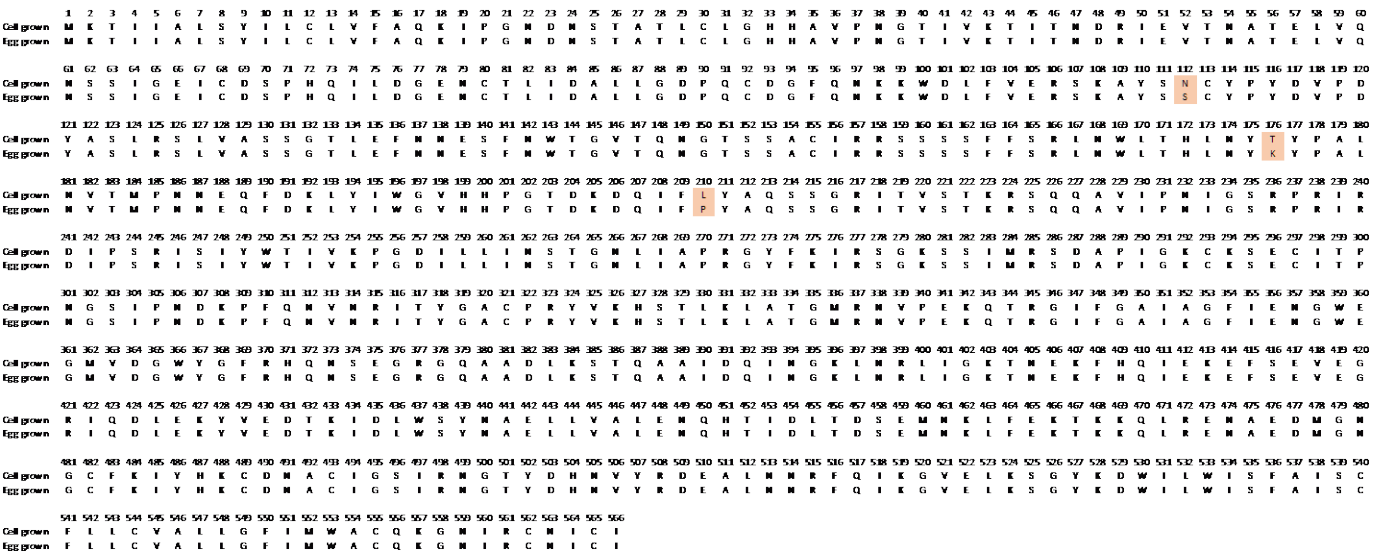
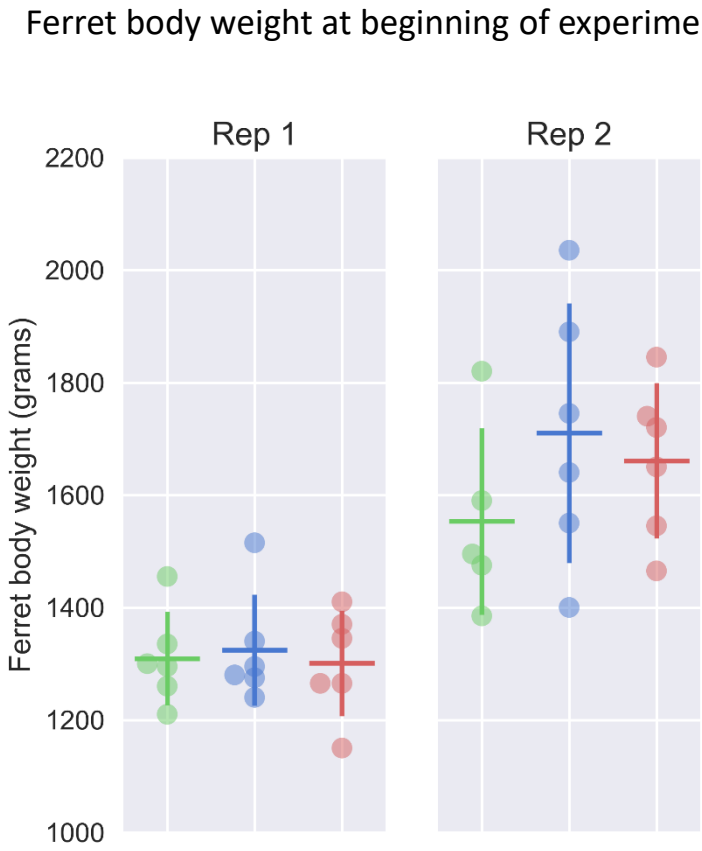
Supplementary Figure 1

