart Zola, director of the Yerkes National Primate Research Laboratory, stated that, "other species will try to

reject these monoclonals, but chimps won't ... because their system is very much like ours."

The importance of this can perhaps best be underscored in the case of the TGN1412 monoclonal antibody. This is a targeted humanized monoclonal antibody that was developed in Germany to treat multiple sclerosis, rheumatoid arthritis and certain cancers. However, it nearly killed six men who voluntarily took the therapy during a 2006 Phase I clinical trial in the United Kingdom. Administration of the antibody evoked a cytokine storm that caused multi-organ failure in all six participants. This occurred despite the fact that the company and the UK's Medicines and Healthcare Products Regulatory Agency deemed the product safe for human trials after testing in both rabbits and monkeys produced no harmful effects. However, it was not tested in the chimpanzee. If a chimpanzee model had been used, this life-threatening outcome might have been averted since the chimp and human immune systems are extremely similar.

Research involving chimpanzees could also be indispensable in the development of countermeasures in the event of an unforeseen outbreak of a public health threat due to bioterrorism or natural causes. Filoviruses like Ebola and Marburg, which have average mortality rates of greater than 50 percent, have been classified as Category A bioterrorism agents by the CDC. We would need access to a research population of chimpanzees in order to quickly develop and test prophylactic and therapeutic strategies against these deadly viruses to ensure the safety of our population.

We must also not forget the importance that biomedical research plays in developing therapies and vaccines for chimpanzees themselves. Just this past February, researchers at the New Iberia Research Center in Louisiana began a safety study on chimpanzees in order to test an Ebola vaccine for wild gorillas and chimpanzees. The researchers inoculated six chimpanzees and were able to establish that the Ebola vaccine elicits a strong immune response. This vaccine already is being given to wild gorillas. The urgency of these studies is highlighted by the fact that Ebola is ravaging the great ape population in the wild and has killed about one-third of all gorillas. Continued research using chimpanzees is needed not only for human therapies, but also for those that directly benefit chimpanzees and other animals.

Conclusion

In conclusion, chimpanzees play a unique role in biomedical research. Without the use of chimps, vaccine development and anti-virals for hepatitis C and other virus-mediated diseases will be set back many years and adverse events like those that were experienced in the TGN1412 trial in the UK could become more frequent. Since we cannot predict the future, it would be irresponsible to abandon the use of a certain species, which is extremely close to humans in terms of physiology and immunology. Even though the use of chimpanzees has been banned in the new European directive on animal research, it allows exceptions in cases of "conservation of the species itself" or in the case of "a serious pandemic affecting the human population of Europe". Furthermore, it is important to realize that even though other countries around the world do not own chimpanzees, pharmaceutical companies and academic scientists from other countries are highly dependent upon US-owned chimps to test the safety of their monoclonal antibodies and conduct vital biomedical research initiatives.

FASEB believes that the use of animals in research is a privilege and that good animal care and good science go hand-in-hand. We recognize that chimpanzees are a special case that deserves special scrutiny, and that there must be a strong scientific justification for research involving them. The use of chimpanzees is subject to rigorous oversight – as it should be. Before any study can go forward, researchers must demonstrate that chimpanzees are the best model, the study is well designed, as few as

possible are used, and that they are treated humanely. Nevertheless, where there are compelling health needs, research with chimpanzees should be allowed to go forward. We have a responsibility to the population of research chimpanzees in the U.S., but we also have a responsibility for the lives and health of human beings.

Thank you.

FASEB is composed of 23 societies with more than 100,000 members, making it the largest coalition of biomedical research associations in the United States. FASEB enhances the ability of scientists and engineers to improve—through their research—the health, well-being and productivity of all people. Our mission is to advance health and welfare by promoting progress and education in biological and biomedical sciences through service to our member societies and collaborative advocacy.