2848
doi:10.1017/S1431927621009946
Microsc. Microanal. 27 (Suppl 1), 2021

Broad Neutralization of H1 and H3 Viruses by Adjuvanted Influenza HA Stem Vaccines in Non-human Primates

Yanfeng Zhou and Yu Qiu

Sanofi, United States

Title: Broad Neutralization of H1 and H3 Viruses

by Adjuvanted Influenza HA Stem Vaccines in Non-human Primates

Authors: Nicole Darricarrère,[1,§] Yu Qiu,[1] Masaru Kanekiyo,[2] Adrian Creanga,[2] Rebecca A. Gillespie,[2] Syed M. Moin,[2] Jacqueline Saleh,[1] Jose Sancho,[1]Te-Hui Chou,[1] Yanfeng Zhou,[1]Ruijun Zhang,[1]Shujia Dai,[1] Anthony Moody,[3] Kevin O. Saunders,[3] Michelle C. Crank,[2] John R. Mascola, [2] Barney S. Graham,[2]Chih-Jen Wei,[1*¥] and Gary J. Nabel[1*¥]

Affiliations:

[1] Sanofi, 640 Memorial Drive, Cambridge, MA 02139;

[2] Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892;

[3] Duke Human Vaccine Institute, Duke University School of Medicine, Durham, NC 27710 USA

- Current address: Revitope Oncology, 610 Main Street, Cambridge, MA 02139

[¥] Current address: ModeX Therapeutics, 22 Strathmore Road, Natick, MA 01760

*Correspondence to: Gary J. Nabel, Gary.Nabel@ModeXtx.com or Chih-Jen Wei, Chih-Jen.Wei@ModeXtx.com

Abstract: Seasonal influenza vaccines confer protection against specific viral strains but have restricted breadth that limit their protective efficacy. The H1 and H3 subtypes of influenza A virus cause the majority of the seasonal epidemics observed in humans and are the major drivers of influenza A virus-associated mortality. The consequences of pandemic spread of COVID-19 underscore the public health importance of prospective vaccine development. Here, we show that headless hemagglutinin (HA) stabilized-stem immunogens presented on ferritin nanoparticles elicit broadly neutralizing antibody (bnAb) responses to diverse H1 and H3 influenza viruses in non-human primates (NHPs) when delivered with a squalene-based oil-in-water emulsion adjuvant, AF03. The neutralization potency and breadth of antibodies isolated from NHPs were comparable to human bnAbs and extended to mismatched heterosubtypic influenza viruses. Though NHPs lack the immunoglobulin germline VH1-69 residues associated with the most prevalent human stem-directed bnAbs, other gene families compensated to elicit bnAbs. Isolation and structural analyses of vaccine-induced bnAbs revealed extensive interaction with the fusion peptide on the HA stem, which is important for viral entry. Antibodies elicited by these adjuvanted, headless HA stabilized-stem vaccines neutralized diverse H1 and H3 influenza viruses and

shared a mode of recognition analogous to human bnAbs, suggesting that these vaccines have the potential to confer broadly protective immunity against diverse influenza viruses responsible for seasonal and pandemic influenza infections in humans.

One Sentence Summary: Non-human primates immunized with adjuvanted, stabilized headless HA stem nanoparticles generated influenza-specific broadly neutralizing antibodies.

