The virus-immunity ecosystem

P. C. Doherty[1,2] and **S. J. Turner**[1]

[1]Department of Microbiology and Immunology, University of Melbourne, Victoria, Australia
[2]Department of Immunology, St Jude Children's Research Hospital, Memphis, TN, U.S.A.

Summary. The ecology of pathogenic viruses can be considered both in the context of survival in the macro-environments of nature, the theme pursued generally by epidemiologists, and in the micro-environments of the infected host. The long-lived, complex, higher vertebrates have evolved specialized, adaptive immune systems designed to minimise the consequences of such parasitism. Through evolutionary time, the differential selective pressures exerted variously by the need for virus and host survival have shaped both the "one-host" viruses and vertebrate immunity. With the development of vaccines to protect us from many of our most familiar parasites, the most dangerous pathogens threatening us now tend to be those "emerging", or adventitious, infectious agents that sporadically enter human populations from avian or other wild-life reservoirs. Such incursions must, of course, have been happening through the millenia, and are likely to have led to the extraordinary diversity of recognition molecules, the breadth in effector functions, and the persistent memory that distinguishes the vertebrate, adaptive immune system from the innate response mechanisms that operate more widely through animal biology. Both are important to contemporary humans and, particularly in the period immediately following infection, we still rely heavily on an immediate response capacity, elements of which are shared with much simpler, and more primitive organisms. Perhaps we will now move forward to develop useful therapies that exploit, or mimic, such responses. At this stage, however, most of our hopes for minimizing the threat posed by viruses still focus on the manipulation of the more precisely targeted, adaptive immune system.

Introduction

Vertebrates are large, complex multi-cellular, multi-organ systems. In nature, each of us functions as sets of ecological niches for the support of simpler life forms. Our most intimate passengers are the viruses, which only replicate in living cells. Many commensal organisms live in balance on skin and mucosal surfaces. Some

of these apparently innocuous companions are clearly held in check by specific host response mechanisms, as they will invade and cause disease and death when the capacity to mount an effective T cell response is compromised by, for example, HIV/AIDS . This is also true for highly adapted pathogens like Epstein Barr virus (EBV), which may cause infectious mononucleosis following initial exposure, then persists as a substantially latent infection that can drive oncogenesis subsequent to loss of immune control [83]. Clearly, EBV has developed molecular strategies through evolutionary time that facilitate both spread and long-term carriage [69].

It is, in fact, reasonable to think that the current character of the human immune system has been partly shaped by the continuing relationship with EBV and the other herpesviruses that persist in our lymphoid cells and neurons. There can be little doubt that the evolution of adaptive immunity, which first appears with the jawed fishes about 350×10^6 years ago [93], has been driven by the need to deal with infection [34, 68]. The molecular mimics of, for instance, cytokine and chemokine receptors that are found in the large, complex, DNA viruses indicates that the reverse may also be true for many one-host pathogens [94, 116]. Such stable parasitism reflects reciprocal relationships developed through the long march of phylogeny.

Emergence and persistence in macro and micro environments

Pathogens that grow in a variety of hosts are less likely to have achieved a long-term interaction with us and can thus be very dangerous when encountered for the first time. Much of Bob Shope's research career [109, 110] focused on arboviruses that are maintained in wildlife reservoirs and cause only incidental infection of humans. Many totally new viruses were discovered as a consequence of, for example, the Rockefeller Foundation-funded programs of 1950–1970. Some, like Ross River virus [41] were only found to be causative agents of human disease by retrospective analysis of stored serum samples. The arbovirology community of this era included many who were as at home in tropical rain forests as in the laboratory.

Unlike the human herpesviruses, the mosquito-borne viruses that are normally maintained in (for example) birds have been under no selective pressure to accommodate to human immune response mechanisms. The same may be true for many of the "emerging" pathogens that impact on humans and domestic animals suddenly, or sporadically, as a consequence of changes in culture, behaviour and/or environment. The need to deal effectively with this enormous spectrum of novel infectious agents is likely to have been one factor driving the extreme diversity of both the B cell (immunoglobulin) and T cell receptor (TCR) families [1, 7, 42]. Another may be the rapid variation associated with the error-prone copying mechanisms of some RNA viruses. Furthermore, as the T cells focus on complexes (epitopes) formed by the binding of processed viral peptides to major histocompatibility complex (MHC) molecules [131], the extreme polymorphism of the MHC [34, 92] can also be considered to reflect the evolutionary need to attach previously un-encountered spectra of peptides to one or another MHC glycoprotein.

The characteristics of viral emergence and persistence can thus be considered in two independent, though not necessarily unrelated, contexts. The first is in the broad environmental sense that considers such factors as climate, rainfall, forest management, vector and reservoir distribution, changing demographic profiles and so forth. The second concerns the environment within, whether "within" be infected cells and organs in arthropods, vertebrates or humans. Some determining factors are virus growth characteristics, virus escape mechanisms, immune receptor (antibody or TCR) specificity and diversity, immune selective pressure, antigen presentation characteristics, lymphocyte proliferation rates and the quality of immune effector function, both at the cell and the molecular level. When it comes to the practical consideration of developing protective vaccines, it is also necessary to think about the nature and durability of immune memory [21, 40, 115].

This brief discussion concentrates on adaptive immunity, the spectrum of precisely targeted host response mechanisms that maintain the functional integrity of the environment "within" subsequent to virus challenge. It ignores the innate immune system, which may be of great importance in the early stage of infection with some viruses, particularly the herpesviruses [71], but is neither conventionally antigen specific nor capable of generating the long-term memory that is the basis of immunization. Of course, both aspects of immunity work together. The themes of cytotoxic effector function [30] and localized cytokine production [95, 103], particularly γ-interferon (IFN-γ) and tumor necrosis factor-α (TNF-α), are shared by the cells of the innate and adaptive systems.

Plasma cells,B lymphocytes and antibodies

Antibody has been the traditional focus of virologists interested in the immediately practical concern of making effective vaccines. Techniques for generating strong serum antibody response to pathogens, or their products, were known through much of the 20th century, and provided our first opportunity to exploit immunotherapy with products like antitoxins and antivenenes. Many of the first immunologists were, in fact, called serologists. Early pioneering work on the immune system, including the discovery of the role of the plasma cell in antibody production [44] by Astrid Fagraeus (1913–1993), was done, for example, at the State Serum Institute in Copenhagen.

