

infection: implications for vaccination The dynamics of the cellular immune response to HIV

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THE ROYAL SOCIETY
 The dynamics of the cellular immune response to HIV infection: implications for vaccination

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Recent advances in measuring T-cell responses to viruses have led to new insights into how these T cells
respond In th Recent advances in measuring T-cell responses to viruses have led to new insights into how these T cells
respond. In the acute infection there are massive CD8⁺ T-cell responses to both Epstein–Barr virus
(EBV) and to bum respond. In the acute infection there are massive $CD8^+$ T-cell responses to both Epstein–Barr virus (EBV) and to human immunodeficiency virus (HIV). Many of these T cells are effector cells and only a respond. In the acute infection there are massive CD8⁺ T-cell responses to both Epstein–Barr virus (EBV) and to human immunodeficiency virus (HIV). Many of these T cells are effector cells and only a minority appear to b (EBV) and to human immunodeficiency virus (HIV). Many of these T cells are effector cells and only a minority appear to be capable of maintaining immunological memory. In persistent virus infections, high levels of antigen minority appear to be capable of maintaining immunological memory. In persistent virus infections, high
levels of antigen-specific effector cells persist. If virus does not persist, the effectors fade in number but
memory levels of antigen-specific effector cells persist. If virus does not persist, the effectors fade in number but
memory is maintained and is primed to react rapidly to a new challenge. A vaccine that stimulates only
T-cell r T-cell responses may protect when these memory cells respond rapidly enough to generate high numbers

Keywords: HIV; Epstein-Barr virus; CD8⁺ Tcells; memory; vaccination

1. INTRODUCTION

The study of the cellular immune response to infectious The study of the cellular immune response to infectious
agents has been transformed by the recent introduction
of major histocompatibility complex (MHC) tetramers The study of the cellular immune response to infectious
agents has been transformed by the recent introduction
of major histocompatibility complex (MHC) tetramers
(Altman *et al.* 1996: McMichael & O'Callaghan 1998) agents has been transformed by the recent introduction
of major histocompatibility complex (MHC) tetramers
(Altman *et al.* 1996; McMichael & O'Callaghan 1998).
These are complexes of four MHC class I molecules of major histocompatibility complex (MHC) tetramers
(Altman *et al.* 1996; McMichael & O'Callaghan 1998).
These are complexes of four MHC class I molecules
containing the same enitore penticle linked by a biotin (Altman *et al.* 1996; McMichael & O'Callaghan 1998).
These are complexes of four MHC class I molecules
containing the same epitope peptide linked by a biotin
molecule to strentavidin. Such reagents enable direct These are complexes of four MHC class I molecules
containing the same epitope peptide linked by a biotin
molecule to streptavidin. Such reagents enable direct
visualization of antigen-specific T cells for the first time containing the same epitope peptide linked by a biotin
molecule to streptavidin. Such reagents enable direct
visualization of antigen-specific T cells for the first time.
In parallel methods for intracellular cytokine stai molecule to streptavidin. Such reagents enable direct
visualization of antigen-specific T cells for the first time.
In parallel, methods for intracellular cytokine staining of
antigen-specific T cells have also been introd visualization of antigen-specific T cells for the first time.
In parallel, methods for intracellular cytokine staining of
antigen-specific T cells have also been introduced (Butz
 $\&$ Beyan 1998: Pitcher *et al* 1999) Lis In parallel, methods for intracellular cytokine staining of antigen-specific T cells have also been introduced (Butz & Bevan 1998; Pitcher *et al.* 1999). Use of these two technical advances has altered our view of how T cells & Bevan 1998; Pitcher *et al.* 1999). Use of these two technical advances has altered our view of how T cells respond to an invading pathogen. The biggest surprise was the magnitude of the $CD8⁺$ T-cell response to vi technical advances has altered our view of how T cells
respond to an invading pathogen. The biggest surprise
was the magnitude of the CD8⁺ T-cell response to virus
infections ten to 100 times larger than many expected respond to an invading pathogen. The biggest surprise
was the magnitude of the $CD8^+$ T-cell response to virus
infections, ten to 100 times larger than many expected
 $(A\text{Itman et al. 1996: Butz & Revan 1998: Murali-Krishna}$ was the magnitude of the CD8⁺ T-cell response to virus
infections, ten to 100 times larger than many expected
(Altman *et al.* 1996; Butz & Bevan 1998; Murali-Krishna
et al. 1998: Tan *et al.* 1999). Nearly all the act infections, ten to 100 times larger than many expected (Altman *et al.* 1996; Butz & Bevan 1998; Murali-Krishna *et al.* 1998; Tan *et al.* 1999). Nearly all the activated Teells seen in an acute infection are virus specif (Altman *et al.* 1996; Butz & Bevan 1998; Murali-Krishna *et al.* 1998; Tan *et al.* 1999). Nearly all the activated T cells seen in an acute infection are virus specific, very few are activated as by estanders. These fin *et al.* 1998; Tan *et al.* 1999). Nearly all the activated T cells seen in an acute infection are virus specific, very few are activated as bystanders. These findings permit a revision of how T cells respond, of their dy T cells seen in an acute infection are virus specific, very *et al.* 2000). what they do.

2. ACUTE HUMAN IMMUNODEFIENCY VIRUS

SIMIAN IMMONODEFICIENCT VIRUS INFECTION
In acute human immunodeficiency virus (HIV) and
simian immunodeficiency virus (SIV) infection, the virus
replicates in an uncontrolled manner reaching a peak of In acute human immunodeficiency virus (HIV) and
simian immunodeficiency virus (SIV) infection, the virus
replicates in an uncontrolled manner, reaching a peak of
over 10^6 particles per millilitre of blood in about thre simian immunodeficiency virus (SIV) infection, the virus
replicates in an uncontrolled manner, reaching a peak of
over 10^6 particles per millilitre of blood in about three
weeks. The $CD8^+$ T-cell response peaks a few replicates in an uncontrolled manner, reaching a peak of over 10^6 particles per millilitre of blood in about three weeks. The CDB^+ T-cell response peaks a few days later over 10⁶ particles per millilitre of blood in about three
weeks. The CD8⁺ T-cell response peaks a few days later
and at this time there is a fall in the viraemia. It has long
been argued that these antigen-specific Tce weeks. The CD8⁺ T-cell response peaks a few days later
and at this time there is a fall in the viraemia. It has long
been argued that these antigen-specific T cells are respon-
sible for the reduction in virus load (Kou and at this time there is a fall in the viraemia. It has long
been argued that these antigen-specific T cells are respon-
sible for the reduction in virus load (Koup *et al.* 1994).
Strong support for this view comes from