Sequences of cell- and egg-grown A/Hong Kong/4801/2014(H3N2)



**Supplementary Figure 1. Sequence of hemagglutinin from egg- and cell-grown A/Hong Kong/4801/2014(H3N2).** Virus stocks used in these experiments were sequenced to confirm the absence of unexpected mutations. The expected egg-adaptive mutations N96S, L194P, and T160K are highlighted.

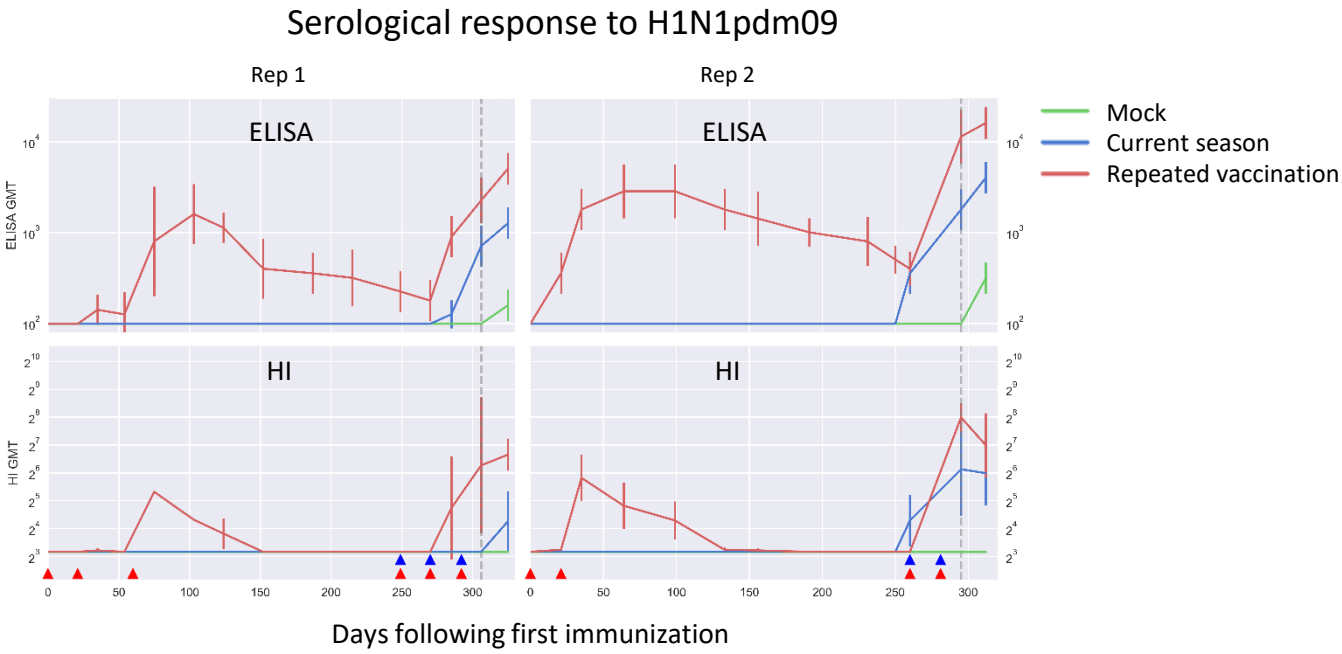
Supplementary Figure 2




**Supplementary Figure 2. Ferret body weights at the onset of the experiments.** Each dot represents one ferret; horizontal bars represent mean values; error bars represent one standard deviation.