Measurement of serum neutralizing antibody is still the best correlate of vaccine-induced immunity for many viruses. In the main, the protective, virus-specific immunoglobulin (Ig) molecules are targeted to tertiary, conformed determinants of glycoproteins expressed on the surface of the virion [76]. Such pre-existing Ig may not completely block infection at (for example) mucosal surfaces [99], but it does prevent the systemic spread of blood-born virus to distal sites of potential pathology such as the large motor neurons in poliomyelitis. One of the challenges for immunologists is to develop strategies for maintaining high levels of mucosal antibody [72]. Can we hope to vaccinate against HIV if the virus cannot be stopped at the initial site of entry?

Antibody-mediated selection pressure drives the diversification of the influenza A viruses manifested as antigenic drift in the broader ecological context [46, 127], while the continuing emergence of antibody escape variants within an infected individual is a depressingly familiar characteristic [54, 63] of pathogens like HIV and hepatitis C virus (HCV). Recent strategies for developing neutralizing antibody response to (for example) the M2 channel protein that is expressed on the surface of the influenza A viruses [84] suggest that it may be possible to generate protective antibodies directed at conserved determinants expressed on molecular structures that have little, if any, capacity to vary. This would, of course, be the "holy grail" for HIV research [23].

Serum antibody is often detected indefinitely after vaccination or primary infection. Recent experiments have shown that B lymphocytes specific for vaccinia virus may be circulating in peripheral blood for as long as 50 years after exposure to the DryVax vaccine [31]. Vaccinia virus is not present in the normal human environment, and it is unlikely that (at least) most urban dwellers will have encountered even a distantly related poxvirus that infects, for example, domestic animals. Memory in the B cell/plasma cell compartment can apparently be maintained in the very long term without further challenge by the inducing antigen.

Antibody production is a property of plasma cells, the terminally-differentiated stage of the B cell lineage. During the acute phase of an infectious process, activated B cells/plasmablasts circulate in the blood and localize to various distal sites. In the viral encephalitides, for instance, B cells/plasmablasts can be seen to transit [32] from the blood to the central nervous system (CNS), where they become plasma cells and continue local antibody production in the long term [52, 98]. Persistent infection with a defective variant of measles virus in subacute sclerosing panencephalitis is characterized by massive, long-term local antibody production [114]. Subclinical infection of the CNS with an encephalitic virus can also lead to the sustained presence of neutralizing Ig in cerebrospinal fluid (CSF) at titers that are clearly discordant with levels in serum, providing a clear indication of local Ig synthesis in the brain [98].

Other B cells/plasmablasts find their home in the bone marrow (BM), a process that is clearly independent of antigen [60, 111] localization to that site. Long term Ig production seems, in fact, to be a function of the BM compartment [112]. The mammalian BM functions to provide continuous replacements for cells in the hemopoietic lineages, including naïve B cell precursors. Perhaps the spectrum of growth and differentiation factors that are required for this purpose also act to sustain the antibody-producing plasma cells [26].

Though we have been studying antibodies for a very long time, there are still big gaps in our understanding of topics like virus neutralization. The traditional neutralization assay done in tissue culture does not, for example, take account of the possible role of complement activation [132], or of opsonization and destruction by macrophages, mechanisms that are likely to be operational in the *in vivo* situation. The possible role of enhancing antibodies as a mechanism for promoting virus growth and damage in macrophages and epithelial cells has been

a major focus for those interested in hemorrhagic dengue [55]. Similar questions have been raised for HIV, though more in the context of promoting virus growth and persistence [80].The structural basis of antibody neutralization is clearly an important focus [8]. More research is being done on antibody neutralization, particularly as attempts are made to develop immunization strategies to limit the ravages of the AIDS pandemic [23, 70].

Helper and effector $CD4^+$ T cells

No long-term, protective antibody response is generated in the absence of $CD4^+$ helper T cell function. Viruses can promote some IgM production, but even the generation of substantial IgM titers depends on the involvement of helper T cells [104]. In general, the requirement is for "cognate help": the two categories of lymphocytes must interact directly via TCR-mediated $CD4^+$ T cell recognition of viral peptide in the binding site of the appropriate MHC class II glycoprotein on the surface of the B cell. Early IgA production may break this rule [105], but there is still an absolute requirement for the concurrent stimulation of $CD4^+$ T cells by other antigen presenting cells, particularly dendritic cells (DCs). The possible mechanism is that the T cells promote IgA production by B cells that have bound viral components via surface Ig and are in sufficient proximity to be stimulated by secreted lymphokines and cytokines. However, this is likely to be an exceptional situation.

Though a concurrent $CD4^+$ T cell response does not seem to be required for the development of an effective $CD8^+$ T cell response [14], it is clear that both the qualitative and quantitative character of virus-specific $CD8^+$ T cell memory may be compromised in the absence of concurrent $CD4^+$ T help [13]. This applies to both the generation and the recall of memory $CD8^+$ T cells. Unlike the B cell/antibody response, $CD4^+$ T help for the $CD8^+$ responders is thought to operate via the DCs, with the role of the $CD4^+$ T cells being to activate the DCs to be more effective antigen presenting cells [15, 100]. High-level virus persistence in the absence of $CD4^+$ T help is also associated with a progressive loss of functional capacity by $CD8^+$ T cell effectors [79, 82, 133]. This "immune exhaustion" effect is seen most clearly with LCMV, and is less apparent for persistent infections that are characterized by less fulminant antigen production [75, 117].

Activated $CD4^+$ T cells play a very important role as direct mediators of immune control in the host response to intracellular bacteria [67] and herpesviruses [81]. In general, a primary requirement for these $CD4^+$ T cell effectors [28] is the production of IFN-γ. Mice that are $CD4^+$ T cell deficient as a consequence of disruption of the H2I-A^b gene can only partially limit the lytic phase of murine γ herpesvirus 68 (γ HV68) infection, and succumb after about 100 days with a late-onset, wasting disease [25]. Experiments with the influenza A viruses suggest that $CD4^+$ T cells promote recovery by providing help for the antibody response [121], though there is other evidence that they can function directly in the site of pathology [136]. Selective priming of $CD4^+$ T cell memory can lead to a more rapid antibody response to Sendai virus, to greater localization of $CD4^+$ T cells to

the infected lung and to more rapid virus clearance [136]. Recent evidence with the mouse hepatitis coronavirus neurological disease model suggests that $CD4^+$ T cells can mediate virus clearance in the absence of antibody, but with substantially delayed kinetics (S. Perlman, personal communication).