macaques where $CD8^+$ T cells were removed by antibody
treatment *in nino*: when challenged with SIV the viraemia macaques where $C\text{D}8^+$ T cells were removed by antibody treatment *in vivo*; when challenged with SIV the viraemia macaques where $CD8^+$ T cells were removed by antibody
treatment *in vivo*; when challenged with SIV the viraemia
was not controlled until the $CD8^+$ T cells recovered from
their suppression (Schmitz *et al.* 1999). The p treatment *in vivo*; when challenged with SIV the viraemia
was not controlled until the CD8⁺ T cells recovered from
their suppression (Schmitz *et al.* 1999). The peak of the
CD8⁺ T-cell response reaches $1-10\%$ of al was not controlled until the CD8⁺ T cells recovered from
their suppression (Schmitz *et al.* 1999). The peak of the
CD8⁺ T-cell response reaches $1-10\%$ of all CD8⁺ T cells
in the blood both for HIV (Wilson *et al.* their suppression (Schmitz *et al.* 1999). The peak of the CD8⁺ T-cell response reaches $1-10\%$ of all CD8⁺ T cells in the blood, both for HIV (Wilson *et al.* 2000) and SIV $CD8^+$ T-cell response reaches $1-10\%$ of all $CD8^+$ T cells
in the blood, both for HIV (Wilson *et al.* 2000) and SIV
(Kuroda *et al.* 1999). It is not possible to measure the
number of HIV-specific T cells in uninfecte in the blood, both for HIV (Wilson *et al.* 2000) and SIV (Kuroda *et al.* 1999). It is not possible to measure the number of HIV-specific T cells in uninfected and unexposed people because the assays are not sensitive an (Kuroda *et al.* 1999). It is not possible to measure the number of HIV-specific T cells in uninfected and unexposed people because the assays are not sensitive and accurate enough but it is safe to estimate that the number of HIV-specific T cells in uninfected and
unexposed people because the assays are not sensitive and
accurate enough, but it is safe to estimate that the
number is less than one in a million. Therefore it is likely unexposed people because the assays are not sensitive and
accurate enough, but it is safe to estimate that the
number is less than one in a million. Therefore it is likely
that the T cells responding at the peak of the inf accurate enough, but it is safe to estimate that the
number is less than one in a million. Therefore it is likely
that the T cells responding at the peak of the infection
have divided over 15 times (figure 1). Essential to that the T cells responding at the peak of the infection have divided over 15 times (figure 1). Essential to the use that the T cells responding at the peak of the infection
have divided over 15 times (figure 1). Essential to the use
of the tetramer assay is knowledge of the dominant
enitone pertide and it does appear that for many virus have divided over 15 times (figure 1). Essential to the use
of the tetramer assay is knowledge of the dominant
epitope peptide and it does appear that for many viruses
the acute phase immune response is focused on very few of the tetramer assay is knowledge of the dominant
epitope peptide and it does appear that for many viruses
the acute phase immune response is focused on very few
epitopes out of the many that are theoretically possible epitope peptide and it does appear that for many viruses
the acute phase immune response is focused on very few
epitopes out of the many that are theoretically possible the acute phase immune response is focused on very few
epitopes out of the many that are theoretically possible
(Chen *et al.* 2000). It looks as if the immunodominance is
decided early on for reasons that are still not cl epitopes out of the many that are theoretically possible (Chen *et al.* 2000). It looks as if the immunodominance is decided early on, for reasons that are still not clear (Chen *et al.* 2000) (Chen *et al.* 2
decided early
et al. 2000).
HIV and S decided early on, for reasons that are still not clear (Chen *et al.* 2000). HIV and SIV infect dendritic cells and CD4⁺ helper T

response. Although the primary CD8⁺ T-cell response to
2. ACUTE HUMAN IMMUNODEFIENCY VIRUS HIV looks large, it appears to be smaller than the acute
AND SIMIAN IMMUNODEFICIENCY VIRUS INFECTION CH^+ T-cell response to In acute human immunodeficiency virus (HIV) and have been found at levels as high as 44% of CD8⁺ Tcells cells, both of which are critical cells of the immune HIV and SIV infect dendritic cells and $CD4^+$ helper T
cells, both of which are critical cells of the immune
system. Their infection could affect the $CD8^+$ T-cell
response Although the primary $CD8^+$ T-cell response to cells, both of which are critical cells of the immune
system. Their infection could affect the $CD8^+$ T-cell
response. Although the primary $CD8^+$ T-cell response to
HIV looks large it appears to be smaller than the acute system. Their infection could affect the $CD8^+$ T-cell
response. Although the primary $CD8^+$ T-cell response to
HIV looks large, it appears to be smaller than the acute
 $CD8^+$ T-cell response to Enstein–Barr virus (EBV) response. Although the primary $CD8^+$ T-cell response to HIV looks large, it appears to be smaller than the acute $CD8^+$ T-cell response to Epstein–Barr virus (EBV) (Callan *et al.* 1998). Here $CD8^+$ T cells specific for HIV looks large, it appears to be smaller than the acute
CD8⁺ T-cell response to Epstein–Barr virus (EBV)
(Callan *et al.* 1998). Here CD8⁺ T cells specific for EBV
have been found at levels as high as 44% of CD8⁺ T CD8⁺ T-cell response to Epstein-Barr virus (EBV)
(Callan *et al.* 1998). Here CD8⁺ T cells specific for EBV
have been found at levels as high as 44% of CD8⁺ T cells
in the blood of patients with infectious mononu in the blood of patients with infectious mononucleosis; the have been found at levels as high as 44% of $CD8^+$ T cells
in the blood of patients with infectious mononucleosis; the
range is between 5% and 45% . In acute infection with
lymphocytic choriomeningitis virus in mi in the blood of patients with infectious mononucleosis; the range is between 5% and 45%. In acute infection with lymphocytic choriomeningitis virus in mice, similar high numbers were observed (Murali-Krishna *et al.* 1998 range is between 5% and 45%. In acute infection w
lymphocytic choriomeningitis virus in mice, similar h
numbers were observed (Murali-Krishna *et al.* 1998).
In acute infectious mononucleosis, the expanded CI

been argued that these antigen-specific Tcells are respon-
sible for the reduction in virus load (Koup *et al.* 1994). They can kill antigen-expressing target cells at about the
Strong support for this view comes from stu Iymphocytic choriomeningitis virus in mice, similar high
numbers were observed (Murali-Krishna *et al.* 1998).
In acute infectious mononucleosis, the expanded CD8⁺
T-cell population is capable of function (Callan *et al.* In acute infectious mononucleosis, the expanded $CD8^+$
T-cell population is capable of function (Callan *et al.* 2000).
They can kill antigen-expressing target cells at about the
level expected. They release cytokines (X-T-cell population is capable of function (Callan $et al. 2000$).

