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For Immediate Release

New Ebola virus research boosts pandemic preparedness

Promising antibody may prove useful against deadly outbreaks

LA JOLLA, CA—New research led by scientists at La Jolla Institute for Immunology (LJI) reveals the workings of a human antibody called mAb 3A6, which may prove to be an important component for Ebola virus therapeutics.

This antibody was isolated from blood samples from an Ebola survivor treated at Emory University Hospital during the 2014-2016 Ebola virus outbreak, an outbreak that began in West Africa and killed more than 11,300 people.

In their new study, the researchers showed that mAb 3A6 helps block infection by binding to an important part of Ebola's viral structure, called the "stalk." Study collaborators at the NIH's National Institute of Allergy and Infectious Diseases (NIAID) found that treatment with mAb 3A6 can benefit non-human primates in advanced stages of Ebola virus disease.

"This antibody offers the best protection in primates, at the lowest dose yet seen for any single antibody," says LJI Professor, President & CEO Erica Ollmann Saphire, Ph.D., MBA, who led the recent *Nature Communications* study alongside John A. G. Briggs, Ph.D., of Cambridge University and the Max Planck Institute of Biochemistry; Gabriella Worwa, D.V.M., and Jens H. Kuhn, M.D., Ph.D., of NIAID; and Carl W. Davis, Ph.D., and Rafi Ahmed, Ph.D., of the Emory Vaccine Center.

The discovery that mAb 3A6 appears effective at a very low dose is also exciting. "The lower the amount of an antibody you can deliver to someone, the easier it will be to manufacture a treatment—and the lower the cost," says study first author Kathryn Hastie, Ph.D., LJI Instructor and Director of LJI's Center for Antibody Discovery.

How the antibody works

The key to treating Ebola virus is to find antibodies that anchor tightly to and block essential machinery of the virus. The researchers zeroed in on mAb 3A6 because it appears to target a structure on Ebola virus called the "stalk." The stalk is an important part of the Ebola virus structure because it anchors Ebola's glycoprotein structure (which drives entry into a host cell) to Ebola's viral membrane.

The team spearheaded efforts to capture images of mAb 3A6 in action. The researchers used two imaging techniques, called cryoelectron tomography and x-ray crystallography, to show how mAb 3A6 binds to Ebola virus to interrupt the infection process.

The researchers found that mAb 3A6 binds to a site normally concealed by a shifting landscape of viral proteins. "There's a dynamic movement in these proteins," says Hastie. "They might kind of wiggle around, move back and forth, maybe lean over a little bit or go up and down."

Antibody mAb 3A6 takes advantage of this little protein dance. It has such a strong affinity for its viral target that it can slip between the proteins, lift them up, and latch on its target.

Hastie says mAb 3A6's ability to bind to this target is important for several reasons. First, the site is conserved across different species of Ebola virus, making antibodies that target this region an attractive component in "pan-Ebolavirus" therapeutics. Second, the new understanding of how mAb 3A6 "lifts up" proteins in the viral stalk gives scientists a clearer view of Ebola's weaknesses. MAb 3A6 also shows us how similar antibodies against the stalks of other viruses might work as well.

"This study gives us some hints for how to design vaccines that are specifically against this region of Ebola virus," says Hastie.

Additional authors of the study, "Anti-Ebola virus mAb 3A6 protects highly viremic animals from fatal outcome via binding $GP_{(1,2)}$ in a position elevated from the virion membrane," include Zhe "Jen" Li Salie, who solved the X-ray structure; Zunlong Ke, who performed the cryoelectron tomography; Lisa Evans DeWald, Sara McArdle, Ariadna Grinyó, Edgar Davidson, Sharon L. Schendel, Chitra Hariharan, Michael J. Norris, Xiaoying Yu, Chakravarthy Chennareddy, Xiaoli Xiong, Megan Heinrich, Michael R. Holbrook, Benjamin Doranz, Ian Crozier, Yoshihiro Kawaoka, Luis M. Branco, Jens H. Kuhn

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