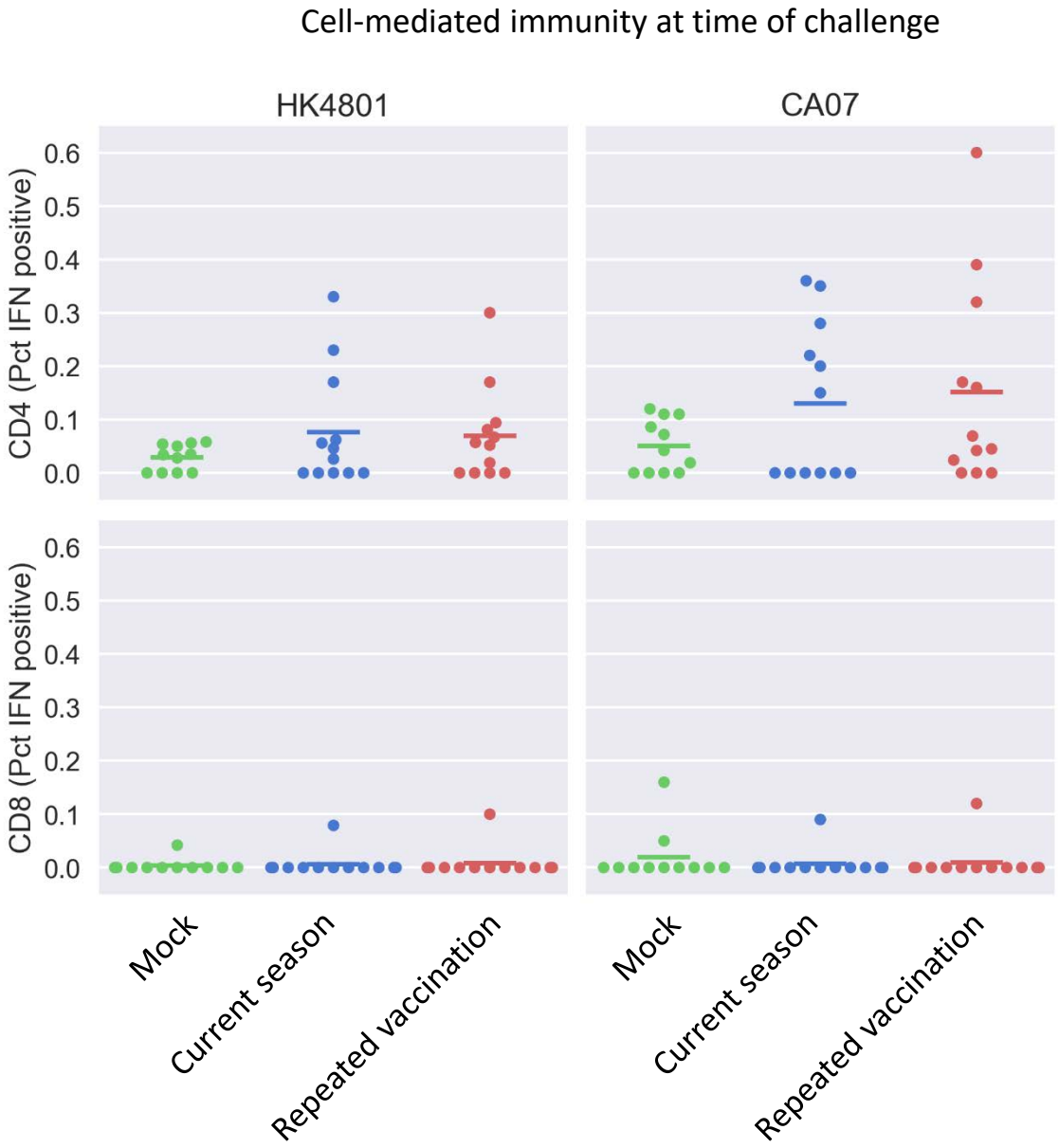
Supplementary Figure 3

A



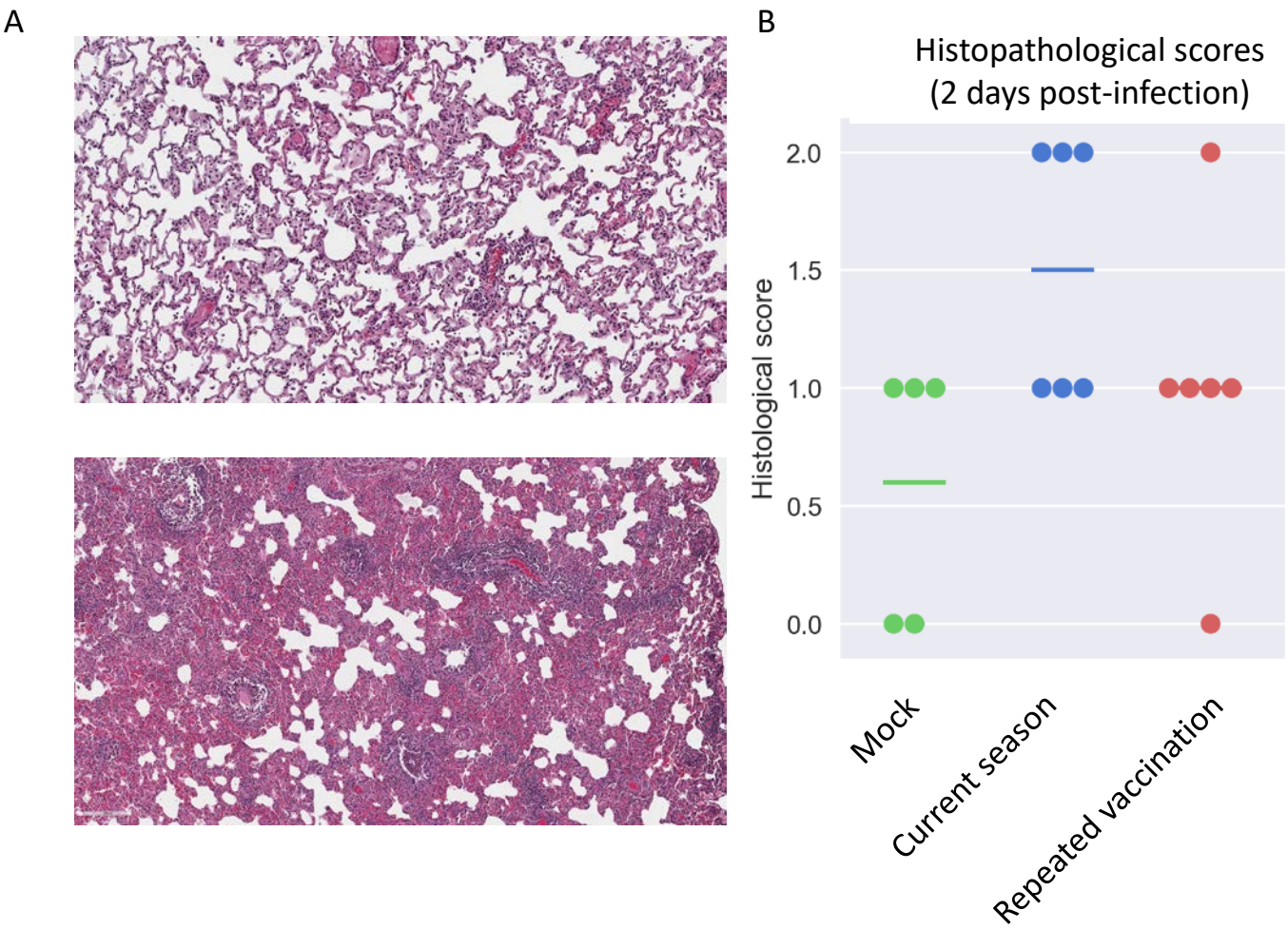

**Supplementary Figure 3. Serological responses to (H1N1)pdm09.** Ferrets were vaccinated with commercial quadrivalent inactivated vaccine (QIV) containing (Rep 1) A/California/07/2009 (H1N1)pdm09 or (Rep 2) the antigenically similar A/Michigan/45/2015 (H1N1)pdm09 as well as HK/4801. Geometric mean titers against CA/07 measured by ELISA (top panels) or HI (bottom panels) are shown