?10 days long-term memory CD8⁺ T cells, ca. 0.01%

et al. (1999), Wilson *et al.* (2000) and Evans *et al.* (1999).
(IFN- γ), tumour necrosis factor- α (TNF- α) and macro-Figure 1. Possible dynamics of CD8⁺ T-cell response to (*a*) HIV, (*b*) a vaccine and (*c*) HIV after vaccination. In (*a*), the Figure 1. Possible dynamics of CD8⁺ T-cell response to (a) HIV, (b) a vaccine and (c) HIV after vaccination. In (a), the
calculated numbers of naive HIV-specific T cells (estimate), expanded effectors (detected with tet Figure 1. Possible dynamics of $CD8^+$ T-cell response to (*a*) HIV, (*b*) a vaccine and (*c*) HIV after vaccination. In (*a*), the calculated numbers of naive HIV-specific T cells (estimate), expanded effectors (detected calculated numbers of naive HIV-specific T cells (estimate), expanded effectors (detected with tetramers) and long-term memory
cells (detected by limiting dilution assay) are shown. In (b) , the similar response to a non*eells* (detected by limiting dilution assay) are shown. In (*b*) vaccine is shown. (*c*) The response to HIV in a vaccinated *et al.* (1999), Wilson *et al.* (2000) and Evans *et al.* (1999).

phage inflammatory protein-1 β (MIP-1 β)) rapidly on (IFN- γ), tumour necrosis factor- α (TNF- α) and macro-
phage inflammatory protein-1 β (MIP-1 β)) rapidly on I
contact with antigen-presenting cells, although not all T it
cells can do this However on removal fr phage inflammatory protein-1 β (MIP-1 β)) rapidly on
contact with antigen-presenting cells, although not all T
cells can do this. However, on removal from the body,
they die rapidly by apontosis (Callan *et al.* 2000) contact with antigen-presenting cells, although not all T
cells can do this. However, on removal from the body,
they die rapidly by apoptosis (Callan *et al.* 2000). Simi-
larly when stimulated by a non-persisting immunoge cells can do this. However, on removal from the body, conventional antigen-stimulated proliferation assay; only they die rapidly by apoptosis (Callan *et al.* 2000). Simi- a few long-term survivors show a response. Howeve (DNA and recombinant modified vaccinia virus Ankara) larly, when stimulated by a non-persisting immunogen
(DNA and recombinant modified vaccinia virus Ankara)
the high $CD8^+$ T-cell peak decays rapidly with a half-life
in the blood of about seven days (Hanke et al. 1999) Th (DNA and recombinant modified vaccinia virus Ankara)
the high CD8⁺ T-cell peak decays rapidly with a half-life
in the blood of about seven days (Hanke *et al.* 1999). The
expanded Tcells appear therefore to be end-stage the high $CD8^+$ T-cell peak decays rapidly with a half-life
in the blood of about seven days (Hanke *et al.* 1999). The
expanded T cells appear therefore to be end-stage T cells,
functioning but not canable of dividing fu in the blood of about seven days (Hanke *et al.* 1999). The expanded T cells appear therefore to be end-stage T cells, functioning but not capable of dividing further. Memory is maintained by a minor subset of T cells within the same functioning but not capable of dividing further. Memory
is maintained by a minor subset of T cells within the same
clonal population that are able to divide further (Tan
 et ^d d¹ 1999). The functional status of T cells is maintained by a minor subset of Tcells within the same
clonal population that are able to divide further (Tan
et al. 1999). The functional status of Tcells in acute HIV
infection is not yet known: preliminary experime clonal population that are able to divide further (Tan *et al.* 1999). The functional status of T cells in acute HIV infection is not yet known; preliminary experiments suggest some impairment of cytokine release and of *et al.* 1999). The functional status of T cells in acute HIV infection is not yet known; preliminary experiments suggest some impairment of cytokine release and of perforin expression (V. Appay, unpublished data).

In acute HIV infection there is an early CD4⁺ T-cell perforin expression (V. Appay, unpublished data).
In acute HIV infection there is an early CD4⁺ T-cell
response, but this has been hard to demonstrate, possibly
because the acutely reacting T cells are infected and In acute HIV infection there is an early $CD4^+$ T-cell
response, but this has been hard to demonstrate, possibly
because the acutely reacting T cells are infected and
damaged by the HIV However Pitcher et al. (1999) have response, but this has been hard to demonstrate, possibly
because the acutely reacting T cells are infected and
damaged by the HIV. However, Pitcher *et al.* (1999) have
been able to demonstrate HIV-specific CD4⁺ T cells because the acutely reacting T cells are infected and
damaged by the HIV. However, Pitcher *et al.* (1999) have
been able to demonstrate HIV-specific $CD4^+$ T cells by
using intracellular cytokine staining (after a few ho damaged by the HIV. However, Pitcher *et al.* (1999) have been able to demonstrate HIV-specific $CD4^+$ T cells by using intracellular cytokine staining (after a few hours of exposure to antigen). The number found was subs been able to demonstrate HIV-specific CD4⁺ T cells by
using intracellular cytokine staining (after a few hours of
exposure to antigen). The number found was substantial
in patients with stable infection but less than the using intracellular cytokine staining (after a few hours of exposure to antigen). The number found was substantial
in patients with stable infection but less than the number

