Immunity to Influenza Infection

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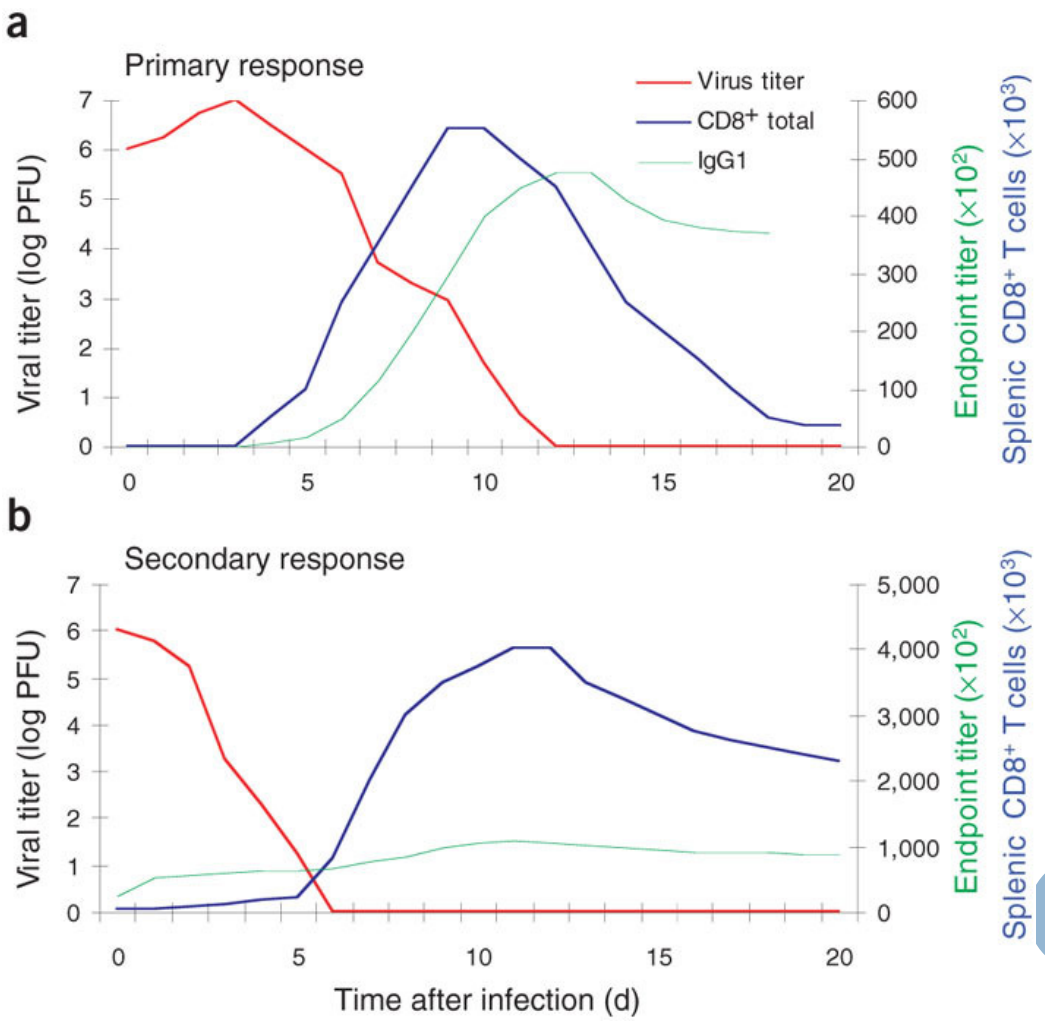
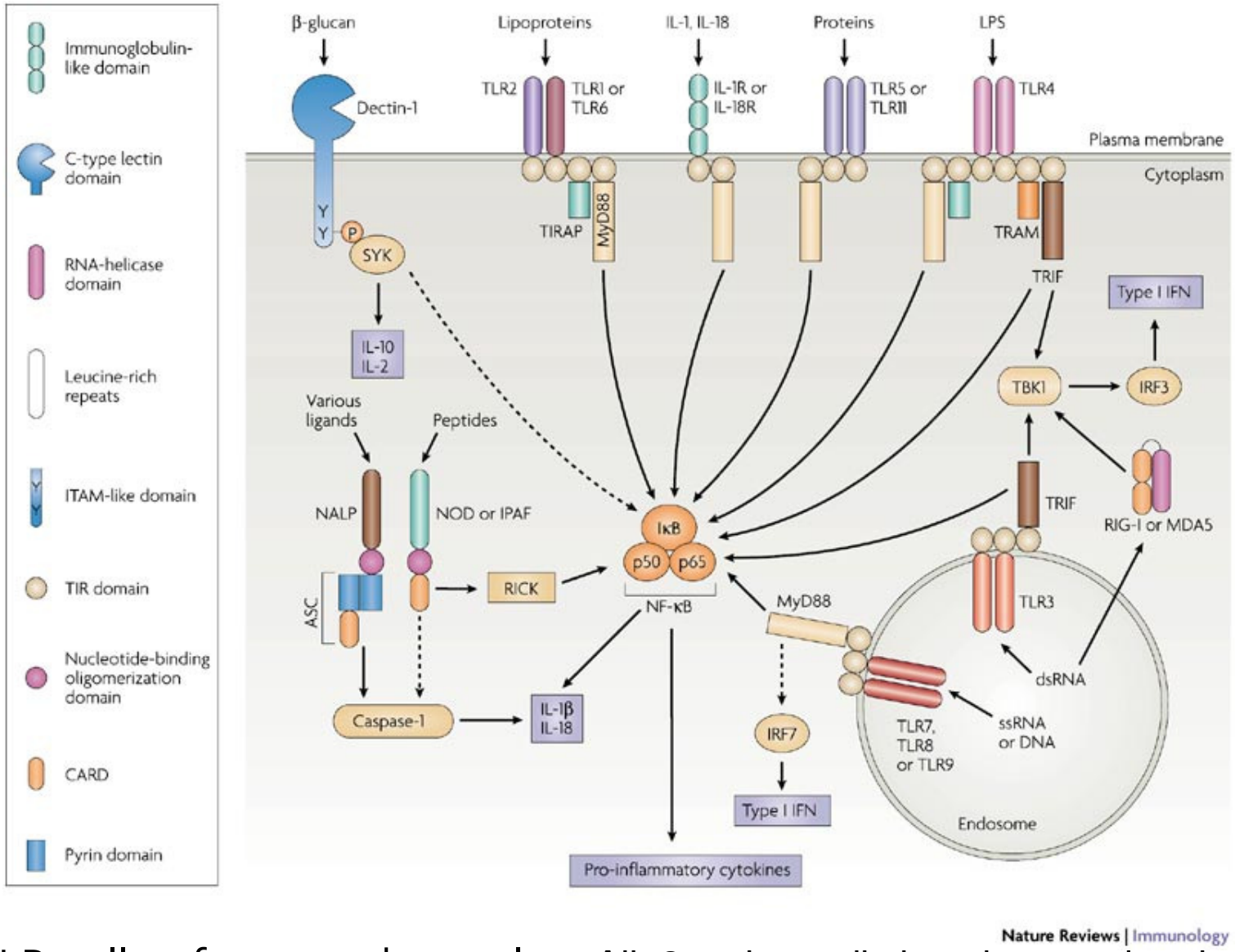
COURSE OF INFLUENZA INFECTION

