Protective swine influenza T cell epitopes can be identified using PigMatrix and are conserved in field strains from 2013 to 2017

Quantifying the persistence of vaccine T cell epitopes in circulating swine influenza strains from 2013 - 2017

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Introduction

When swine influenza vaccine and circulating strains are poorly matched, vaccine-induced antibodies may not protect, but highly conserved T-cell epitopes may still have a disease-mitigating effect. This is T cell-mediated protection.

Challenge

Can I predict if my vaccine will induce T cell-mediated protection against a new flu strain?

Rationale

Higher conservation = higher protection.

Conservation of T cell epitopes between vaccine and novel swine influenza A virus (IAV) strains is variable and may explain variability in vaccine efficacy.

Approach

Analyze the degree of epitope cross-conservation between a **T cell-directed DNA vaccine** (class I and II) and **1272 swine influenza** outbreak strains **over five years** (Figure 1) by **immunoinformatics** methods (Figure 2).

Results

Cross-conserved T cell epitopes are crucial to confer protection as viral sequence similarity changes from year to year (Figure 3). Whole proteome EpiCC score of all IAV field strains suggests that the epitope-based DNA vaccine is able to drive better CD4+ immune response by having cross-conserved T cell epitope content (Figure 4). Consistency of the area under the curve (AUC) relative to 2013 implies the T cell epitope in the prototype vaccine should be able to drive good immune response over time (Figure 5).

Conclusions

The higher the EpiCC score, the higher T cell epitope content relatedness to the vaccine of interest. This case study shows good coverage of flu strains by a single vaccine over many years.

Figure 1| Availability of swine IAV sequences from 2013 to 2017

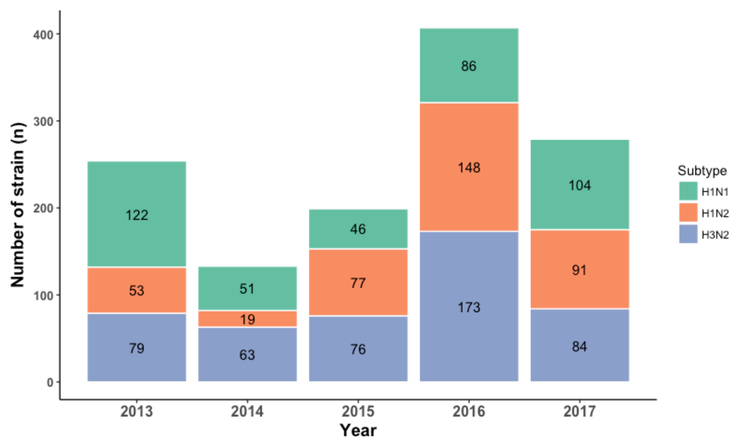
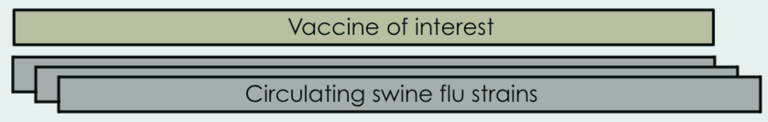


Figure 2| Summary of analyses flow and immunoinformatics tools

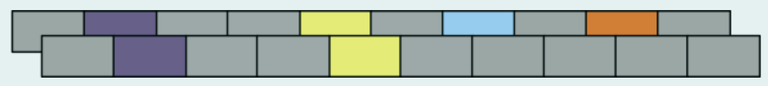


Conservation analysis (Conservatrix)

- 9-mer sequences were searched for identically matched segments and ranked by peptide conservation among IAV strains

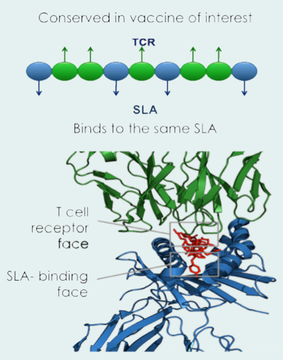
T cell epitope prediction (PigMatrix)

- Matrices that are built based on the pocket profile method using EpiMatrix **pocket profiles** for HLA epitope prediction and were designed based on the binding preferences of the best-matched HLA pocket for each **SLA pocket**.
- PigMatrix raw scores were standardized to Z-scores to compare potential epitopes across multiple SLA alleles. Peptides with Z-scores ≥ 1.64 (the top 5% of any given sample of 9-mers) were identified as likely to be SLA ligands.