Cytokine production by $CD4^+$ T cells can also have profound deleterious effects. Mice that lack $CD8^+$ T cells as a consequence of disruption of the β2-microgloubulin (β2-m) light chain of the MHC class I glycoprotein fail to clear lymphocytic choriomeningitis virus (LCMV) and develop a chronic, wasting disease [37]. This was shown to reflect the persistent stimulation of $CD4^+$ T cells by the otherwise non-pathogenic LCMV. Also, if mice acutely infected with LCMV (or with an influenza A virus) are dosed with a "superantigen" (staphylococcal enterotoxin B), the resultant, massive, cytokine "dump" by highly activated, virus-specific $CD4^+$ T cells can lead to death from TNFα-mediated shock [106, 134]. It is also possible that cross-reactive $CD4^+$ memory T cell stimulation [77] and the resultant cytokine release could be a factor in the hemorrhagic syndrome that can follow secondary infection with heterologous dengue viruses [87].

The great majority of autoimmune disease that are though to be T cell mediated have been associated with $CD4^+$ [16] rather than $CD8^+$ T cell response, though this perception may be changing [73]. Such syndromes may, of course, reflect the breaking of self-tolerance by exposure to molecular mimics of self-components expressed by invading viruses or bacteria [88, 108]. The broad alternative is that this apparent autoimmunity is directed at persistent, but as yet uncharacterised, viruses [114].

$CD8^+$ effector T cells

The $CD8^+$ T cell is the primary mediator of virus clearance in the acute phase of most infections, and can act in the absence of $CD4^+$ T help and antibody production to deal with at least some lytic viruses that lack a persistent phenotype [39, 126]. Though activated, virus-specific $CD8^+$ T cells are potent producers of cytokines [113], particularly IFN-γ and TNF-α, the principal effector mechanism in many infectious processes is thought to be cell-mediated cytotoxicity. Activated $CD8^+$ cytotoxic T lymphocytes (CTL) contain large intracytoplasmic granules that express the pore-forming protein, perforin, and a range of serine esterases, or granzymes [62, 74]. These discharge their contents at the "immunological synapse" that forms at the interface between the "killer" lymphocyte, and the infected cell, with the perforin and granzymes then acting synergistically to trigger the classical apoptosis pathway [45].

Apoptotic elimination can, if the perforin/granzyme pathway is disrupted, also be induced via the interaction of Fas ligand on the CTL with Fas expressed on the infected cell [120]. The latter mechanism may, however, be less precisely constrained by TCR/epitope recognition, and thus more likely to induce bystander killing of other cells that happened to have increased Fas expression [122]. Even in the absence of such "promiscuous" lysis, some immunopathology is an inevitable

consequence of any virus-specific CTL response [33, 90, 128]. The simultaneous elimination of large numbers of infected cells in (particularly) sensitive sites like the CNS can lead to massive functional impairment and even death.

The nature of the infectious process can determine the relative significance of different $CD8^+$ T cell effector mechanisms. While IFN-γ seems to play (at most) an ancillary role in the control of influenza pneumonia [50, 96], local production of IFN-γ by $CD8^+$ T cells is clearly important for the clearance of respiratory syncytial virus from the lung [90]. Another situation where IFN-γ produced by the $CD8^+$ T cell is the primary mediator of virus control is in the transgenic mouse, human hepatitis model studied by F. Chisari and colleagues [53]. Production of IFN-γ by $CD8^+$ T cells is also central to the limitation of alphavirus [18, 19] and enterovirus infections [101] in the central nervous system. Though inflammation may alter the normal profile [24, 97], neurons do not generally express MHC class I glycoproteins [124]. Any T cell-mediated control of neuronal infection is thus likely to work via locally secreted factors rather than by the precisely targeted, direct T cell/target contact that is required for cytotoxic elimination.

What we learned through the 1990's from experiments with genetically disrupted, "knockout" mice is that disabling molecular mechanisms that are thought to constitute the primary mode of virus control often serves simply to reveal the existence of potent, alternative, effector functions [36]. In the phylogenetic sense, it is easy to see the reason for this divergence. The large DNA viruses, such as the herpesviruses [49] and poxviruses [86], have evolved a number of strategies for defeating cell-mediated immunity. It is important, both for the survival of the host and the parasite in the evolutionary sense, that there should always be an alternative means of control, at least to the level that allows for some persistent virus production, or reactivation from latency.

T cell memory and the recall response

The development of FACS staining approaches utilizing tetrameric complexes [2] of MHC class I glycoprotein + peptide (tetramers) has greatly facilitated the analysis of both the effector and memory phases of virus-specific $CD8^+$ T cell responses [20, 40]. This technology has moved more slowly for the $CD4^+$ T cell subset [5, 6, 58], partly because the comparable MHC class II + peptide reagents are more difficult to produce [129], and partly because $CD4^+$ T cell responses can tend to be both more diverse and smaller in magnitude.

The most useful techniques for analysing $CD4^+$ T cell memory depend on the measurement of IFN-γ production by peptide-stimulated lymphocytes, measured either in a flow cytometric assay or by ELISpot analysis after 24–48 hours of *in vitro* culture [66]. Persistent $CD4^+$ T cell memory is, for example, found for adenoviruses in healthy humans [89]. Lack of progression to AIDS has been correlated with the continued presence of more HIV-specific IFN-γ than IL-10-producing $CD4^+$T cells in the peripheral circulation [91]. Priming $CD4^+$ T cell memory to a prominent Sendai virus epitope led to a more rapid antibody

response and enhanced virus clearance [136]. Low-level γHV68 persistence induced continuing $CD4^+$ and $CD8^+$ T cell responses that substantially prevented the establishment of further lytic, but not latent, infection following respiratory challenge of antibody-negative, μMT mice with the same virus [4]. Immune $CD4^+$ and $CD8^+$ T cells contributed to this protective effect in an additive way. Though adoptively-transferred $CD4^+$ and $CD8^+$ T cells promoted the recovery of μMT mice from influenza virus infection, the $CD8^+$ set was clearly more effective in this regard [51]. In general, we understand less about $CD4^+$ than $CD8^+$ T cell memory.

Persistent $CD8^+$ T cell memory can be demonstrated in both mice and humans following a single exposure to an inducing virus [38, 56, 61, 65, 78]. These long-lived T cells and their progeny express high levels of telomerase activity [57] though, under conditions of continuing antigen stimulation, telomere length may be shortened to the extent that clonal survival is impaired [102, 125]. The maintenance of $CD8^+$ T cell memory reflects the survival of clontotypes expanded during the initial, antigen driven phase of the host response [123], but does not seem to require either the persistence of the inducing epitope or even the continued presence of MHC class I glycoprotein [59, 85]. What does seem to be important is exposure to the cytokines IL-7 and IL-15, both during the acute response phase and in the long term. [17, 64, 107, 119, 135].