responding to cytomegalovirus, another persisting virus. Despite the clear presence of HIV-specific $CD4^+$ T cells, responding to cytomegalovirus, another persisting virus.
Despite the clear presence of HIV-specific CD4⁺ T cells,
it has been almost impossible to demonstate them by the
conventional antigen-stimulated proliferation assa Despite the clear presence of HIV-specific CD4⁺ T cells,
it has been almost impossible to demonstate them by the
conventional antigen-stimulated proliferation assay; only
a few long-term survivors show a response. Howeve it has been almost impossible to demonstate them by the
conventional antigen-stimulated proliferation assay; only
a few long-term survivors show a response. However,
Rosenberg et al. (1997) showed that it was possible to Rosenberg *et al*. (1997) showed that it was possible to a few long-term survivors show a response. However,
Rosenberg *et al.* (1997) showed that it was possible to
rescue this response by treating acutely infected persons
very early with potent antiretroviral drugs. Thus there Rosenberg *et al.* (1997) showed that it was possible to rescue this response by treating acutely infected persons very early with potent antiretroviral drugs. Thus there annears to be an early impairment of the $CD4^+$ Trescue this response by treating acutely infected persons
very early with potent antiretroviral drugs. Thus there
appears to be an early impairment of the CD4⁺ T-cell
response that might affect the initiation of the CD8 very early with potent antiretroviral drugs. Thus there appears to be an early impairment of the $CD4^+$ T-cell response that might affect the initiation of the $CD8^+$ T-cell response. Nevertheless, the $CD8^+$ T-cell respo T-cell response. Nevertheless, the $CD8⁺$ T-cell response is virus load. The suspicion remains, however, that it is not substantial, mostly functional and important in reducing
virus load. The suspicion remains, however, that it is not
as effective as it might be and that this could result in
higher virus loads at the set-point, once the ac virus load. The suspicion remains, however, that it is not
as effective as it might be and that this could result in
higher virus loads at the set-point, once the acute phase
stabilizes than might otherwise be found as effective as it might be and that this c
higher virus loads at the set-point, once th
stabilizes, than might otherwise be found. stabilizes, than might otherwise be found.
3. CHRONIC HIV INFECTION

chronic infection: effector/expanded $CD8⁺$ T cells $0.1 - 2\%$

> long-term CD8⁺ memory cells *ca*. 0.01%

HIV contact

effector CD8⁺ T cells in vaccinated person after

In chronic HIV infection, during the asymptomatic phase, there is a strong ongoing anti-HIV CD8⁺ T-cell response (Ogg *et al.* 1998). Often antigen-specific CD8⁺ In chronic HIV infection, during the asymptomatic
phase, there is a strong ongoing anti-HIV CD8⁺ T-cell
response (Ogg *et al.* 1998). Often antigen-specific CD8⁺
T cells constitute over 1.0% of all CD8⁺ T cells w response (Ogg *et al.* 1998). Often antigen-specific CD8⁺
T cells constitute over 1.0% of all CD8⁺ T cells when
there is an identifiable, immunodominant T-cell
response Ogg *et al.* (1998) have shown that there is an T cells constitute over 1.0% of all CD8⁺ T cells when
there is an identifiable, immunodominant T-cell
response. Ogg *et al.* (1998) have shown that there is an

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inverse correlation between the number of T cells specific
for immunodominant gag and pol enitones presented by inverse correlation between the number of T cells specific
for immunodominant gag and pol epitopes presented by
HLA-A2 and the plasma virus RNA load This is in a for immunodominant gag and pol epitopes presented by HLA-A2 and the plasma virus RNA load. This is in a for immunodominant gag and pol epitopes presented by
HLA-A2 and the plasma virus RNA load. This is in a
pseudo-equilibrium state and has been the subject of
considerable discussion (see McMichael *et al.* 2000) In HLA-A2 and the plasma virus RNA load. This is in a
pseudo-equilibrium state and has been the subject of
considerable discussion (see McMichael *et al.* 2000). In
HTIV-1 infection C. Bangham (personal communicapseudo-equilibrium state and has been the subject of considerable discussion (see McMichael *et al.* 2000). In HTLV-1 infection, C. Bangham (personal communica-
tion) has shown that there is a positive correlation considerable discussion (see McMichael *et al.* 2000). In humans (Connor *et al.* 1998), much attention has now HTLV-1 infection, C. Bangham (personal communica-
tion) has shown that there is a positive correlation There between virus load and $CD8^+$ T-cell number, suggesting that the negative correlation reported by Ogg *et al.* tion) has shown that there is a positive correlation
between virus load and CD8⁺ T-cell number, suggesting
that the negative correlation reported by Ogg *et al.*
(1998) might reflect suppression of the CD8⁺ T-cell
resp that the negative correlation reported by Ogg *et al.* (1998) might reflect suppression of the $CD8^+$ T-cell response by the virus, presumably through the effects on HIV-specific $CD4^+$ T cells. Mathematical modelling (1998) might reflect suppression of the $CD8^+$ T-cell
response by the virus, presumably through the effects on
HIV-specific $CD4^+$ T cells. Mathematical modelling
arguments support this model (D Wodarz and M Nowak response by the virus, presumably through the effects on HIV-specific CD4⁺ T cells. Mathematical modelling arguments support this model (D.Wodarz and M. Nowak, personal communication) as does the obvious finding arguments support this model (D. Wodarz and M. Nowak, personal communication), as does the obvious finding arguments support this model (D. Wodarz and M. Nowak,
personal communication), as does the obvious finding a
that no virus means no detectable HIV-specific CD8⁺ T
cells. We have suggested therefore that the relationship personal communication), as does the obvious finding
that no virus means no detectable HIV-specific CD8⁺ T
cells. We have suggested therefore that the relationship
between virus load and cytotoxic T-lymphocyte (CTL) between virus load and cytotoxic T-lymphocyte (CTL) cells. We have suggested therefore that the relationship
between virus load and cytotoxic T-lymphocyte (CTL)
number is biphasic with a positive correlation at low
virus load, but that above a certain virus level HIV between virus load and cytotoxic T-lymphocyte (CTL) ti
number is biphasic with a positive correlation at low
virus load, but that above a certain virus level, HIV ki
effectively suppresses the CTL response—most of the number is biphasic with a positive correlation at low
virus load, but that above a certain virus level, HIV
effectively suppresses the CTL response—most of the
patients seen are in this second phase (D Wodarz and virus load, but that above a certain virus level, HIV kill virus-infected cells and prevent them from producing
effectively suppresses the CTL response—most of the new virus particles, but they cannot prevent infection, as effectively suppresses the CTL response—most of the
patients seen are in this second phase (D. Wodarz and
M. Nowak, personal communication). This does not
mean that the CTLs fail to suppress the virus patients seen are in this second phase (D. Wodarz and the M. Nowak, personal communication). This does not the mean that the CTLs fail to suppress the virus— large macaque experiments where the CDR^+ T cells are ger M. Nowak, personal communication). This does not
mean that the CTLs fail to suppress the virus—
macaque experiments where the CDB^+ T cells are
removed in vivo in ongoing SIV infection resulting in mean that the CTLs fail to suppress the virus—
macaque experiments where the CD8⁺ T cells are
removed *in vivo* in ongoing SIV infection, resulting in
higher virus loads support this view (Jin *et al* 1999. macaque experiments where the CD8⁺ T cells are
removed *in vivo* in ongoing SIV infection, resulting in
higher virus loads, support this view (Jin *et al.* 1999;
Schmitz *et al.* 1999). However it does argue that the removed *in vivo* in ongoing SIV infection, resulting in higher virus loads, support this view (Jin *et al.* 1999; Schmitz *et al.* 1999). However it does argue that the CD8⁺ T-cell response is not as effective as it mig higher virus loads, support this view (Jin *et al.* 1999; Schmitz *et al.* 1999). However it does argue that the $CD8^+$ T-cell response is not as effective as it might be in HIV infection Schmitz *et al.* 1999). However it does argue that the $CD8^+$ T-cell response is not as effective as it might be in HIV infection.