Conservation at the TCR face (JanusMatrix)

- At the level of an SLA-bound peptide, JanusMatrix is applied to identify PigMatrix-predicted epitopes that are in contact with the SLA molecule itself while others are accessible to the TCR.
- Each epitope has two faces: a TCR-binding face (**green** amino acids); a SLA-binding face (**blue** amino acids).



T cell epitope content comparison (EpiCC)

- Built based on both PigMatrix and JanusMatrix
- Facilitates pairwise comparison of protein sequences based on T cell epitope content rather than sequence identity
- Capable to classify swine IAV strain relatedness to estimate cross-protective potential of a vaccine strain for circulating viruses

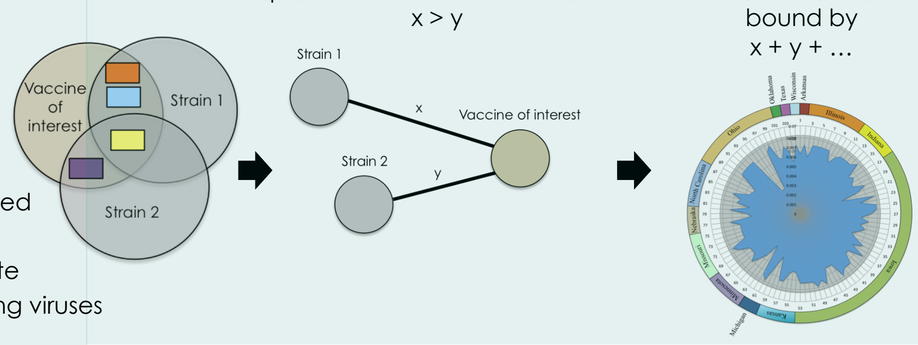
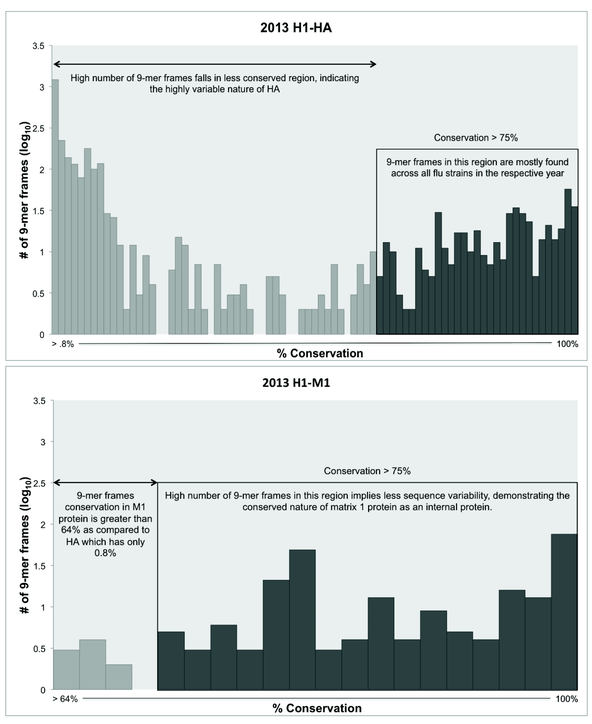


Figure 3| Relatedness of IAV strains to the DNA epitope-based vaccine



- High degree of variability of 9-mers in HA (surface antigen) and M1 (conserved antigen) over time
- T cell response could vary
- This illustrates the importance of selecting conserved T cell epitope