The recall of $CD8^+$ T cell memory can certainly provide a measure of protection against virus challenge [27], a possibility that is particularly attractive for viruses that vary their surface glycoproteins as a consequence of antibody-mediated selection pressure. Virus-specific $CD8^+$ T cell responses tend to be directed at peptides derived from conserved, internal proteins [12, 130], a situation that may be quite different from that found with $CD4^+$ T cell responses [22]. This cross-reactivity is, for instance, a good reason for thinking about the use of live influenza vaccines, combined with other mechanisms for boosting CTL memory [29, 43].

The problem with relying on the recall of $CD8^+$ T cell memory for protection is that, though the injection of peptide-pulsed cells is generally associated with rapid elimination [9], the recall of effective $CD8^+$ T cell memory to a distal site of virus growth is substantially delayed [35, 47]. When memory T cell numbers are at what might be thought of as physiological levels, there is a clear necessity for further proliferation in the lymphoid tissue, followed by emigration into the blood and localization to the target organ [48]. Even when memory T cell numbers are very high in, for example, the lung, a rapidly growing influenza A virus will still become fully established before $CD8^+$ T cell effectors operate to eliminate the infected cells and control the growth of the pathogen [29].

Thus, though vaccines directed at promoting $CD8^+$ T cell memory can limit the damage done by lytic viruses that do not have a capacity for persistence, they seem unable to prevent the establishment of persistent infections [4, 118]. This has been clearly demonstrated for monkeys primed with candidate HIV vaccines [3, 10]. The T cells function for a time to limit the extent of virus replication, but escape variants eventually emerge [11].

Conclusions

Some virus infections may be controlled by either an effective $CD8^+$ T cell response, or by a high quality B cell/antibody response that depends on $CD4^+$ T help. In general, however, the host response is optimally mediated by all three categories of immune lymphocyte operating together. This is clearly the case for the large DNA viruses, particularly the herpesviruses, which also require the involvement of cytokine-producing $CD4^+$ effector T cells [28]. Most of our successful vaccines to date depend on the capacity of a persistent neutralizing antibody response to limit systemic spread to distal sites of virus growth. Memory $CD8^+$ T cells may not prevent the establishment of an infectious process, though the more rapid recall of CTL effector function is likely to ameliorate the severity of pathology and consequent clinical impairment by speeding virus clearance [29]. Again, with viruses that have the capacity to persist, the available evidence suggests that an optimal vaccine will prime all the components of adaptive immunity [3].

Acknowledgement

PCD is a Burnet Fellow of the Australian National Health and Medical Research Council.

References

1. Ahmadzadeh M, Farber DL (2002) Functional plasticity of an antigen-specific memory CD4 T cell population. Proc Natl Acad Sci USA 99: 11802–11807
2. Altman JD, Moss PA, Goulder PJ, Barouch DH, McHeyzer-Williams MG, Bell JI, McMichael AJ, Davis MM (1996) Phenotypic analysis of antigen-specific T lymphocytes. Science 274: 94–96
3. Amara RR, Smith JM, Staprans SI, Montefiori DC, Villinger F, Altman JD, O'Neil SP, Kozyr NL, Xu Y, Wyatt LS, Earl PL, Herndon JG, McNicholl JM, McClure HM, Moss B, Robinson HL (2002) Critical role for Env as well as Gag-Pol in control of a simian-human immunodeficiency virus 89.6P challenge by a DNA prime/recombinant modified vaccinia virus Ankara vaccine. J Virol 76: 6138–6146
4. Andreansky S, Liu H, Adler H, Koszinowski UH, Efstathiou S, Doherty PC (2004) The limits of protection by "memory" T cells in Ig-/-mice persistently infected with a {gamma}-herpesvirus. Proc Natl Acad Sci USA 101: 2017–2022
5. Arnold PY, La Gruta NL, Miller T, Vignali KM, Adams PS, Woodland DL, Vignali DA (2002) The majority of immunogenic epitopes generate CD4+ T cells that are dependent on MHC class II-bound peptide-flanking residues. J Immunol 169: 739–749
6. Arnold PY, Vignali KM, Miller TB, La Gruta NL, Cauley LS, Haynes L, Scott Adams P, Swain SL, Woodland DL, Vignali DA (2002) Reliable generation and use of MHC class II:gamma2aFc multimers for the identification of antigen-specific CD4(+) T cells. J Immunol Meth 271: 137–151
7. Arstila TP, Casrouge A, Baron V, Even J, Kanellopoulos J, Kourilsky P (1999) A direct estimate of the human alphabeta T cell receptor diversity. Science 286: 958–961
8. Barbato G, Bianchi E, Ingallinella P, Hurni WH, Miller MD, Ciliberto G, Cortese R, Bazzo R, Shiver JW, Pessi A (2003) Structural analysis of the epitope of the anti-HIV antibody 2F5 sheds light into its mechanism of neutralization and HIV fusion. J Mol Biol 330: 1101–1115