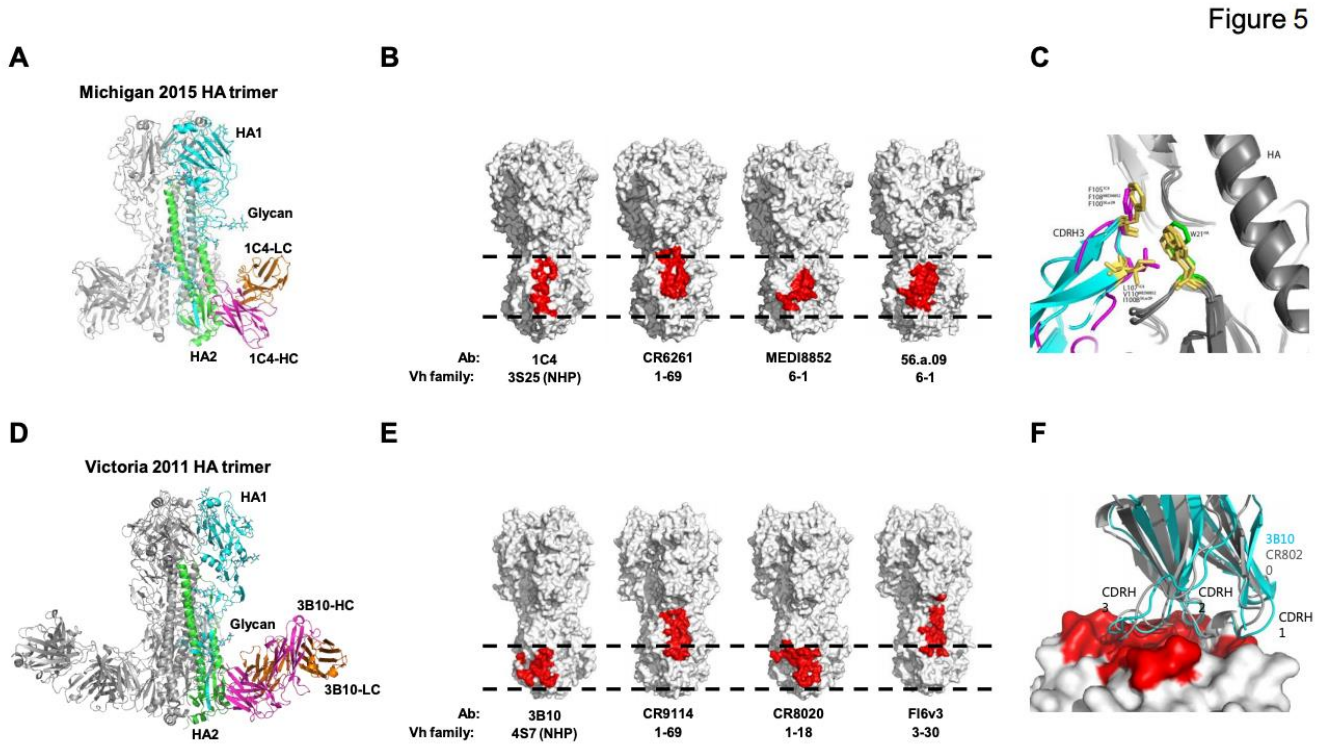

Figure 1. Figure 5. Vaccine-induced NHP Fabs bind to a conserved epitope on the influenza hemagglutinin stem. (A) Trimeric 2015 H1 HA-1C4 complex, with one HA/Fab protomer colored with HA1 in cyan, HA2 in green, Fab heavy chain in pink, and Fab light chain in orange; the other two HA monomers and Fabs in the trimer are colored in gray. Glycans are depicted as their component atoms. (B) Broadly neutralizing antibodies recognize overlapping epitopes (red) within the HA stem (light grey). Antibodies and Vh families are indicated below. Dashed lines demarcate the top and bottom boundaries of the 1C4 epitope as a visual guide to compare the epitope footprint of bnAbs on the HA stem. (C) Superimposition of 1C4-HA structure with 56.a.09-HA (PDB: 5K9K) and MEDI8852-HA (PDB: 5JW4) structures reveals a conserved motif of hydrophobic residues at the tip of CDR-H3. 1C4 is colored in magenta, 56.a.09 and MEDI8852 are colored in cyan. F105 and L107 of 1C4 are colored in magenta, and corresponding residues of 56.a.09 and MEDI8852 are colored in gold. W21 of 2015 H1 HA is colored in green, and corresponding residues are colored in gold. (D) Trimeric 2011 H3 HA3B10 complex, with the same color scheme as in (A). (E) Epitope footprint of indicated are shown in red as in (B). Dashed lines placed on the top and bottom boundaries of the 3B10 epitope also delineates the CR8020 epitope. (F) Superimposition of 3B10-HA structure with CR8020 (PDB: 3SDY) shows extensive overlap and conservation of the structural mechanism of binding. Contacts with the epitope are observed for the CDR-H1, H2 and H3 of the heavy chain. Epitope of 3B10 on 2011 H3 HA is shown in red.

https://doi.org/10.1017/S1431927621009946 Published online by Cambridge University Press