Figure 4| T cell epitope conservation between the T cell-directed multi-epitope DNA vaccine against swine IAV circulating strains over five years

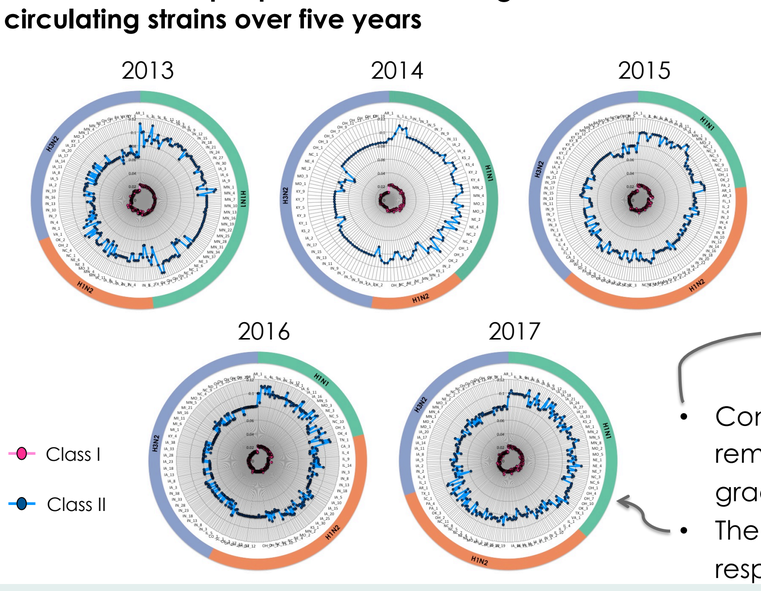
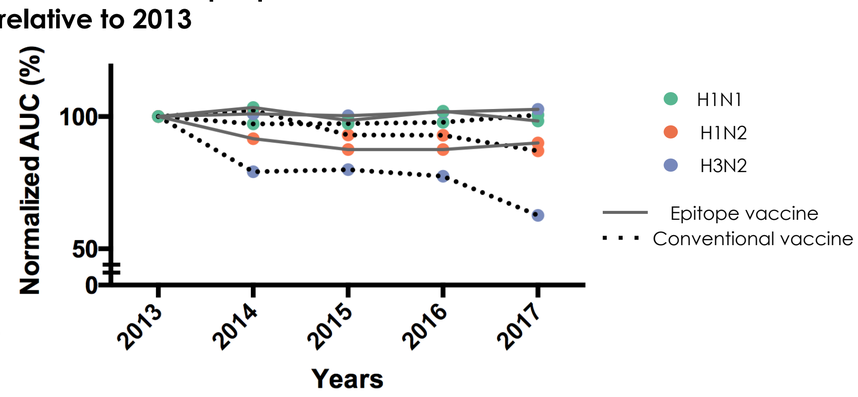


Figure 5| T cell epitope content conservation comparison (HA) of the T cell multi-epitope DNA vaccine and conventional vaccines relative to 2013



- Conservation of T cell epitope content of the multi-epitope DNA vaccine remains high and steady compared to conventional vaccines that gradually reduce over time
- The multi-epitope DNA vaccine is able to drive better CD4 immune response

References:

1) Gutiérrez, A. H., C. Loving, L. Moise, F. E. Terry, S. L. Brockmeier, H. R. Hughes, W. D. Martin, and A. S. De Groot. 2016. In vivo validation of predicted and conserved T cell epitopes in a swine influenza model. PLoS One 11.
2) Gutiérrez, A., Rapp-Gabrielson, V., Terry, F., Loving, C., Moise, L., Martin, W., & De Groot, A. (2017). T-cell epitope content comparison (EpiCC) of swine H1 influenza A virus hemagglutinin. Influenza and Other Respiratory Viruses, 11(6), 531-542.
3) https://www.npr.org/sections/health-shots/2019/06/11/729314248/to-save-the-science-poster-researchers-want-to-kill-it-and-start-over

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