9. Barber DL, Wherry EJ, Ahmed R (2003) Cutting edge: rapid in vivo killing by memory CD8 T cells. J Immunol 171: 27–31
10. Barouch DH, Santra S, Schmitz JE, Kuroda MJ, Fu TM, Wagner W, Bilska M, Craiu A, Zheng XX, Krivulka GR, Beaudry K, Lifton MA, Nickerson CE, Trigona WL, Punt K, Freed DC, Guan L, Dubey S, Casimiro D, Simon A, Davies ME, Chastain M, Strom TB, Gelman RS, Montefiori DC, Lewis MG, Emini EA, Shiver JW, Letvin NL (2000) Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination. Science 290: 486–492
11. Barouch DH, Kunstman J, Kuroda MJ, Schmitz JE, Santra S, Peyerl FW, Krivulka GR, Beaudry K, Lifton MA, Gorgone DA, Montefiori DC, Lewis MG, Wolinsky SM, Letvin NL (2002) Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. Nature 415: 335–339
12. Belz GT, Xie W, Doherty PC (2001) Diversity of epitope and cytokine profiles for primary and secondary influenza a virus-specific CD8+ T cell responses. J Immunol 166: 4627–4633
13. Belz GT, Wodarz D, Diaz G, Nowak MA, Doherty PC (2002) Compromised influenza virus-specific CD8(+)-T-cell memory in CD4(+)-T-cell-deficient mice. J Virol 76: 12388–12393
14. Belz GT, Liu H, Andreansky S, Doherty PC, Stevenson PG (2003) Absence of a functional defect in CD8+ T cells during primary murine gammaherpesvirus-68 infection of I-A(b-/-) mice. J Gen Virol 84: 337–341
15. Bennett SR, Carbone FR, Karamalis F, Miller JF, Heath WR (1997) Induction of a CD8+ cytotoxic T lymphocyte response by cross-priming requires cognate CD4+ T cell help. J Exp Med 186: 65–70
16. Bennett SR, Falta MT, Bill J, Kotzin BL (2003) Antigen-specific T cells in rheumatoid arthritis. Curr Rheumatol Rep 5: 255–263
17. Berard M, Brandt K, Bulfone-Paus S, Tough DF (2003) IL-15 promotes the survival of naive and memory phenotype CD8+ T cells. J Immunol 170: 5018–5026
18. Binder GK, Griffin DE (2001) Interferon-gamma-mediated site-specific clearance of alphavirus from CNS neurons. Science 293: 303–306
19. Binder GK, Griffin DE (2003) Immune-mediated clearance of virus from the central nervous system. Microbes Infect 5: 439–448
20. Blattman JN, Sourdive DJ, Murali-Krishna K, Ahmed R, Altman JD (2000) Evolution of the T cell repertoire during primary, memory, and recall responses to viral infection. J Immunol 165: 6081–6090
21. Blattman JN, Antia R, Sourdive DJ, Wang X, Kaech SM, Murali-Krishna K, Altman JD, Ahmed R (2002) Estimating the precursor frequency of naive antigen-specific CD8 T cells. J Exp Med 195: 657–664
22. Brown SA, Stambas J, Zhan X, Slobod KS, Coleclough C, Zirkel A, Surman S, White SW, Doherty PC, Hurwitz JL (2003) Clustering of Th cell epitopes on exposed regions of HIV envelope despite defects in antibody activity. J Immunol 171: 4140–4148
23. Burton DR, Desrosiers RC, Doms RW, Koff WC, Kwong PD, Moore JP, Nabel GJ, Sodroski J, Wilson IA, Wyatt RT (2004) HIV vaccine design and the neutralizing antibody problem. Nat Immunol 5: 233–236
24. Cabarrocas J, Bauer J, Piaggio E, Liblau R, Lassmann H (2003) Effective and selective immune surveillance of the brain by MHC class I-restricted cytotoxic T lymphocytes. Eur J Immunol 33: 1174–1182
25. Cardin RD, Brooks JW, Sarawar SR, Doherty PC (1996) Progressive loss of CD8+ T cell-mediated control of a gamma-herpesvirus in the absence of CD4+ T cells. J Exp Med 184: 863–871

26. Cassese G, Arce S, Hauser AE, Lehnert K, Moewes B, Mostarac M, Muehlinghaus G, Szyska M, Radbruch A, Manz RA (2003) Plasma cell survival is mediated by synergistic effects of cytokines and adhesion-dependent signals. J Immunol 171: 1684–1690
27. Castrucci MR, Hou S, Doherty PC, Kawaoka Y (1994) Protection against lethal lymphocytic choriomeningitis virus (LCMV) infection by immunization of mice with an influenza virus containing an LCMV epitope recognized by cytotoxic T lymphocytes. J Virol 68: 3486–3490
28. Christensen JP, Cardin RD, Branum KC, Doherty PC (1999) CD4(+) T cell-mediated control of a gamma-herpesvirus in B cell-deficient mice is mediated by IFN-gamma. Proc Natl Acad Sci USA 96: 5135–5140
29. Christensen JP, Doherty PC, Branum KC, Riberdy JM (2000) Profound protection against respiratory challenge with a lethal H7N7 influenza A virus by increasing the magnitude of CD8(+) T-cell memory. J Virol 74: 11690–11696
30. Clark R, Griffiths GM (2003) Lytic granules, secretory lysosomes and disease. Curr Opin Immunol 15: 516–521
31. Crotty S, Felgner P, Davies H, Glidewell J, Villarreal L, Ahmed R (2003) Cutting edge: long-term B cell memory in humans after smallpox vaccination. J Immunol 171: 4969–4973
32. Doherty PC, Reid HW, Smith W (1971) Louping-ill encephalomyelitis in the sheep. IV. Nature of the perivascular inflammatory reaction. J Comp Pathol 81: 545–549
33. Doherty PC, Zinkernagel RM (1974) T-cell-mediated immunopathology in viral infections. Transplant Rev 19: 89–120
34. Doherty PC, Zinkernagel RM (1975) A biological role for the major histocompatibility antigens. Lancet 1: 1406–1409
35. Doherty PC, Allan W, Boyle DB, Coupar BE, Andrew ME (1989) Recombinant vaccinia viruses and the development of immunization strategies using influenza virus. J Infect Dis 159: 1119–1122
36. Doherty PC (1993) Virus infections in mice with targeted gene disruptions. Curr Opin Immunol 5: 479–483
37. Doherty PC, Hou S, Southern PJ (1993) Lymphocytic choriomeningitis virus induces a chronic wasting disease in mice lacking class I major histocompatibility complex glycoproteins. J Neuroimmunol 46: 11–17
38. Doherty PC, Topham DJ, Tripp RA (1996) Establishment and persistence of virus-specific CD4+ and CD8+ T cell memory. Immunol Rev 150: 23–44
39. Doherty PC, Topham DJ, Tripp RA, Cardin RD, Brooks JW, Stevenson PG (1997) Effector CD4+ and CD8+ T-cell mechanisms in the control of respiratory virus infections. Immunol Rev 159: 105–117
40. Doherty PC, Christensen JP (2000) Accessing complexity: the dynamics of virus-specific T cell responses. Annu Rev Immunol 18: 561–592
41. Doherty RL, Carley JG, Best JC (1972) Isolation of Ross River virus from man. Med J Aust 1: 1083–1084
42. Edwards BM, Barash SC, Main SH, Choi GH, Minter R, Ullrich S, Williams E, Du Fou L, Wilton J, Albert VR, Ruben SM, Vaughan TJ (2003) The remarkable flexibility of the human antibody repertoire; isolation of over one thousand different antibodies to a single protein, BLyS. J Mol Biol 334: 103–118
43. Ennis FA, Cruz J, Jameson J, Klein M, Burt D, Thipphawong J (1999) Augmentation of human influenza A virus-specific cytotoxic T lymphocyte memory by influenza vaccine and adjuvanted carriers (ISCOMS). Virology 259: 256–261
44. Fagraeus A (1958) Cellular reaction in antibody formation. Acta Haematol 20: 1–8

