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Neutralizing antibodies directed against the influenza hemagglutinin head domain are more potent *in vivo* than those directed against the broadly conserved stem domain

Joshua DiNapoli
Sanofi Pasteur Biologics LLC, USA

Sanofi Pasteur is developing Universal Influenza Vaccine (UIV) strategies to address breadth of vaccine coverage and increased efficacy against drifted strains. Influenza vaccines designed to preferentially elicit broadly cross-neutralizing antibody responses against HA are a key feature of these UIVs. The HA protein can be broadly divided into 1) a highly immunogenic, yet variable "head" region containing the receptor-binding domain (RBD); and 2) a less immunogenic, yet well conserved stem region. Antibody responses against both the head and the stem region are known to afford efficacy in preclinical studies, with responses against the stem region tending to be broadly reactive due to sequence conservation in this region. However, the mechanism of action by which anti-head and anti-stem antibodies mediate protection, breadth of neutralization and their potency are still topics for discussion in defining their relative contributions to protective efficacy and breadth. Some data suggests that stem-specific antibodies provide greater breadth whereas head-specific antibodies are more potent in terms of protection from disease. To offer insight into these topics, broadly cross-neutralizing antibodies directed against either the head or stem of HA, were assessed for potency after passive transfer in both homologous and heterologous murine challenge models. Two head specific mAbs and three stem-specific bn-mAbs were delivered intraperitoneally to BALB/c mice in a dose-dependent manner. The head antibodies demonstrate broad neutralizing activity against post-2009 H1 viruses as well as seasonal strains from 1977 and earlier. The stem antibodies utilized demonstrate broad neutralizing activity against group 1 influenza viruses. Animals were challenged 1 day later with a lethal dose of a mouse adapted A/Belgium/2009 strain that is reflective of the currently circulating H1 strains in humans. Comparisons of efficacy were made in the context of disease. The strongly neutralizing head-specific mAbs were more effective in protecting against influenza replication and disease at 10 to 20-fold lower concentrations than any stem bn-mAb tested, indicating superior potency as well as a different mechanism of action. Further, only head-directed antibodies were capable of mediating sterilizing immunity in our model, as measured by pulmonary virus replication. The results of this study suggest that if an immune response was directed against broadly neutralizing head-specific HA epitopes, it could provide the basis for a universal influenza vaccine by eliciting broad and potent protection.

Biography

Joshua DiNapoli received his PhD in Microbiology and Immunology in the lab of Dr. Robert C. Rose at the University of Rochester School of Medicine and Dentistry in 2005. He went on to perform his post-doctoral work in the lab of Dr. Peter L. Collins at the National Institute of Allergy and Infectious Diseases from 2005 to 2010. He has since been with Sanofi Pasteur, where his current roles are Deputy Director of Viral Immunology and Research Lead for the Universal Flu Vaccine program.

Joshua.Dinapoli@sanofipasteur.com

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