- Influenza is initially controlled by antibody and CD8+ T cells
- Secondary infection with heterologous virus is cleared with CD8+ T cell activity much more rapidly
- Homologous infection can be prevented by antibody (sterilizing immunity)



Innate Immune Pattern Recognition

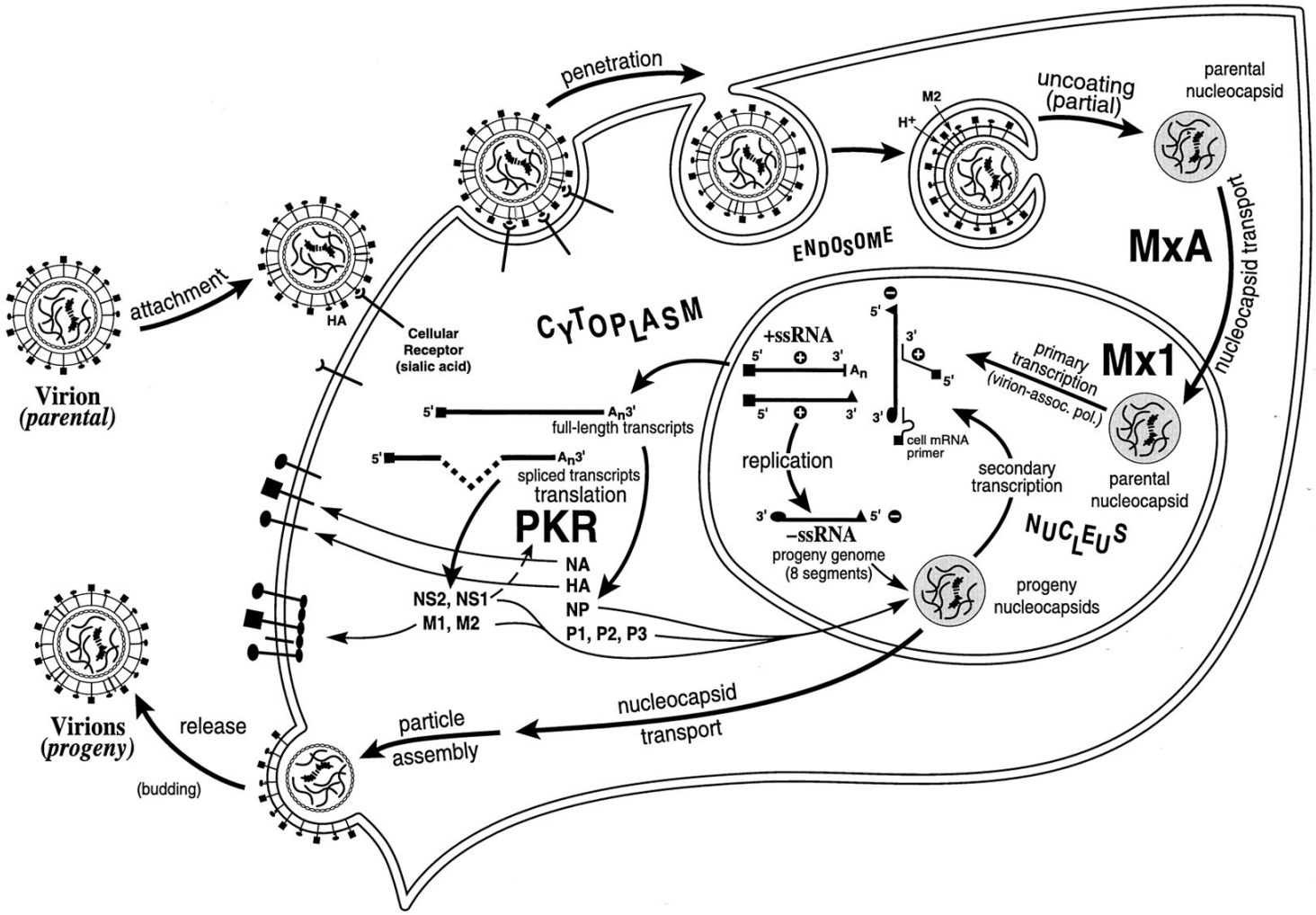


Nature Reviews | Immunology

- TLR: cell surface or endosomal
- NLR and RLR: cytoplasmic

All 3 activate distinct, but overlapping, host response pathways

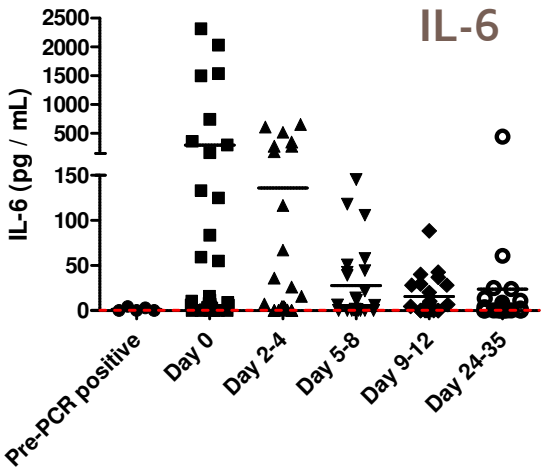
Schematic diagram of the influenza virus multiplication cycle including sites of action of the IFN-induced Mx and PKR proteins.