45. Faroudi M, Utzny C, Salio M, Cerundolo V, Guiraud M, Muller S, Valitutti S (2003) Lytic versus stimulatory synapse in cytotoxic T lymphocyte/target cell interaction: manifestation of a dual activation threshold. Proc Natl Acad Sci USA 100: 14145–14150
46. Ferguson NM, Galvani AP, Bush RM (2003) Ecological and immunological determinants of influenza evolution. Nature 422: 428–433
47. Flynn KJ, Belz GT, Altman JD, Ahmed R, Woodland DL, Doherty PC (1998) Virus-specific CD8+ T cells in primary and secondary influenza pneumonia. Immunity 8: 683–691
48. Flynn KJ, Riberdy JM, Christensen JP, Altman JD, Doherty PC (1999) In vivo proliferation of naive and memory influenza-specific CD8(+) T cells. Proc Natl Acad Sci USA 96: 8597–8602
49. Gewurz BE, Gaudet R, Tortorella D, Wang EW, Ploegh HL (2001) Virus subversion of immunity: a structural perspective. Curr Opin Immunol 13: 442–450
50. Graham MB, Dalton DK, Giltinan D, Braciale VL, Stewart TA, Braciale TJ (1993) Response to influenza infection in mice with a targeted disruption in the interferon gamma gene. J Exp Med 178: 1725–1732
51. Graham MB, Braciale TJ (1997) Resistance to and recovery from lethal influenza virus infection in B lymphocyte-deficient mice. J Exp Med 186: 2063–2068
52. Griffin D, Levine B, Tyor W, Ubol S, Despres P (1997) The role of antibody in recovery from alphavirus encephalitis. Immunol Rev 159: 155–161
53. Guidotti LG, Borrow P, Brown A, McClary H, Koch R, Chisari FV (1999) Noncytopathic clearance of lymphocytic choriomeningitis virus from the hepatocyte. J Exp Med 189: 1555–1564
54. Hahn YS (2003) Subversion of immune responses by hepatitis C virus: immunomodulatory strategies beyond evasion? Curr Opin Immunol 15: 443–449
55. Halstead SB (2003) Neutralization and antibody-dependent enhancement of dengue viruses. Adv Virus Res 60: 421–467
56. Hammarlund E, Lewis MW, Hansen SG, Strelow LI, Nelson JA, Sexton GJ, Hanifin JM, Slifka MK (2003) Duration of antiviral immunity after smallpox vaccination. Nat Med 9: 1131–1137
57. Hathcock KS, Kaech SM, Ahmed R, Hodes RJ (2003) Induction of telomerase activity and maintenance of telomere length in virus-specific effector and memory CD8+ T cells. J Immunol 170: 147–152
58. Homann D, Teyton L, Oldstone MB (2001) Differential regulation of antiviral T-cell immunity results in stable CD8+ but declining CD4+ T-cell memory. Nat Med 7: 913–919
59. Hou S, Hyland L, Ryan KW, Portner A, Doherty PC (1994) Virus-specific CD8+ T-cell memory determined by clonal burst size. Nature 369: 652–654
60. Hyland L, Sangster M, Sealy R, Coleclough C (1994) Respiratory virus infection of mice provokes a permanent humoral immune response. J Virol 68: 6083–6086
61. Jameson J, Cruz J, Terajima M, Ennis FA (1999) Human CD8+ and CD4+ T lymphocyte memory to influenza A viruses of swine and avian species. J Immunol 162: 7578–7583
62. Johnson BJ, Costelloe EO, Fitzpatrick DR, Haanen JB, Schumacher TN, Brown LE, Kelso A (2003) Single-cell perforin and granzyme expression reveals the anatomical localization of effector CD8+ T cells in influenza virus-infected mice. Proc Natl Acad Sci USA 100: 2657–2662
63. Johnson WE, Desrosiers RC (2002) Viral persistance: HIV's strategies of immune system evasion. Annu Rev Med 53: 499–518

64. Kaech SM, Tan JT, Wherry EJ, Konieczny BT, Surh CD, Ahmed R (2003) Selective expression of the interleukin 7 receptor identifies effector CD8 T cells that give rise to long-lived memory cells. Nat Immunol 4: 1191–1198
65. Kapasi ZF, Murali-Krishna K, McRae ML, Ahmed R (2002) Defective generation but normal maintenance of memory T cells in old mice. Eur J Immunol 32: 1567–1573
66. Karlsson AC, Martin JN, Younger SR, Bredt BM, Epling L, Ronquillo R, Varma A, Deeks SG, McCune JM, Nixon DF, Sinclair E (2003) Comparison of the ELISPOT and cytokine flow cytometry assays for the enumeration of antigen-specific T cells. J Immunol Meth 283: 141–153
67. Kaufmann SH, Doherty PC (1997) Immunity to infection. Curr Opin Immunol 9: 453–455
68. Kaverin NV, Rudneva IA, Ilyushina NA, Varich NL, Lipatov AS, Smirnov YA, Govorkova EA, Gitelman AK, Lvov DK, Webster RG (2002) Structure of antigenic sites on the haemagglutinin molecule of H5 avian influenza virus and phenotypic variation of escape mutants. J Gen Virol 83: 2497–2505
69. Klein G (1994) Epstein-Barr virus strategy in normal and neoplastic B cells. Cell 77: 791–793
70. Koch M, Pancera M, Kwong PD, Kolchinsky P, Grundner C, Wang L, Hendrickson WA, Sodroski J, Wyatt R (2003) Structure-based, targeted deglycosylation of HIV-1 gp120 and effects on neutralization sensitivity and antibody recognition. Virology 313: 387–400
71. Krmpotic A, Busch DH, Bubic I, Gebhardt F, Hengel H, Hasan M, Scalzo AA, Koszinowski UH, Jonjic S (2002) MCMV glycoprotein gp40 confers virus resistance to CD8+ T cells and NK cells in vivo. Nat Immunol 3: 529–535
72. Lehner T (2003) Innate and adaptive mucosal immunity in protection against HIV infection. Vaccine 21[Suppl] 2: 68–76
73. Liblau RS, Wong FS, Mars LT, Santamaria P (2002) Autoreactive CD8 T cells in organ-specific autoimmunity: emerging targets for therapeutic intervention. Immunity 17: 1–6
74. Lieberman J (2003) The ABCs of granule-mediated cytotoxicity: new weapons in the arsenal. Nat Rev Immunol 3: 361–370
75. Liu H, Andreansky S, Diaz G, Hogg T, Doherty PC (2002) Reduced functional capacity of CD8(+) T cells expanded by post-exposure vaccination of gamma-herpesvirus-infected CD4-deficient mice. J Immunol 168: 3477–3483
76. Malby RL, Tulip WR, Harley VR, McKimm-Breschkin JL, Laver WG, Webster RG, Colman PM (1994) The structure of a complex between the NC10 antibody and influenza virus neuraminidase and comparison with the overlapping binding site of the NC41 antibody. Structure 2: 733–746
77. Mangada MM, Ennis FA, Rothman AL (2004) Quantitation of dengue virus specific CD4+ T cells by intracellular cytokine staining. J Immunol Meth 284: 89–97
78. Marshall DR, Turner SJ, Belz GT, Wingo S, Andreansky S, Sangster MY, Riberdy JM, Liu T, Tan M, Doherty PC (2001) Measuring the diaspora for virus-specific CD8+ T cells. Proc Natl Acad Sci USA 98: 6313–6318
79. Matloubian M, Concepcion RJ, Ahmed R (1994) CD4+ T cells are required to sustain CD8+ cytotoxic T-cell responses during chronic viral infection. J Virol 68: 8056–8063
80. Matsuda S, Gidlund M, Chiodi F, Cafaro A, Nygren A, Morein B, Nilsson K, Fenyo EM, Wigzell H (1989) Enhancement of human immunodeficiency virus (HIV) replication in human monocytes by low titres of anti-HIV antibodies in vitro. Scand J Immunol 30: 425–434