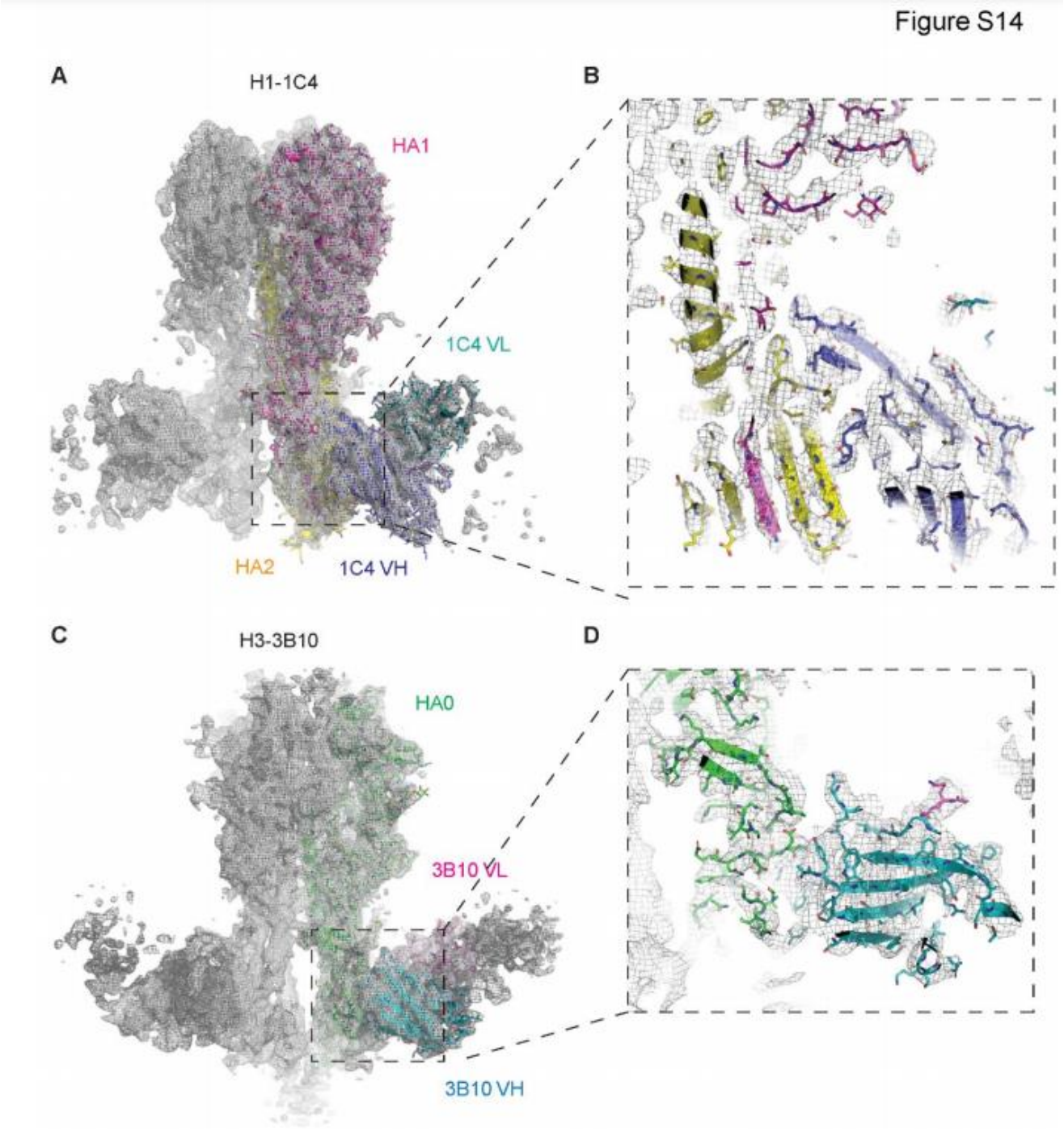

Figure 2. CryoEM maps and models of H1-1C4 and H3-3B10 complexes (A) cryoEM map and model of H1-1C4 complex, demonstrating the quality of the map and model of one of the asymmetric units of the trimer. (B) A zoomed-in view of the 1C4/HA interface. (C) cryoEM map and model of H3-3B10 complex, demonstrating the quality of the map and model of one of the asymmetric units of the trimer. (D) Zoomed-in view of the 3B10/HA interface. Contour levels for both cryoEM maps are set at 2σ.

References

Over max. Can be provided separately

https://doi.org/10.1017/S1431927621009946 Published online by Cambridge University Press