This view is reinforced by the findings of Appay *et al.* HIV infection.
This view is reinforced by the findings of Appay *et al.*
(2000), who examined HIV-specific $CD8^+$ T-cell func-
tion in samples from chronically infected persons This view is reinforced by the findings of Appay *et al.* (2000), who examined HIV-specific $CD8^+$ T-cell function in samples from chronically infected persons.
Whereas these T cells responded well to antigen stimula-(2000), who examined HIV-specific $CD8^+$ T-cell function in samples from chronically infected persons.
Whereas these T cells responded well to antigen stimula-
tion to make $JEN- γ TN- γ and MIP-18 levels of$ tion in samples from chronically infected persons.
Whereas these Tcells responded well to antigen stimulation to make IFN- γ , TNF- α and MIP-1 β , levels of perforin were very low This was particularly striking Whereas these T cells responded well to antigen stimulation to make IFN- γ , TNF- α and MIP-1 β , levels of perforin were very low. This was particularly striking when the HIV-specific T-cell responses were compared tion to make IFN- γ , TNF- α and MIP-1 β , levels of
perforin were very low. This was particularly striking
when the HIV-specific T-cell responses were compared
to extomegalovirus-specific T-cells in the same patients perforin were very low. This was particularly striking
when the HIV-specific T-cell responses were compared
to cytomegalovirus-specific T cells in the same patients.
The low perforin levels were found regardless of the when the HIV-specific T-cell responses were compared
to cytomegalovirus-specific T cells in the same patients.
The low perforin levels were found regardless of the
virus load, even when undetectable as the result of to cytomegalovirus-specific T cells in the same patients.
The low perforin levels were found regardless of the
virus load, even when undetectable as the result of
aggressive antiretroviral drug therapy Therefore it seems virus load, even when undetectable as the result of aggressive antiretroviral drug therapy. Therefore it seems virus load, even when undetectable as the result of aggressive antiretroviral drug therapy. Therefore it seems
that perforin expression is impaired, perhaps a failure of CDB^+ T-cell maturation due to poor $CD4^+$ T-cell b aggressive antiretroviral drug therapy. Therefore it seems
that perforin expression is impaired, perhaps a failure of
 $CD8^+$ T-cell maturation due to poor $CD4^+$ T-cell help
(Zaiac et al. 1998) that perforin expres

CD8⁺ T-cell matur

(Zajac *et al.* 1998).

The high number $CD8^+$ T-cell maturation due to poor $CD4^+$ T-cell help (Zajac *et al.* 1998).
The high number of tetramer-staining cells in late

(Zajac *et al.* 1998).
The high number of tetramer-staining cells in late
HIV infection implies that they are surviving well or
are actively replaced from long-term memory T after The high number of tetramer-staining cells in late
HIV infection implies that they are surviving well or
are actively replaced, from long-term memory T, after
apoptosis We favour the latter though data to distin-HIV infection implies that they are surviving well or
are actively replaced, from long-term memory T, after
apoptosis. We favour the latter, though data to distin-
quich these possibilities are lacking. The number of are actively replaced, from long-term memory T, after
apoptosis. We favour the latter, though data to distinguish these possibilities are lacking. The number of
CD8⁺ T cells specific for HIV remains high throughout apoptosis. We favour the latter, though data to distinguish these possibilities are lacking. The number of $CD8^+$ T cells specific for HIV remains high throughout the infection but the infection nevertheless progresses guish these possibilities are lacking. The number of CD8⁺ Tcells specific for HIV remains high throughout the infection nevertheless progresses. Contributing factors to this are possible progressively CDB^+ T cells specific for HIV remains high throughout
the infection but the infection nevertheless progresses.
Contributing factors to this are possible progressively
greater impairment of CDB^+ T-cell function and the the infection but the infection nevertheless progresses.
Contributing factors to this are possible progressively
greater impairment of CD8⁺ T-cell function and the
selection of escape mutants. Appearance and selection Contributing factors to this are possible progressively
greater impairment of $CD8^+$ T-cell function and the
selection of escape mutants. Appearance and selection
of escape mutants has now been shown in several greater impairment of CD8⁺ T-cell function and the selection of escape mutants. Appearance and selection of escape mutants has now been shown in several selection of escape mutants. Appearance and selection
of escape mutants has now been shown in several
patients and also in macaques (Evans *et al.* 1999;
Goulder *et al.* 1997; Phillips *et al.* 1991). The conseof escape mutants has now been shown in several
patients and also in macaques (Evans *et al.* 1999;
Goulder *et al.* 1997; Phillips *et al.* 1991). The conse-
quences are uncertain but at the very least new CD8⁺ patients and also in macaques (Evans *et al.* 1999; ti

Goulder *et al.* 1997; Phillips *et al.* 1991). The consequences are uncertain, but at the very least new CD8⁺ th

T-cell responses to alternative epitopes, i.e. n quences are uncertain, but at the very least new $CD8^+$
T-cell responses to alternative epitopes, i.e. new
primary T-cell responses, must be required. Again,
impaired $CD4^+$ T-cell belp must weaken these new T-cell responses to alternative epitopes, i.e. new reprimary T-cell responses, must be required. Again, a impaired $CD4^+$ T-cell help must weaken these new fire primary T-cell responses, must be required. Again,
impaired CD4⁺ T-cell help must weaken these new
responses and could contribute significantly to the
gradual and harmful increase in virus load that occurs impaired $CD4^+$ T-cell help must weaken these new responses and could contribute significantly to the gradual and harmful increase in virus load that occurs as the infection progresses. responses and could contribute significantly to the