81. Mikloska Z, Cunningham AL (1998) Herpes simplex virus type 1 glycoproteins gB, gC and gD are major targets for CD4 T-lymphocyte cytotoxicity in HLA-DR expressing human epidermal keratinocytes. J Gen Virol 79: 353–361
82. Moskophidis D, Lechner F, Pircher H, Zinkernagel RM (1993) Virus persistence in acutely infected immunocompetent mice by exhaustion of antiviral cytotoxic effector T cells. Nature 362: 758–761
83. Moss DJ, Burrows SR, Silins SL, Misko I, Khanna R (2001) The immunology of Epstein-Barr virus infection. Philos Trans R Soc Lond B Biol Sci 356: 475–488
84. Mozdzanowska K, Feng J, Eid M, Kragol G, Cudic M, Otvos L Jr, Gerhard W (2003) Induction of influenza type A virus-specific resistance by immunization of mice with a synthetic multiple antigenic peptide vaccine that contains ectodomains of matrix protein 2. Vaccine 21: 2616–2626
85. Murali-Krishna K, Lau LL, Sambhara S, Lemonnier F, Altman J, Ahmed R (1999) Persistence of memory CD8 T cells in MHC class I-deficient mice. Science 286: 1377–1381
86. Nash P, Barrett J, Cao JX, Hota-Mitchell S, Lalani AS, Everett H, Xu XM, Robichaud J, Hnatiuk S, Ainslie C, Seet BT, McFadden G (1999) Immunomodulation by viruses: the myxoma virus story. Immunol Rev 168: 103–120
87. Nguyen TH, Lei HY, Nguyen TL, Lin YS, Huang KJ, Le BL, Lin CF, Yeh TM, Do QH, Vu TQ, Chen LC, Huang JH, Lam TM, Liu CC, Halstead SB (2004) Dengue hemorrhagic fever in infants: a study of clinical and cytokine profiles. J Infect Dis 189: 221–232
88. Oldstone MB (1998) Molecular mimicry and immune-mediated diseases. Faseb J 12: 1255–1265
89. Olive M, Eisenlohr LC, Flomenberg P (2001) Quantitative analysis of adenovirus-specific CD4+ T-cell responses from healthy adults. Viral Immunol 14: 403–413
90. Ostler T, Davidson W, Ehl S (2002) Virus clearance and immunopathology by CD8(+) T cells during infection with respiratory syncytial virus are mediated by IFN-gamma. Eur J Immunol 32: 2117–2123
91. Ostrowski MA, Gu JX, Kovacs C, Freedman J, Luscher MA, MacDonald KS (2001) Quantitative and qualitative assessment of human immunodeficiency virus type 1 (HIV-1)-specific CD4+ T cell immunity to gag in HIV-1-infected individuals with differential disease progression: reciprocal interferon-gamma and interleukin-10 responses. J Infect Dis 184: 1268–1278
92. Parham P, Adams EJ, Arnett KL (1995) The origins of HLA-A,B,C polymorphism. Immunol Rev 143: 141–180
93. Parham P (1999) Virtual reality in the MHC. Immunol Rev 167: 5–15
94. Parry CM, Simas JP, Smith VP, Stewart CA, Minson AC, Efstathiou S, Alcami A (2000) A broad spectrum secreted chemokine binding protein encoded by a herpesvirus. J Exp Med 191: 573–578
95. Pien GC, Nguyen KB, Malmgaard L, Satoskar AR, Biron CA (2002) A unique mechanism for innate cytokine promotion of T cell responses to viral infections. J Immunol 169: 5827–5837
96. Price GE, Gaszewska-Mastarlarz A, Moskophidis D (2000) The role of alpha/beta and gamma interferons in development of immunity to influenza A virus in mice. J Virol 74: 3996–4003
97. Redwine JM, Buchmeier MJ, Evans CF (2001) In vivo expression of major histocompatibility complex molecules on oligodendrocytes and neurons during viral infection. Am J Pathol 159: 1219–1224
98. Reid HW, Doherty PC, Dawson AM (1971) Louping-ill encephalomyelitis in the sheep. 3. Immunoglobulins in cerebrospinal fluid. J Comp Pathol 81: 537–543