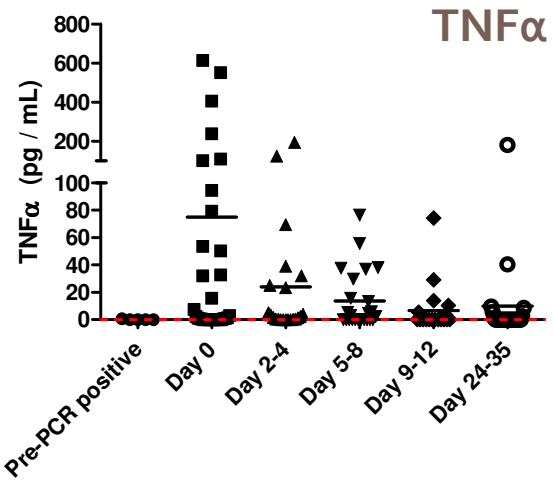


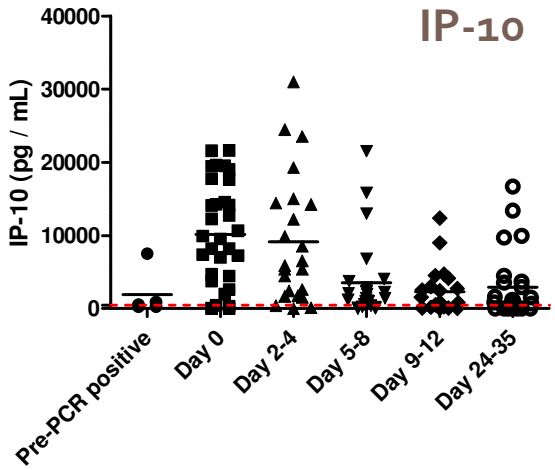
Samuel C E Clin. Microbiol. Rev. 2001;14:778-809

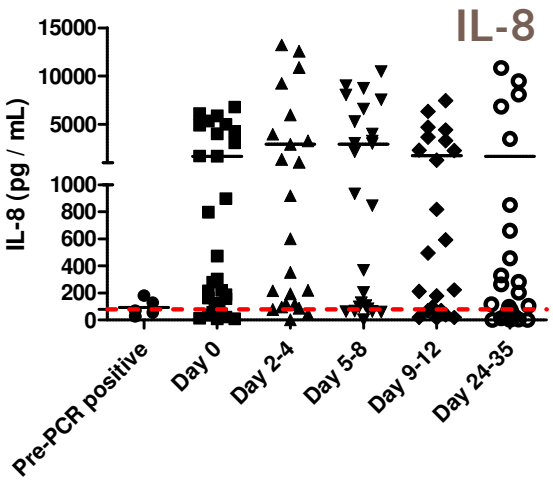
NASAL WASH CYTOKINES AND CHEMOKINES:

TYPICAL INFLAMMATORY MEDIATORS ARE INCREASED FOLLOWING INFLUENZA A INFECTION



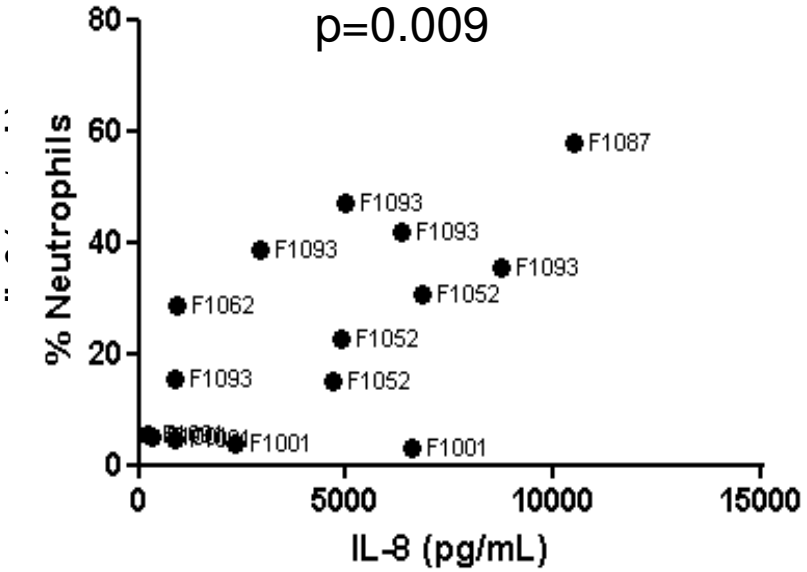


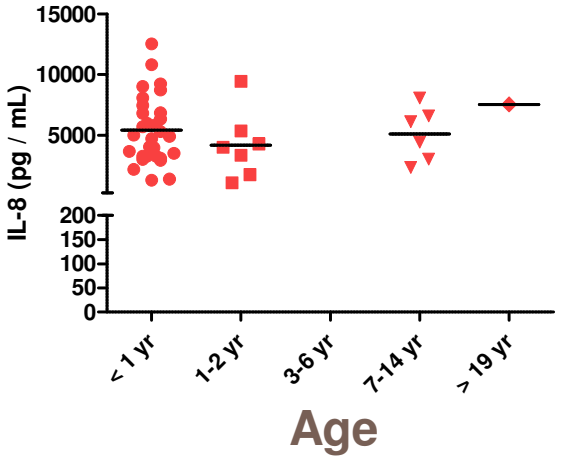


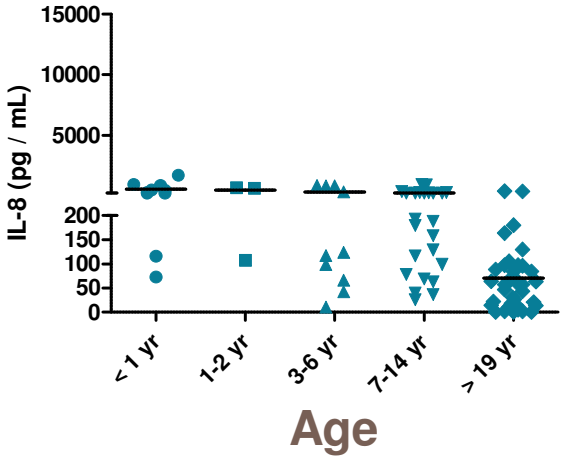


~100x plasma levels from patients

POTENTIAL AGE-ASSOCIATED DIFFERENCES



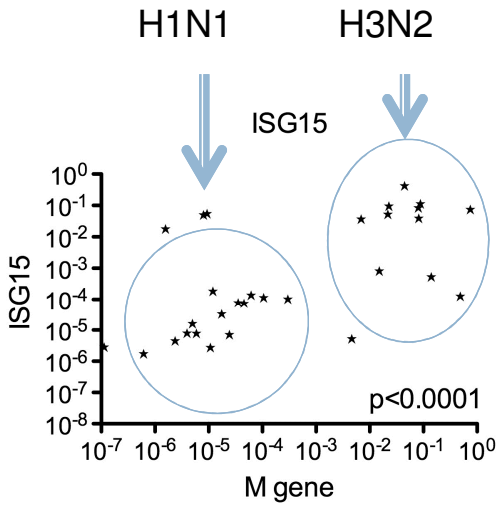




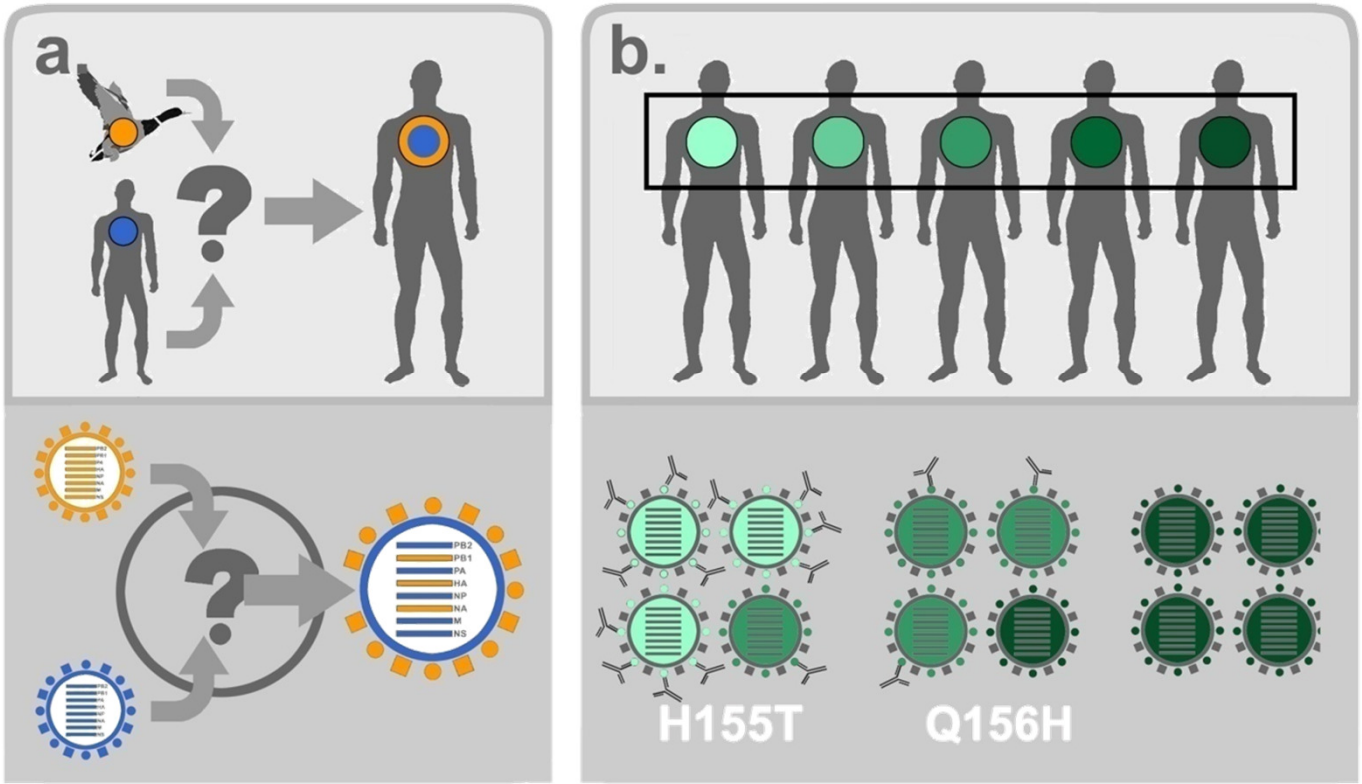
Strong association between age, IL-8 production and neutrophil recruitment.

INNATE RESPONSES AS A FUNCTION OF VIRUS

- qRT-PCR multiplex measurements of a panel of innate immune mediators in nasal wash pellets
- Not separated by cell type
- Include viral M-gene to normalize viral titer