4. IMPLICATIONS FOR VACCINES

Given the difficulty of current strategies to stimulate 4. INFLICATIONS FOR VACCINES

Effective HIV-neutralizing antibodies in animals and

humans (Connor *et al.* 1998) much attention has now Given the difficulty of current strategies to stimulate
effective HIV-neutralizing antibodies in animals and
humans (Connor *et al.* 1998), much attention has now
heen directed towards stimulating CDA^+ T-cell responses effective HIV-neutralizing antibodies in animals and
humans (Connor *et al.* 1998), much attention has now
been directed towards stimulating $CD8^+$ T-cell responses.
There are good data in animal models of other virus and been directed towards stimulating CD8⁺ T-cell responses. been directed towards stimulating CD8⁺ T-cell responses.
There are good data in animal models of other virus and
parasite infections that CTL can protect against new
infection (Brehm *et al.* 1997: En *et al.* 1999: Schn There are good data in animal models of other virus and
parasite infections that CTL can protect against new
infection (Brehm *et al.* 1997; Fu *et al.* 1999; Schneider *et al.*
1998). In HIV infection, extensive data from infection (Brehm *et al.* 1997; Fu *et al.* 1999; Schneider *et al.* 1998). In HIV infection, extensive data from a small subset of African sex workers who are highly exposed to 1998). In HIV infection, extensive data from a small subset of African sex workers who are highly exposed to HIV but not infected, implies that their CTL response protects them from infection as long as the CTL levels subset of African sex workers who are highly exposed to HIV but not infected, implies that their CTL response
protects them from infection, as long as the CTL levels
are maintained (Rowland-Jones *et al.* 1999). In macaque HIV but not infected, implies that their CTL response
protects them from infection, as long as the CTL levels
are maintained (Rowland-Jones *et al.* 1999). In macaque
SIV infection models, data suggest that vaccine-induced protects them from infection, as long as the CTL levels
are maintained (Rowland-Jones *et al.* 1999). In macaque
SIV infection models, data suggest that vaccine-induced are maintained (Rowland-Jones *et al.* 1999). In macaque SIV infection models, data suggest that vaccine-induced CTL can protect or at least lower virus loads when infection occurs (Kent *et al.* 1998: Robinson *et al.* 1 SIV infection models, data suggest that vaccine-in CTL can protect or at least lower virus loads when
tion occurs (Kent *et al.* 1998; Robinson *et al.* 1999).
How do CTLs protect against HIV infection? FL can protect or at least lower virus loads when infec-
n occurs (Kent *et al.* 1998; Robinson *et al.* 1999).
How do CTLs protect against HIV infection? CTLs
l virus-infected cells and prevent them from producing tion occurs (Kent *et al.* 1998; Robinson *et al.* 1999).
How do CTLs protect against HIV infection? CTLs

How do CTLs protect against HIV infection? CTLs
kill virus-infected cells and prevent them from producing
new virus particles, but they cannot prevent infection, as
they have no activity against naked virus. Furthermore kill virus-infected cells and prevent them from producing
new virus particles, but they cannot prevent infection, as
they have no activity against naked virus. Furthermore,
the kinetics of the antivirus CTL response shows new virus particles, but they cannot prevent infection, as
they have no activity against naked virus. Furthermore,
the kinetics of the antivirus CTL response shows that
large numbers of activated effector T cells can be re they have no activity against naked virus. Furthermore, the kinetics of the antivirus CTL response shows that large numbers of activated effector T cells can be readily generated, but if antigen does not persist, they disa large numbers of activated effector T cells can be readily large numbers of activated effector T cells can be readily
generated, but if antigen does not persist, they disappear
rapidly (Hanke *et al.* 1999; figure 1*b*). Current vaccine
constructs are designed not to persist, for generated, but if antigen does not persist, they disappear
rapidly (Hanke *et al.* 1999; figure 1*b*). Current vaccine
constructs are designed not to persist, for safety reasons
demanded by the regulatory authorities. Ther rapidly (Hanke *et al.* 1999; figure 1*b*). Current vaccine constructs are designed not to persist, for safety reasons demanded by the regulatory authorities. Therefore it is likely that any protection will have to come f constructs are designed not to persist, for safety reasons
demanded by the regulatory authorities. Therefore it is
likely that any protection will have to come from the
long-term memory population. demanded by the regulatory authorities. Therefore it is

Long-term memory T cells are probably best detected long-term memory population.

