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From Kenema to Our Krios: Medical Defense Against Lassa Virus and Emerging Infectious Disease

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Emerging infectious diseases threaten human health with annual outbreaks, epidemics and occasional pandemics. Our laboratory is the headquarters of an international, multidisciplinary consortium aimed at discovery and characterization of antibody therapeutics against these viruses and use of the resulting tools and information to develop vaccines. Among the viruses we study is Lassa virus, which causes hemorrhagic fever and lifelong health complications. Lassa is endemic in Western Africa with perhaps hundreds of thousands of annual infections. There is not yet any vaccine against Lassa virus. One obstacle toward that goal is the difficulty in eliciting an effective antibody response against the virus, because of the extensive glycosylation and structural instability and heterogeneity of the viral surface target. Our multidisciplinary team developed engineered versions of the Lassa surface protein, and used those engineered proteins to discover and characterize antibodies from human survivors in collaboration with a Lassa ward and research facility in Kenema, Sierra Leone. This collaborative effort yielded a first-in-class antibody treatment for Lassa virus that confers complete survival in non-human primates at a very low dose, even late in disease course. Here we present cryoEM structures of the Lassa surface glycoprotein in complex with these and other therapeutic antibodies and illuminate their likely mechanism of action. We identify key sites for recognition, and identify the biochemical differences that separate weak from potent antibodies, and strain-specific from broadly reactive antibodies. Importantly, this structural information provided us with the roadmaps to engineer more potent and broadly reactive antibodies to directly use as therapeutics, and also to design versions of the surface protein that better react with the germline antibodies to would lead to an effective immune response after vaccination. Immunization trials are now in progress with immunogens directed by the structural biology program.

References

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