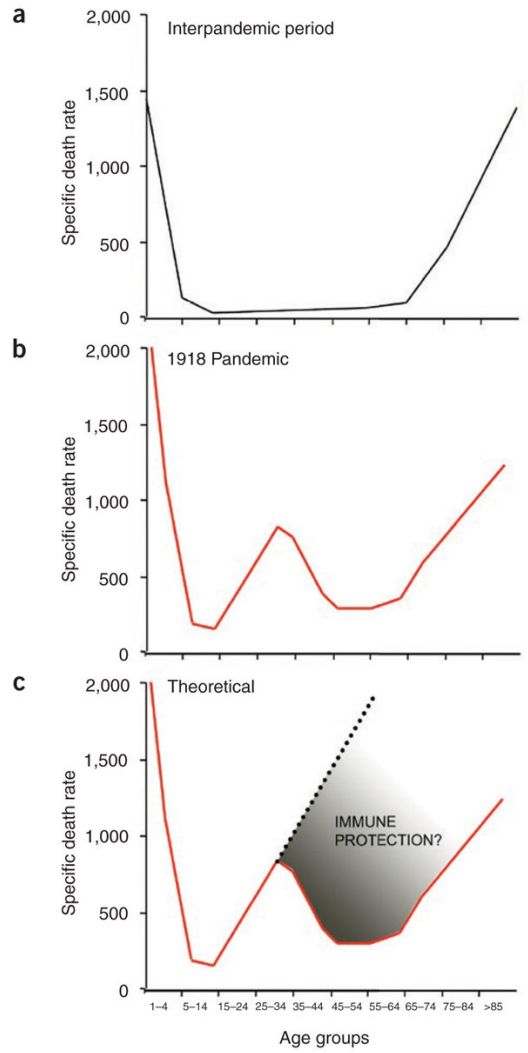


Influenza evolution by Antigenic Shift and Antigenic Drift

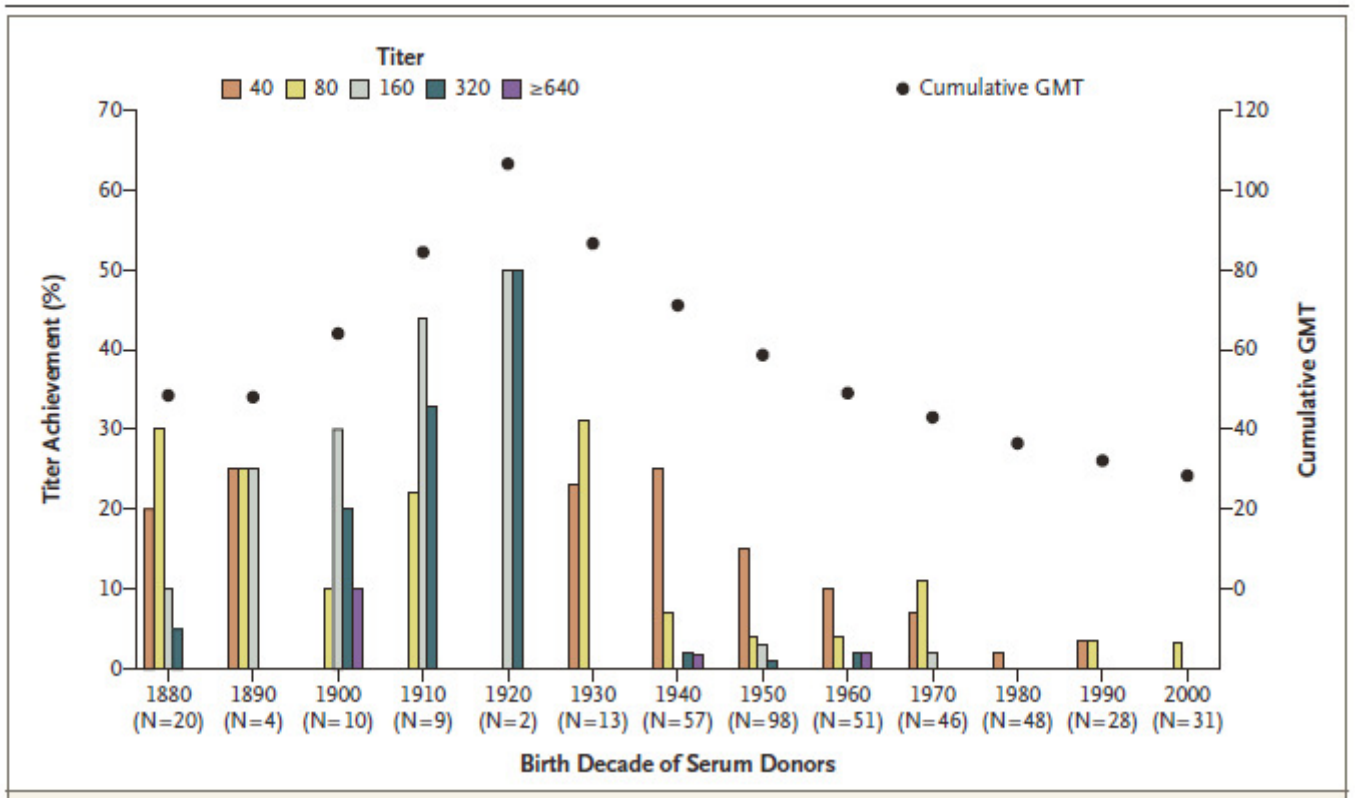


1918 (AND POSSIBLY SWORH1N1) MORTALITY CURVES SUGGEST PREVIOUS EXPOSURE

- The "U" shaped curve of regular influenza infection demonstrates the highest mortality among children (naïve) and the elderly (immunocomprimised)
- The 1918 pandemic had a "W" shaped curve, with a spike in deaths among young adults—immunopathology or prior protection for ~40 year olds?