Supplementary Figure 4



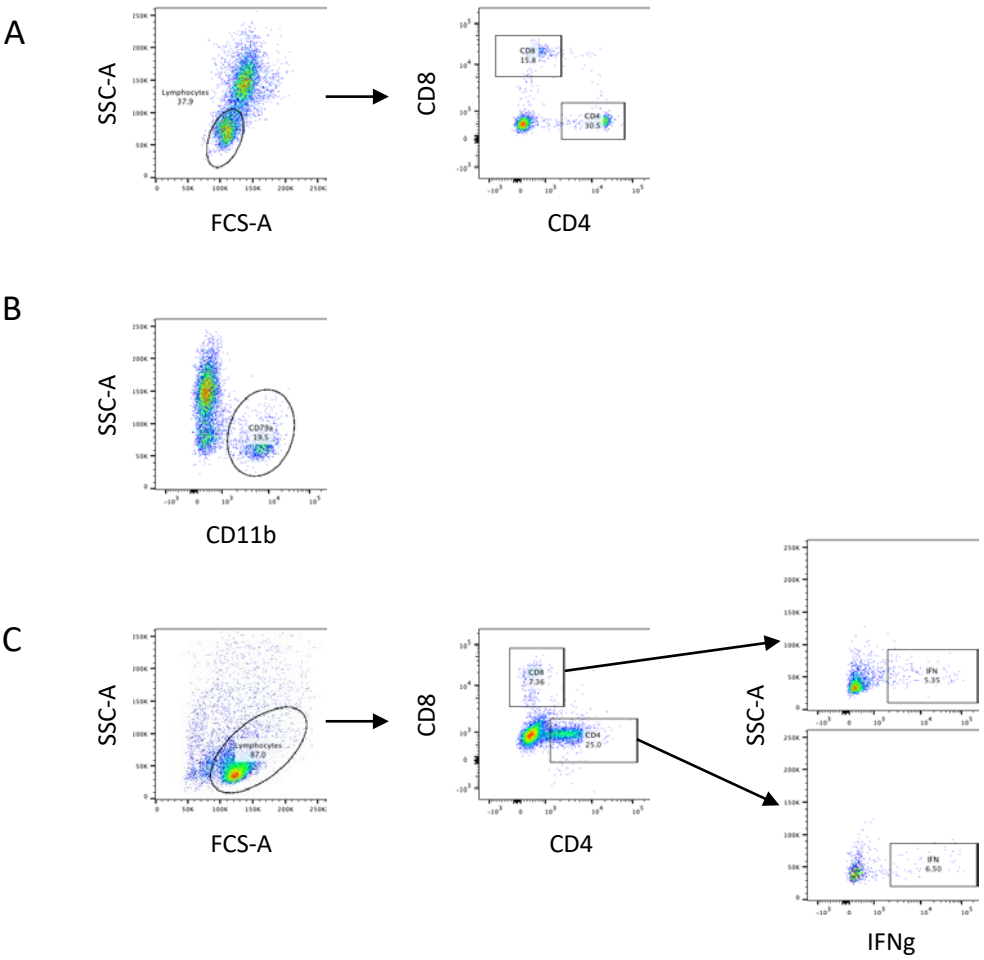

**Supplementary Figure 4. Cell mediated immunity before influenza challenge.** Following immunization with QIV by the various regimens as described, peripheral blood leukocytes were collected and the percent of CD3/CD4+ (top row) or CD3/CD8+ (bottom row) T cells expressing interferon-γ after overnight stimulation with HK/4801(H3N2) (left panels) or influenza A/California/07/2009(H1N1pdm09) (right panels) was measured by flow cytometry. The difference between groups was not statistically significant ($p > 0.05$). Each dot represents an individual ferret; the bar represents the mean for each group.

Supplementary Figure 5




**Supplementary Figure 5. Histopathologic evaluation of ferret tissues.** Two days after intranasal challenge with cell-grown HK/4801, three ferrets per group were sacrificed and lungs were collected and processed for histopathology. **(A)** Representative tissue samples to illustrate the range of inflammation seen. The upper panel shows focal mild perivascular infiltrates. The lower panel shows moderate interstitial and perivacular infiltrates. (Hematoxylin and Eosin stain, Scale Bars: 100 mm) **(B)** Each lung sample was given a score based on degrees of inflammation (0 = no inflammation; 1 = mild inflammation; 2 = moderate inflammation). Each dot represents an individual ferret; the bar represents the mean for each group. The difference between groups was not statistically significant ($p > 0.05$). Each dot represents an individual ferret; the bar represents the mean for each group.

Supplementary Figure 6




**Supplementary Figure 6. Gating strategies for flow cytometry. (A)** For peripheral blood lymphocyte counts, lymphocytes were selected based on forward and side scatter, and T lymphocytes were stained with anti-CD4 and anti-CD8. **(B)** For peripheral blood granulocyte counts, granulocytes were stained with CD11b. **(C)** For intracellular cytokines, following stimulation and permeablization, lymphocytes were selected based on forward and side scatter, T lymphocytes were gated using anti-CD4 and anti-CD8, and stimulated cells were identified with intracellular interferon γ staining.