A PRE-FUSION, TRIMERIC SUBUNIT INFLUENZA HA-BASED VACCINE ELICITS CROSS-PROTECTION BETWEEN HIGHLY DIVERGENT INFLUENZA A VIRUSES

Christopher McMillan, Australian Infectious Disease Research Centre, School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia.
c.mcmillan1@uq.edu.au
Keith Chappell, Australian Infectious Disease Research Centre, School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia.
Stacey Cheung, Australian Infectious Disease Research Centre, School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia.
Daniel Watterson, Australian Infectious Disease Research Centre, School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia.
Kirsty Short, Australian Infectious Disease Research Centre, School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia.
Paul Young, Australian Infectious Disease Research Centre, School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia.

Despite our best efforts to vaccinate against influenza viruses they remain a major cause of morbidity and mortality worldwide, resulting in 3-5 million severe infections and more than 250,000 deaths annually. Constant antigenic changes in circulating viruses means current vaccines must be updated and re-administered annually. This approach is time-consuming and expensive, and is often hindered by mismatches between circulating and vaccine strains. Strain mismatch can contribute to insufficient vaccine efficacy, which has ranged from just 10-60% over the last decade. Furthermore, recent sporadic zoonotic outbreaks of novel highly pathogenic viruses from avian species, to which current vaccines provide no immunity, have been observed, with fatality rates around 40%. This raises serious concerns of a global pandemic with the potential to spread rapidly before a vaccine can be manufactured. Novel approaches to influenza vaccination are clearly needed in order to overcome these limitations with "universal" flu vaccines being the holy grail. We have stabilized recombinant influenza haemagglutinin (rHA) in its native, pre-fusion conformation by the addition of a novel "clamp" stabilization motif to enhance subunit vaccine potency and breadth of protection. Immunisation of mice with clamp-stabilized prefusion rHA elicited a potent neutralizing antibody response (~4-fold improvement over current vaccines). Most importantly, antibodies elicited upon immunisation with clamp-stabilised prefusion rHA showed an 80-fold increase in cross-reactivity to rHA derived from a divergent, highly pathogenic avian virus (H5N1) when compared to the current influenza vaccines. We have also shown that vaccination with clamp-stabilisted rHA based on the H3 subtype (group 2) is capable of providing cross-protection to a challenge with a highly-divergent group 1 virus (H1N1). Ultimately, this approach could represent a potential universal influenza vaccine, providing enhanced cross-protection against both group 1 and 2 seasonal influenza virus strains while simultaneously providing an increased cross-reactive humoral immune response to potential zoonotic pandemic strains.
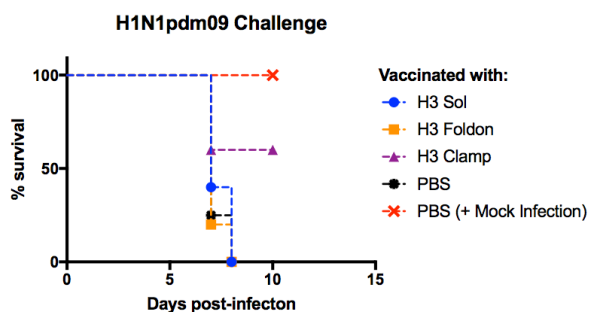
Figure 1 – Mice were vaccinated with rHA with (H3 Clamp) or without (H3 Sol) the molecular clamp trimerisation domain. A previously published influenza vaccine candidate utilizing the foldon trimerisation domain (H3 Foldon) was included as a direct comparison. Mice were challenged with a lethal dose of highly divergent H1N1pdm09 virus. Partial cross-protection was seen only in H3 clamp-vaccinated mice, but not with H3 Sol or H3 Foldon groups.