99. Riberdy JM, Flynn KJ, Stech J, Webster RG, Altman JD, Doherty PC (1999) Protection against a lethal avian influenza A virus in a mammalian system. J Virol 73: 1453–1459
100. Ridge JP, Di Rosa F, Matzinger P (1998) A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper and a T-killer cell. Nature 393: 474–478
101. Rodriguez M, Zoecklein LJ, Howe CL, Pavelko KD, Gamez JD, Nakane S, Papke LM (2003) Gamma interferon is critical for neuronal viral clearance and protection in a susceptible mouse strain following early intracranial Theiler's murine encephalomyelitis virus infection. J Virol 77: 12252–12265
102. Roth A, Yssel H, Pene J, Chavez EA, Schertzer M, Lansdorp PM, Spits H, Luiten RM (2003) Telomerase levels control the lifespan of human T lymphocytes. Blood 102: 849–857
103. Saikh KU, Lee JS, Kissner TL, Dyas B, Ulrich RG (2003) Toll-like receptor and cytokine expression patterns of CD56+ T cells are similar to natural killer cells in response to infection with Venezuelan equine encephalitis virus replicons. J Infect Dis 188: 1562–1570
104. Sangster MY, Topham DJ, D'Costa S, Cardin RD, Marion TN, Myers LK, Doherty PC (2000) Analysis of the virus-specific and nonspecific B cell response to a persistent B-lymphotropic gammaherpesvirus. J Immunol 164: 1820–1828
105. Sangster MY, Riberdy JM, Gonzalez M, Topham DJ, Baumgarth N, Doherty PC (2003) An early CD4+ T cell-dependent immunoglobulin A response to influenza infection in the absence of key cognate T–B interactions. J Exp Med 198: 1011–1021
106. Sarawar SR, Blackman MA, Doherty PC (1994) Superantigen shock in mice with an inapparent viral infection. J Infect Dis 170: 1189–1194
107. Schluns KS, Lefrancois L (2003) Cytokine control of memory T-cell development and survival. Nat Rev Immunol 3: 269–279
108. Schwimmbeck PL, Dyrberg T, Drachman DB, Oldstone MB (1989) Molecular mimicry and myasthenia gravis. An autoantigenic site of the acetylcholine receptor alpha-subunit that has biologic activity and reacts immunochemically with herpes simplex virus. J Clin Invest 84: 1174–1180
109. Shope RE (1994) The discovery of arbovirus diseases. Ann N Y Acad Sci 740: 138–145
110. Shope RE (2003) Epidemiology of other arthropod-borne flaviviruses infecting humans. Adv Virus Res 61: 373–391
111. Slifka MK, Matloubian M, Ahmed R (1995) Bone marrow is a major site of long-term antibody production after acute viral infection. J Virol 69: 1895–1902
112. Slifka MK, Ahmed R (1998) Long-lived plasma cells: a mechanism for maintaining persistent antibody production. Curr Opin Immunol 10: 252–258
113. Slifka MK, Whitton JL (2000) Antigen-specific regulation of T cell-mediated cytokine production. Immunity 12: 451–457
114. Smith-Jensen T, Burgoon MP, Anthony J, Kraus H, Gilden DH, Owens GP (2000) Comparison of immunoglobulin G heavy-chain sequences in MS and SSPE brains reveals an antigen-driven response. Neurology 54: 1227–1232
115. Sprent J, Tough DF (2001) T cell death and memory. Science 293: 245–248
116. Spriggs MK (1996) One step ahead of the game: viral immunomodulatory molecules. Annu Rev Immunol 14: 101–130
117. Stevenson PG, Belz GT, Altman JD, Doherty PC (1998) Virus-specific CD8(+) T cell numbers are maintained during gamma-herpesvirus reactivation in CD4-deficient mice. Proc Natl Acad Sci USA 95: 15565–15570
118. Stevenson PG, Belz GT, Castrucci MR, Altman JD, Doherty PC (1999) A gamma-herpesvirus sneaks through a CD8(+) T cell response primed to a lytic-phase epitope. Proc Natl Acad Sci USA 96: 9281–9286

119. Tan JT, Dudl E, LeRoy E, Murray R, Sprent J, Weinberg KI, Surh CD (2001) IL-7 is critical for homeostatic proliferation and survival of naive T cells. Proc Natl Acad Sci USA 98: 8732–8737
120. Topham DJ, Tripp RA, Doherty PC (1997) CD8+ T cells clear influenza virus by perforin or Fas-dependent processes. J Immunol 159: 5197–5200
121. Topham DJ, Doherty PC (1998) Clearance of an influenza A virus by CD4+ T cells is inefficient in the absence of B cells. J Virol 72: 882–885
122. Topham DJ, Cardin RC, Christensen JP, Brooks JW, Belz GT, Doherty PC (2001) Perforin and Fas in murine gammaherpesvirus-specific CD8(+) T cell control and morbidity. J Gen Virol 82: 1971–1981
123. Turner SJ, Diaz G, Cross R, Doherty PC (2003) Analysis of clonotype distribution and persistence for an influenza virus-specific CD8+ T cell response. Immunity 18: 549–559
124. Turnley AM, Starr R, Bartlett PF (2002) Failure of sensory neurons to express class I MHC is due to differential SOCS1 expression. J Neuroimmunol 123: 35–40
125. Valenzuela HF, Effros RB (2002) Divergent telomerase and CD28 expression patterns in human CD4 and CD8 T cells following repeated encounters with the same antigenic stimulus. Clin Immunol 105: 117–125
126. Webby RJ, Andreansky S, Stambas J, Rehg JE, Webster RG, Doherty PC, Turner SJ (2003) Protection and compensation in the influenza virus-specific CD8+ T cell response. Proc Natl Acad Sci USA 100: 7235–7240
127. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y (1992) Evolution and ecology of influenza A viruses. Microbiol Rev 56: 152–179
128. Wodarz D, Krakauer DC (2000) Defining CTL-induced pathology: implications for HIV. Virology 274: 94–104
129. Woodland DL, Dutton RW (2003) Heterogeneity of CD4(+) and CD8(+) T cells. Curr Opin Immunol 15: 336–342
130. Yewdell J, Anton LC, Bacik I, Schubert U, Snyder HL, Bennink JR (1999) Generating MHC class I ligands from viral gene products. Immunol Rev 172: 97–108
131. Yewdell JW, Norbury CC, Bennink JR (1999) Mechanisms of exogenous antigen presentation by MHC class I molecules in vitro and in vivo: implications for generating CD8+ T cell responses to infectious agents, tumors, transplants, and vaccines. Adv Immunol 73: 1–77
132. Yoder SM, Zhu Y, Ikizler MR, Wright PF (2004) Role of complement in neutralization of respiratory syncytial virus. J Med Virol 72: 688–694
133. Zajac AJ, Blattman JN, Murali-Krishna K, Sourdive DJ, Suresh M, Altman JD, Ahmed R (1998) Viral immune evasion due to persistence of activated T cells without effector function. J Exp Med 188: 2205–2213
134. Zhang WJ, Sarawar S, Nguyen P, Daly K, Rehg JE, Doherty PC, Woodland DL, Blackman MA (1996) Lethal synergism between influenza infection and staphylococcal enterotoxin B in mice. J Immunol 157: 5049–5060
135. Zhang X, Fujii H, Kishimoto H, LeRoy E, Surh CD, Sprent J (2002) Aging leads to disturbed homeostasis of memory phenotype CD8(+) cells. J Exp Med 195: 283–293
136. Zhong W, Marshall D, Coleclough C, Woodland DL (2000) CD4+ T cell priming accelerates the clearance of Sendai virus in mice, but has a negative effect on CD8+ T cell memory. J Immunol 164: 3274–3282

Author's address: Peter C. Doherty, Department of Microbiology and Immunology, University of Melbourne, Parkville, Vic 3010, Australia; e-mail: pcd@unimelb.edu.au