PEOPLE BORN PRIOR TO 1940 HAVE "PROTECTIVE" LEVELS OF ANTIBODY TO 2009/H1N1



The NEW ENGLAND JOURNAL of MEDICINE

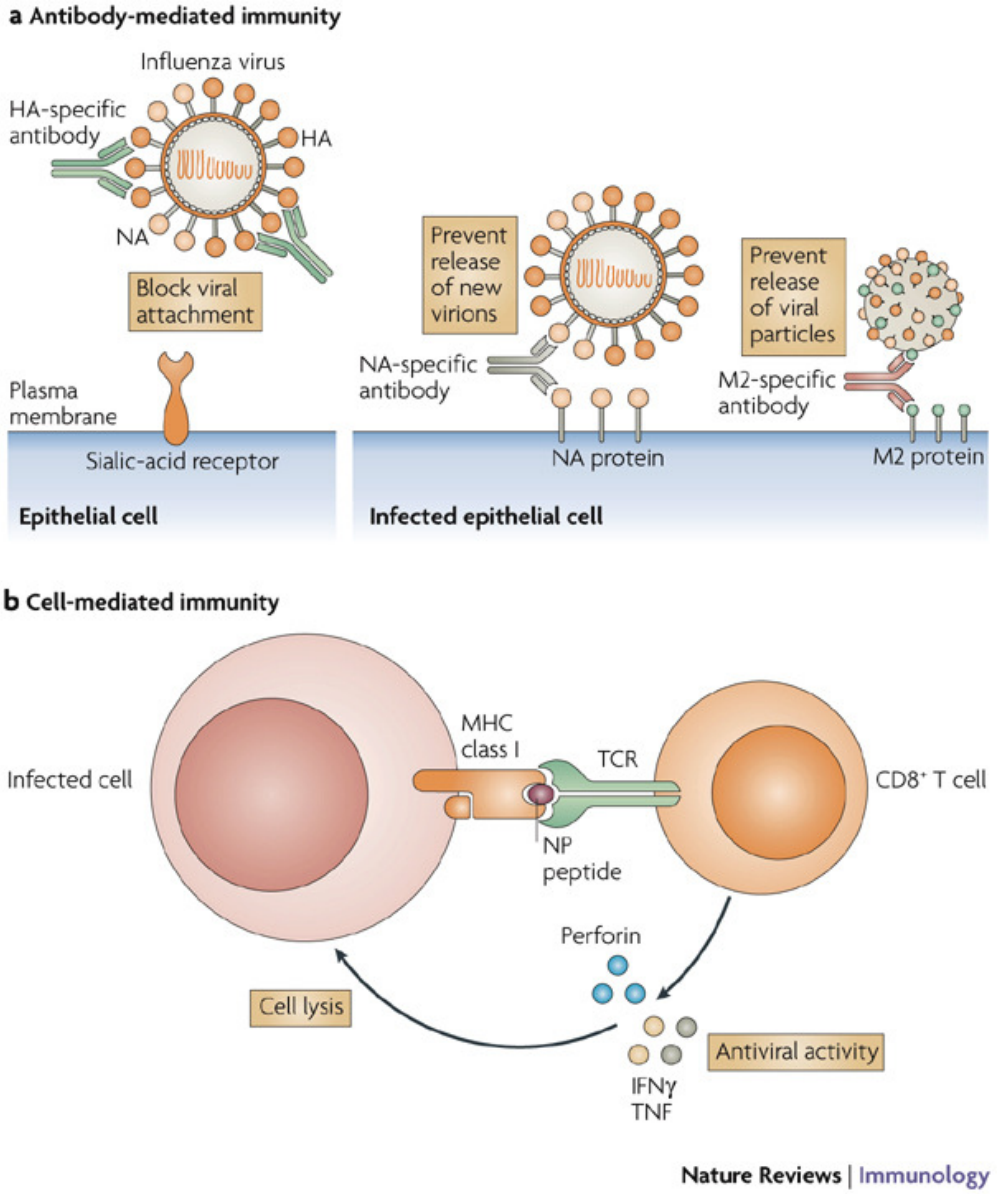
ORIGINAL ARTICLE

Cross-Reactive Antibody Responses to the 2009 Pandemic H1N1 Influenza Virus

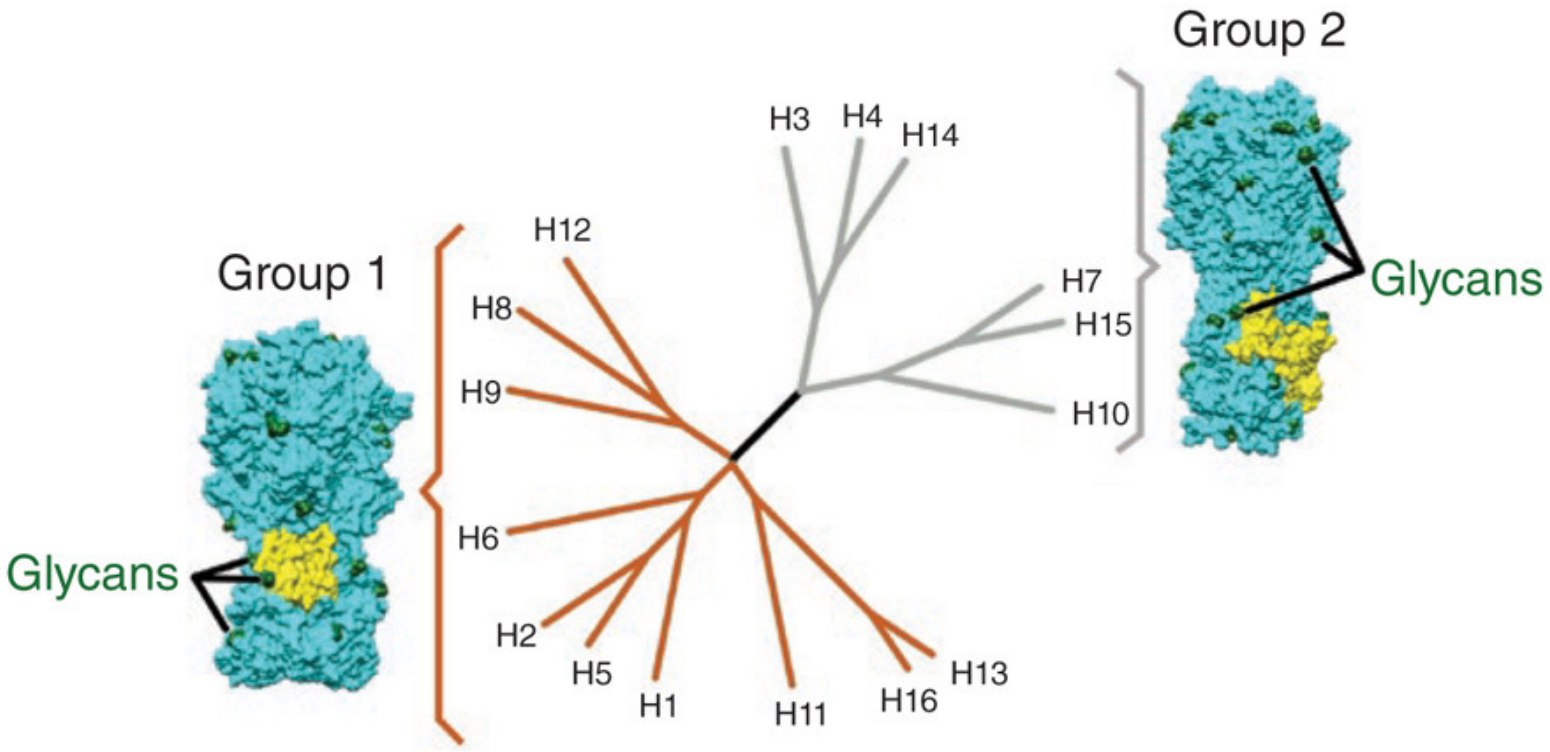
Kathy Hancock, Ph.D., Vic Veguilla, M.P.H., Xiuhua Lu, M.D., Weimin Zhong, Ph.D., Eboneé N. Butler, M.P.H., Hong Sun, M.D., Feng Liu, M.D., Ph.D., Libo Dong, M.D., Ph.D., Joshua R. DeVos, M.P.H., Paul M. Gargiullo, Ph.D., T. Lynnette Brammer, M.P.H., Nancy J. Cox, Ph.D., Terrence M. Tumpey, Ph.D., and Jacqueline M. Katz, Ph.D.

Immune Mechanisms of Protection

- Antibody mediated immunity exerts the most pressure on the virus, leading to seasonal antigenic drift and pandemic strains of antigenic shift
- Internal proteins are relatively conserved allowing heterologous cellular protection
- Mutation of dominant CD8 epitopes over time suggests that CTLs provide immunological pressure



UNIVERSAL ANTIBODIES AGAINST THE HA



Conserved structures (mainly in the HA stalk) may provide an invariant target for vaccination and therapeutics

