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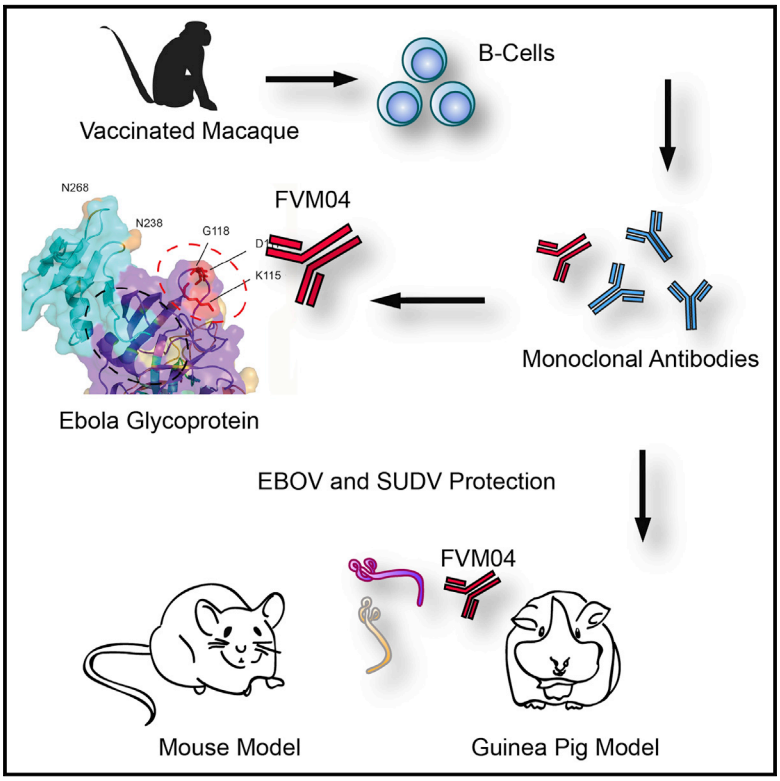
Antibody Treatment of Ebola and Sudan Virus Infection via a Uniquely Exposed Epitope within the Glycoprotein Receptor-Binding Site

Graphical Abstract



Highlights

- Monoclonal antibody FVM04 blocks interaction of ebolavirus with its host receptor
- FVM04 cross-neutralizes and protects against EBOV and SUDV in rodents
- A new ZMapp version that includes FVM04 protects guinea pigs from EBOV and SUDV
- Specific GP mutations expose epitopes for FVM04 and other cross-neutralizing mAbs

Authors

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In Brief

Howell et al. examine a mAb, FVM04, that binds the ebolavirus receptor-binding site and find that FVM04 protects against EBOV and SUDV. When combined with two ZMapp™ components, the antibody cocktail retains EBOV protection similar to that of ZMapp™ and extends protection against SUDV. Specific glycoprotein mutations that enhance the exposure of cross-neutralizing epitopes are described.

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Antibody Treatment of Ebola and Sudan Virus Infection via a Uniquely Exposed Epitope within the Glycoprotein Receptor-Binding Site

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SUMMARY

Previous efforts to identify cross-neutralizing antibodies to the receptor-binding site (RBS) of ebolavirus glycoproteins have been unsuccessful, largely because the RBS is occluded on the viral surface. We report a monoclonal antibody (FVM04) that targets a uniquely exposed epitope within the RBS; cross-neutralizes Ebola (EBOV), Sudan (SUDV), and, to a lesser extent, Bundibugyo viruses; and shows protection against EBOV and SUDV in mice and guinea pigs. The antibody cocktail ZMapp™ is remarkably effective against EBOV (Zaire) but does not cross-neutralize other ebolaviruses. By replacing one of the ZMapp™ components with FVM04, we retained the anti-EBOV efficacy while extending the breadth of protection to SUDV, thereby generating a cross-protective antibody cocktail. In addition, we report several mutations at the base of the ebolavirus glycoprotein that enhance the binding of FVM04 and other cross-reactive antibodies. These findings have important implications for pan-ebolavirus vaccine development and defining broadly protective antibody cocktails.

INTRODUCTION

Filoviruses are the causative agents of severe hemorrhagic fever in humans and nonhuman primates (NHPs) (Kuhn et al., 2014). Members of the family *Filoviridae* include two marburgviruses: Marburg virus (MARV) and Ravn virus (RAVV), and five ebolaviruses: Ebola virus (EBOV), Sudan virus (SUDV), Bundibugyo virus (BDBV), Reston virus (RESTV), and Taï Forest virus (TAFV) (Kuhn et al., 2014). The EBOV (Zaire) has caused the largest number of outbreaks, including the 2014 EBOV disease (EVD) epidemic that led to over 28,637 cases and 11,315 deaths. Due to the higher frequency of outbreaks caused by EBOV, most efforts toward vaccine and therapeutic development have focused on this agent. Several studies have shown remarkable efficacy of antibody therapeutics against EBOV (Dye et al., 2012; Marzi et al., 2012; Olinger et al., 2012; Pettitt et al., 2013; Qiu et al., 2012a, 2012b, 2013a, 2014). However, until recently (Bounds et al., 2015; Flyak et al., 2016; Frei et al., 2016; Holtsberg et al., 2015; Keck et al., 2015), the development of cross-protective monoclonal antibodies (mAbs) targeting multiple species of ebolavirus has been lagging behind.

The filovirus surface glycoprotein, comprising disulfide-linked subunits GP1 and GP2, is the primary target for vaccines and immunotherapeutics (Marzi and Feldmann, 2014). The crystal structures of the trimeric EBOV $GP_{1,2}$ spike (henceforth termed GP) in complex with KZ52 (Lee et al., 2008), a neutralizing mAb