Long-term memory T cells are probably best detected

by limiting dilution assays, which demand multiple

(about 12) divisions in vitro and maturation to effectors Long-term memory T cells are probably best detected
by limiting dilution assays, which demand multiple
(about 12) divisions *in vitro* and maturation to effectors.
The Elisnot assay probably detects the same population by limiting dilution assays, which demand multiple (about 12) divisions *in vitro* and maturation to effectors.
The Elispot assay probably detects the same population in a situation where antigenic challenge occurred many (about 12) divisions *in vitro* and maturation to effectors.
The Elispot assay probably detects the same population
in a situation where antigenic challenge occurred many The Elispot assay probably detects the same population
in a situation where antigenic challenge occurred many
months ago and antigen is no longer present, e.g.
influenza infection and detects very similar cell numbers in a situation where antigenic challenge occurred many
months ago and antigen is no longer present, e.g.
influenza infection, and detects very similar cell numbers
to the limiting dilution assay (Lalvani et al. 1997). Thi months ago and antigen is no longer present, e.g.
influenza infection, and detects very similar cell numbers
to the limiting dilution assay (Lalvani *et al.* 1997). This
indicates that long-term memory T cells can be activ influenza infection, and detects very similar cell numbers
to the limiting dilution assay (Lalvani *et al.* 1997). This
indicates that long-term memory T cells can be activated to the limiting dilution assay (Lalvani *et al.* 1997). This indicates that long-term memory T cells can be activated to function (interferon secretion) within 6 h and before the cell divides (Lalvani *et al.* 1997). Thus indicates that long-term memory T cells can be activated
to function (interferon secretion) within 6 h and before
the cell divides (Lalvani *et al.* 1997). Thus in a person who
was vaccinated several months ago by a CTL-in to function (interferon secretion) within 6 h and before
the cell divides (Lalvani *et al.* 1997). Thus in a person who
was vaccinated several months ago by a CTL-inducing
vaccine, there may not be instant killing of any the cell divides (Lalvani *et al.* 1997). Thus in a person who was vaccinated several months ago by a CTL-inducing vaccine, there may not be instant killing of any HIV-infected cells that appear, but there is a response t was vaccinated several months ago by a CTL-inducing
vaccine, there may not be instant killing of any HIV-
infected cells that appear, but there is a response that
differs substantially from that of the primary CTI. vaccine, there may not be instant killing of any HIV-
infected cells that appear, but there is a response that
differs substantially from that of the primary CTL infected cells that appear, but there is a response that
differs substantially from that of the primary CTL
response (figure 1*c*). The first advantage is in antigen-
specific Leell numbers: 10⁶ for an unprimed person an differs substantially from that of the primary CTL
response (figure $1c$). The first advantage is in antigen-
specific T-cell numbers: 10^6 for an unprimed person and
 10^4 for a nerson with memory. This would give an $10⁴$ for a person with memory. This would give an specific T-cell numbers: 10^6 for an unprimed person and specific T-cell numbers: 10^6 for an unprimed person and 10^4 for a person with memory. This would give an advantage of seven divisions (2^7) , about seven days.
Second it has been shown that memory T cells respond 10^4 for a person with memory. This would give an advantage of seven divisions (2^7) , about seven days.
Second, it has been shown that memory T cells respond
much more ranidly than memory T cells and as indicated advantage of seven divisions (2^7) , about seven days.
Second, it has been shown that memory T cells respond
much more rapidly than memory T cells and, as indicated
above can release cytokines almost immediately Second, it has been shown that memory T cells respond
much more rapidly than memory T cells and, as indicated
above, can release cytokines almost immediately
(Tanchot *et al.* 1998); this could give an advantage of a much more rapidly than memory Tcells and, as indicated above, can release cytokines almost immediately (Tanchot *et al.* 1998); this could give an advantage of a few more days. Thus, the vaccine-primed person should above, can release cytokines almost immediately (Tanchot *et al.* 1998); this could give an advantage of a few more days. Thus, the vaccine-primed person should be able to respond much more rapidly to the new infection although the magnitude of the response might be few more days. Thus, the vaccine-primed person should
be able to respond much more rapidly to the new infec-
tion, although the magnitude of the response might be
less if the virus load was well controlled. In addition be able to respond much more rapidly to the new infection, although the magnitude of the response might be less if the virus load was well controlled. In addition, the ability of a vaccine to stimulate a good T-helper-cell tion, although the magnitude of the response might be
less if the virus load was well controlled. In addition,
the ability of a vaccine to stimulate a good T-helper-cell
response may give the primed person a further crucia less if the virus load was well controlled. In addition,
the ability of a vaccine to stimulate a good T-helper-cell
response may give the primed person a further crucial
advantage ensuring that all the virus-specific T cel the ability of a vaccine to stimulate a good T-helper-cell
response may give the primed person a further crucial
advantage, ensuring that all the virus-specific T cells are
functional and again speeding up the response. Th response may give the primed person a further crucial to be balanced for HIV infection with the possibility functional and again speeding up the response. This has
to be balanced for HIV infection with the possibility
that these activated T cells will be good host cells for the
virus to infect. Whether, these advantages add up to be balanced for HIV infection with the possibility
that these activated T cells will be good host cells for the
virus to infect. Whether these advantages add up

enough to clear an incoming HIV infection remains to
the seen but there is a chance and at the least the level enough to clear an incoming HIV infection remains to
be seen, but there is a chance and at the least, the level
of HIV at the set point should be lower, with a better be seen, but there is a chance and at the least, the level of HIV at the set point should be lower, with a better prognosis.

5. CONCLUSIONS

The studies reviewed here give a kinetic view of HIV infection that is of crucial importance in understanding The studies reviewed here give a kinetic view of HIV
infection that is of crucial importance in understanding
the natural response and how effective it is. This under-
standing is crucial for design of vaccines that can pr infection that is of crucial importance in understanding
the natural response and how effective it is. This under-
standing is crucial for design of vaccines that can prime
the T-cell response to be able to control infecti the natural response and how effective it is. This under-
standing is crucial for design of vaccines that can prime
the T-cell response to be able to control infection and
even clear it when the infecting challenge is low standing is crucial for design of vaccines that can pri-
the T-cell response to be able to control infection a
even clear it when the infecting challenge is low dose.