Nature Medicine
16, 1389–1391 (2010)
doi:10.1038/nm1210-1389

THANKS FOR THE MEMORIES…

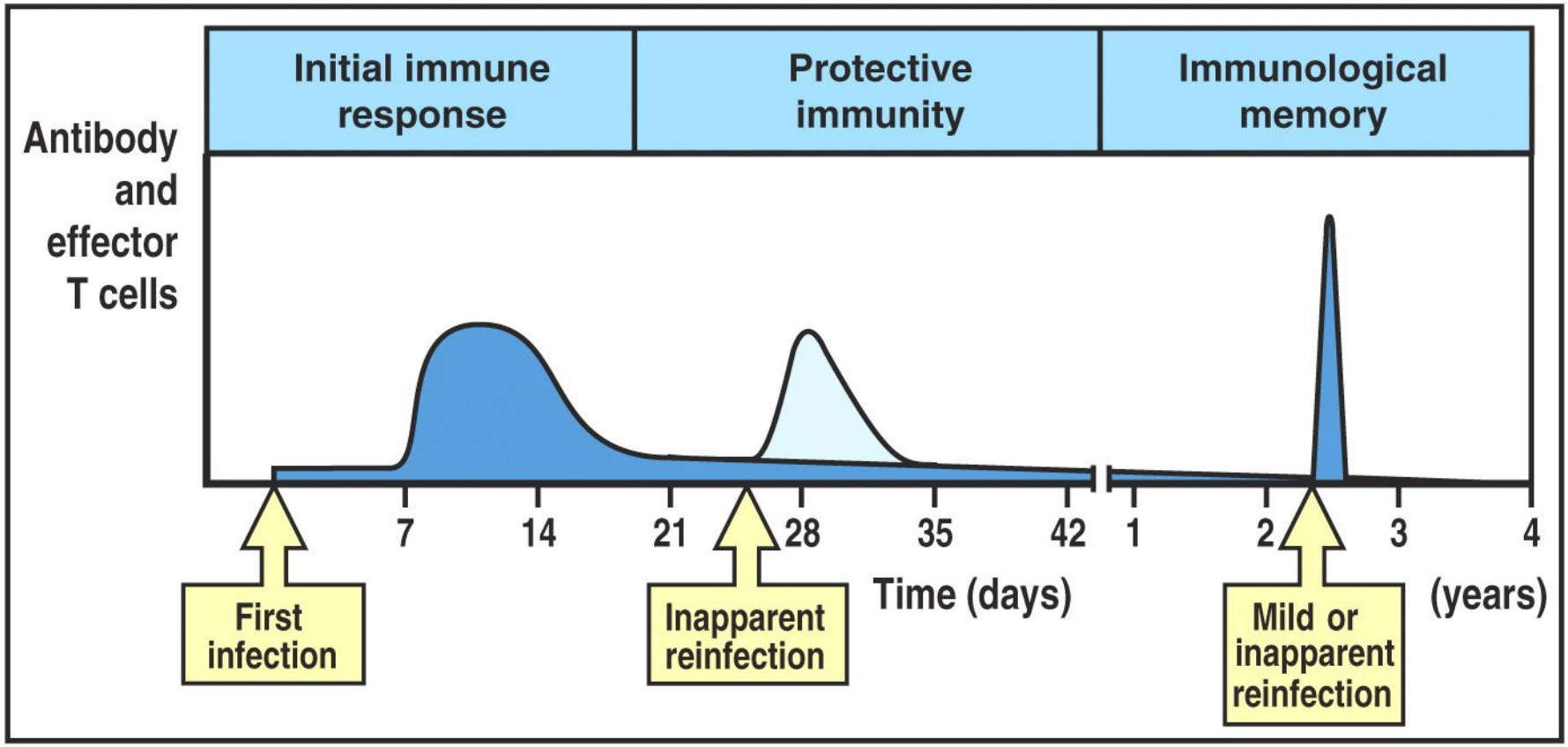
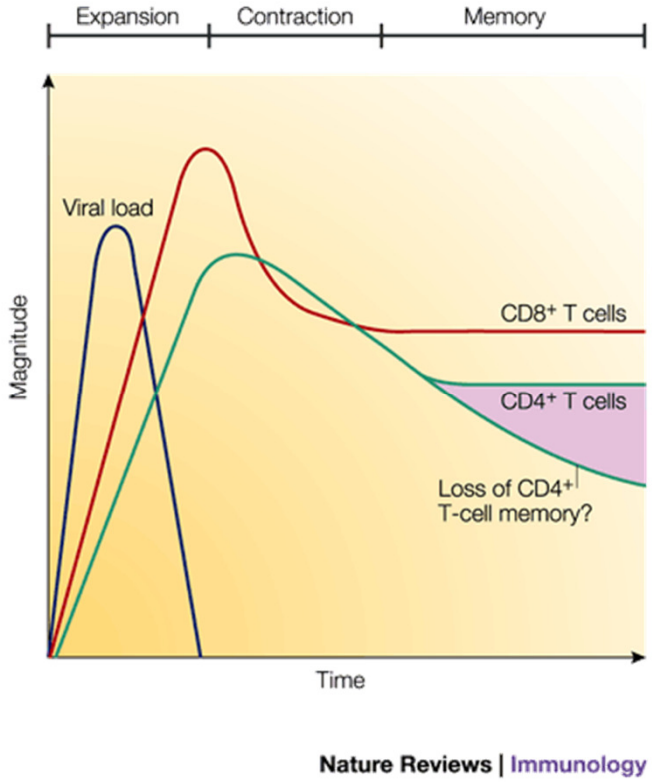


