Structural basis for antibody-mediated neutralization of Lassa virus

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Lassa virus infects over 100,000 individuals and causes ~5,000 deaths from viral hemorrhagic fever every year in West Africa. The trimeric surface glycoprotein of Lassa virus, GPC, is critical for infection, yet no high-resolution structures of GPC in its prefusion state were available. A ten-year protein engineering effort in the lab recently culminated in the crystal structure of Lassa virus GPC in its trimeric, prefusion complex, the first such structure for any virus in its arenavirus family. This landmark structure illuminated new findings: that the properly assembled prefusion trimer is essential for recognition by the cell surface receptor matriglycan and that both subunits of GPC undergo pH-induced conformational changes. Crystal structures of Lassa virus GPC in complex with antibodies isolated from human survivors of Lassa infection in Sierra Leone and Nigeria showed that most of these antibodies recognize quaternary epitopes that form only in the prefusion conformation. This work provides a foundation to develop life-saving small molecule and antibody-based therapeutics as well as vaccines to elicit effective neutralizing antibodies against Lassa virus.