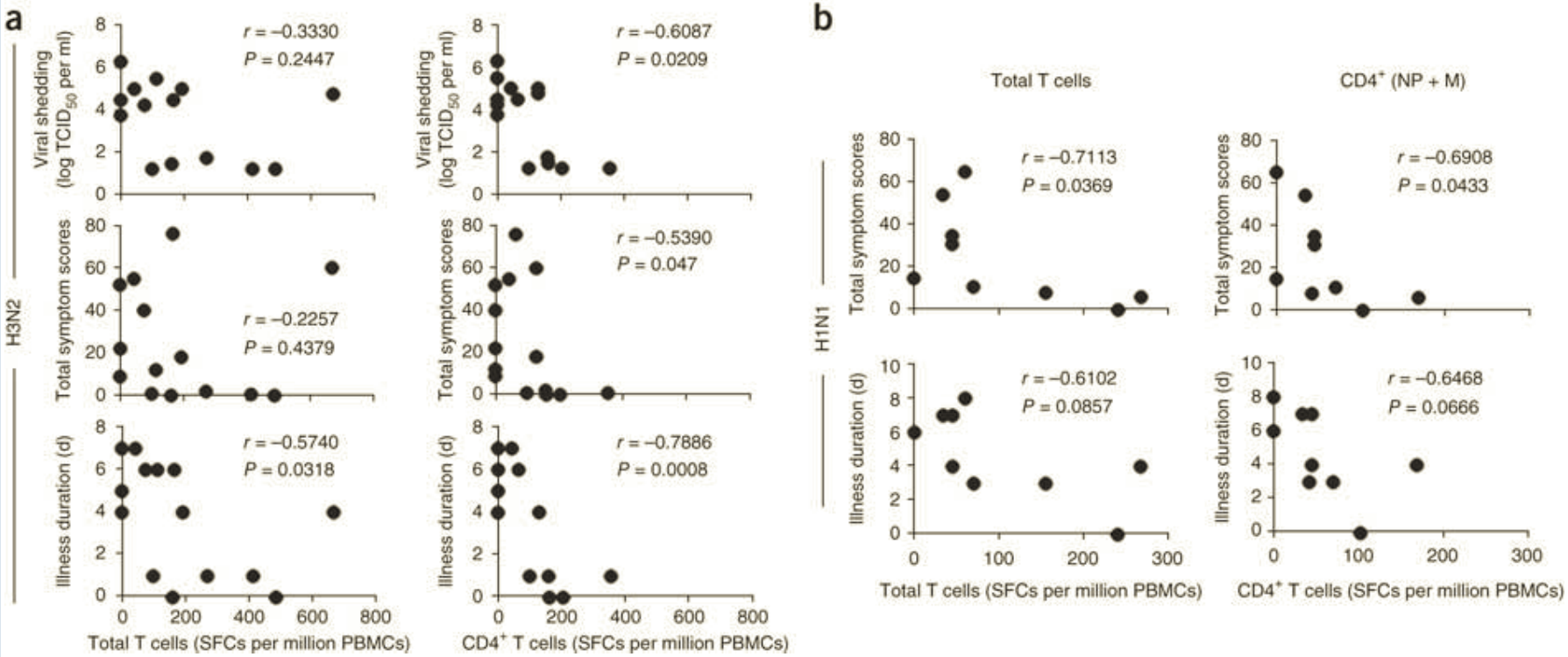
Figure 10-18 Immunobiology, 6/e. (© Garland Science 2005)

Memory

- After contraction, memory CD8 numbers are maintained (active process) while CD_4 cells slowly decline
- Higher precursor numbers are a key feature of memory
- Memory cells more rapidly acquire effector function and have lower thresholds of activation

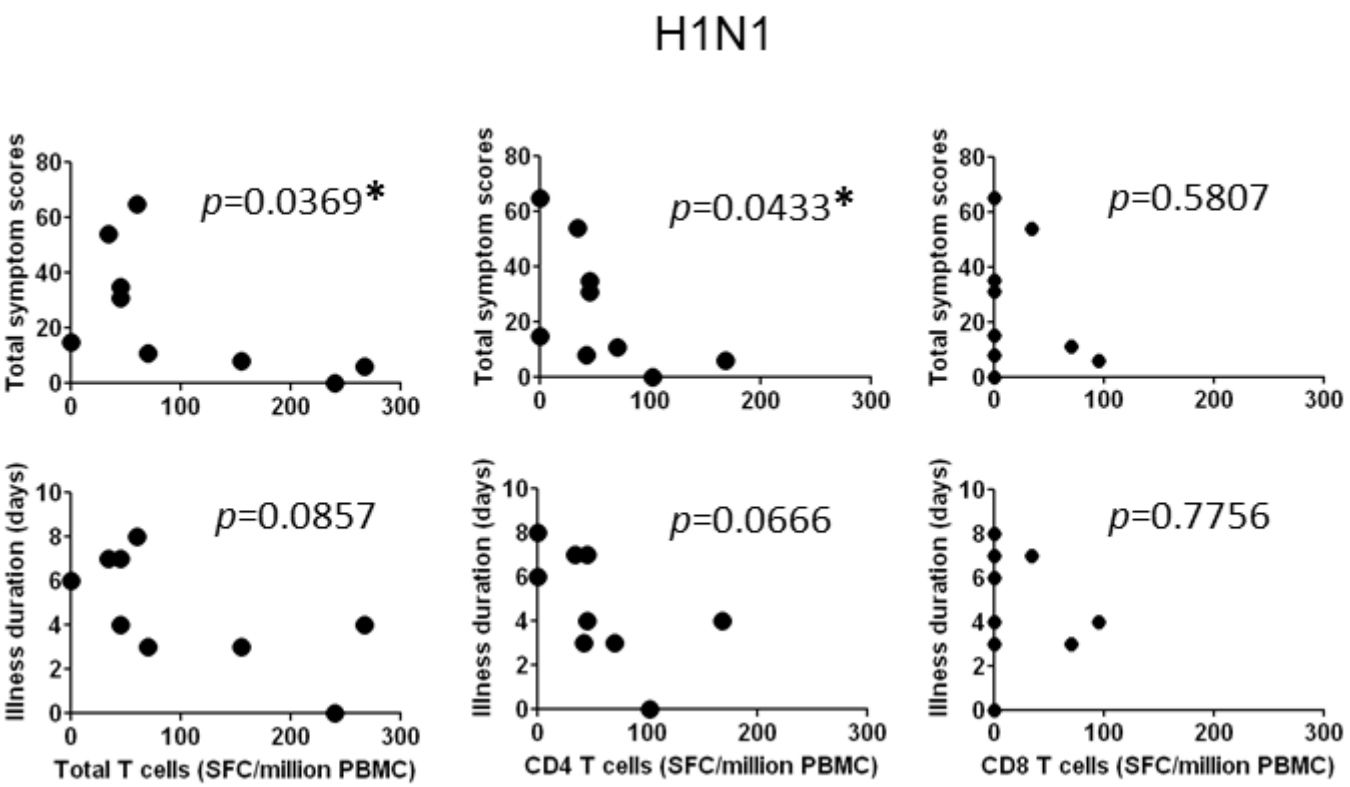


Correlation between CD4+ T cells and Illness outcomes in Experimental Challenge



Nature Medicine 18, 274–280 (2012)
doi:10.1038/nm.2612

CD8 CELLS DID NOT SHOW A SIMILAR CORRELATION



Methods for Measuring immune responses

- Innate
  - Cytokine levels in the blood (serum or plasma)
  - Flow cytometric analysis of cell populations in blood
  - Nasal wash or BAL of infected individuals (cells, cytokines)
- Antibody
  - Microneutralization assay
  - HI assay
  - ELISA
  - *In vivo* challenge
- T cell
  - Tetramer staining (requires HLA typing and known epitopes)
  - ELISPOT (does not require HLA, can be used to map epitopes)
  - Intracellular cytokine staining (high throughput, sample quality can be an issue)