REFERENCES

- Altman, J. D., Moss, P., Goulder, P., Barouch, D. H., MCHENCLO

McHeyzer, W. M., Bell, J. I., McMichael, A. J. & Davis,

M. M. 1996 Phenotypic analysis of antigen-specific T tman, J. D., Moss, P., Goulder, P., Barouch, D. H.,
McHeyzer, W. M., Bell, J. I., McMichael, A. J. & Davis, I.
M. M. 199[6 Phenotypic anal](http://matilde.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0036-8075^28^29274L.94[aid=166090,doi=10.1126/science.274.5284.94,nlm=8810254])ysis of antigen-specific T
lymphocytes Science 274 94–96 (Published erratum appears McHeyzer, W. M., Bell, J. I., McMichael, A. J. & Davis, M. M. 1996 Phenotypic analysis of antigen-specific T
lymphocytes. *Science* 2**74**, 94–96. (Published erratum appears
in *Science* 1998 2**80** 1891) M. M. 1996 Phenotypic
lymphocytes. *Science* **274**, 94
in *Science* 1998 **280**, 1821.)
nnav V (and 15 others) 2 lymphocytes.*Science* **274**, 94–96. (Published erratum appears
in *Science* 1998 **280**, 1821.)
Appay, V. (and 15 others) 2000 HIV-specific CD8⁺ T cells
produce antiviral cytokines but are impaired in cytokitic
- in *Science* 1998 **280**, 1821.)
ppay, V. (and 15 others) 2000 HIV-specific $CD8^+$ T cells
produce antiviral cytokines but are impaired in cytolytic
function $\begin{array}{c} \mathcal{F} \to Kr \mathfrak{h} \mathfrak{h} \mathfrak{h} \end{array}$ (In the press) pay, V. (and 15 others) 2000 HIV-
produce antiviral cytokines but are
function. *J. Exp. Med.* (In the press.)
ehm M. A. Bonneau R. H. Knine 1 produce antiviral cytokines but are impaired in cytolytic
function. J. Exp. Med. (In the press.)
Brehm, M. A., Bonneau, R. H., Knipe, D. M. & Tevethia, S. S.
1997 Immunization with a replication-deficient mutant of
- function. \tilde{j} . *Exp. Med.* (In the press.)
ehm, M. A., Bonneau, R. H., Knipe, D. M. & Tevethia, S. S.
1997 Immunization with a replication-deficient mutant of
herpes simpley virus type 1 (HSV-1) induces a CD8⁺ 1997 Immunization with a replication-deficient mutant of herpes simplex virus type 1 (HSV-1) induces a $CD8^+$ 1997 Immunization with a replication-deficient mutant of
herpes simplex virus type 1 (HSV-1) induces a $CD8^+$
cytotoxic T-lymphocyte response and confers [a level of](http://matilde.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0022-538X^28^2971L.3534[aid=535927])
protection comparable to that of wild-type HSV-1 $\frac{7 \text$ herpes simplex virus type 1 (HSV-1) induces a CD8⁺ cytotoxic T-lymphocyte response and confers a level of protection comparable to that of wild-type HSV-1. *J. Virol.* **71**, 3534–3544. protectioncomparable to that of wild-type HSV-1. *J. Virol.* **71**, 3534–3544.
Butz, E. A. & Bevan, M. J. 1998 Massive expansion of antigen-
- 3534–3544.
tz, E. A. & Bevan, M. J. 1998 Massive expansion of antigen-
specific CD8⁺ Tcells during an acute virus infection. *Immunity*
8 167–175 **12, E. A. &
specific CD8**
8, 167–175.
Illan M F specific CD8⁺ T cells during an acute virus infection. *Immunity*
8, 167–175.
Callan, M. F., Tan, L., Annels, N., Ogg, G. S., Wilson, J. D.,
O'Callaghan, G. A., Steven, N., McMichael, A. J. &
- 8, 167–175.
illan, M. F., Tan, L., Annels, N., Ogg, G. S., Wilson, J. D.,
O'Callaghan, C. A., Steven, N., McMichael, A. J. & P.
Rickinson A. B. 1998 Direct visualization of antigen-specific Illan, M. F., Tan, L., Annels, N., Ogg, G. S., Wilson, J. D., O'Callaghan, C. A., Steven, N., McMichael, A. J. &
Rickinson, A. B. 1998 Direct visualization of antigen-specific
CD8⁺ T cells during the primary immune respo Rickinson, A. B. 1998 Direct visualization of antigen-specific CD8⁺ T cells during the primary immune response to Epstein^Barr virus *in vivo*. *J. Exp. Med.* **¹⁸⁷**, 1395^1402. CD8⁺T cells during the primary immune response to
Epstein-Barr virus *in vivo.* J. Exp. Med. **187**, 1395–1402.
Callan, M. F., Fazou, C., Hatton, C. & McMichael, A. J. 2000
CD8⁺ T cell selection function and death in
- Epstein-Barr virus *in vivo.* J. Exp. Med. 187, 1395-1402.
Illan, M. F., Fazou, C., Hatton, C. & McMichael, A. J. 2000
CD8⁺ T cell selection, function and death in the primary
immune response *in vivo*. (Submitted) CD8⁺ T cell selection, function and death in the primary immune response *in vivo*. (Submitted.) CD8⁺ T cell selection, function and death in the primary
immune response *in vivo*. (Submitted.)
Chen, W., Anton, L. C., Bennink, J. R. & Yewdell, J. W. 2000
Dissection the multifactorial causes of immunodominance in
- immune response *in vivo*. (Submitted.)
ten, W., Anton, L. C., Bennink, J. R. & Yewdell, J. W. 2000
Dissecting the multifactorial causes of immunodominance in
class L-restricted T cell responses to viruses *Immunit*y 12 Dissecting the multifactorial causes of immunodominance in class I-restricted T cell responses to viruses. *Immunity* **12**, 83–93. class I-restricted T cell responses to viruses. *Immunity* 12, $83-93$.
Connor, R. I. (and 10 others) 1998 Temporal analyses of virus replication immune responses and efficacy in rhesus macaques
- 83–93.
pnnor, R. I. (and 10 others) 1998 Temporal analyses of virus
replication, immune responses, and efficacy in rhesus macaques
immunized with a live, attenuated simian immunodeficiency photo, R. I. (and 10 others) 1998 Temporal analyses of virus
replication, immune responses, and efficacy in rhesus macaques
immunized with a live, attenuated simian immunodeficiency
virus vaccine. 7 Viral 72, 7501–7509 replication, immune responses, and efficacy in rhesus macaques
immunized with a live, attenuated simian immunodeficiency
virus vaccine. $\tilde{\jmath}$ *Virol.* **72**, 7501-7509. immunizedwith a live, attenuated simian immunodeficiency
virus vaccine. J . Virol. 72, 7501-7509.
Evans, D. T. (and 16 others) 1999 Virus-specific cytotoxic T-
lymphocyte responses select for amino-acid variation in
- virus vaccine. *J. Virol.* **72**, 7501–7509.
vans, D. T. (and 16 others) 1999 Virus-specific cytotoxic T-
lymphocyte responses select for amino-aci[d variation in](http://matilde.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/1078-8956^28^295L.1270[aid=535929,doi=10.1038/15224,nlm=10545993])
simian immunodeficiency virus Eny and Nef. *Nature Med* 5. rans, D. T. (and 16 others) 1999 Virus-specific cytotoxic T-lymphocyte responses select for amino-acid variation in simian immunodeficiency virus Env and Nef. *Nature Med.* 5, 1270–1276. simianimmunodeficiency virus Env and Nef. Nature Med. 5, 1270-1276.
Fu, T. M., Guan, L., Friedman, A., Schofield, T. L., Ulmer,
- 1270–1276.
, T. M., Guan, L., Friedman, A., Schofield, T. L., Ulmer,
J. B., Liu, M. A. & Donnelly, J. J. 1999 Dose dependence of
CTL precursor frequency induced by a DNA vaccine and T. M., Guan, L., Friedman, A., Schofield, T. L., Ulmer, J. B., Liu, M. A. & Donnelly, J. J. 1999 Dose dependence of CTL precursor frequency induced by a DNA vaccine and correlation with protective immunity against influenz J. B., Liu, M. A. & Donnelly, J. J. 1999 Dose dependence of CTL precursor frequency induced by a DNA vaccine and correlation with protective immunity against influenza virus challenge $\frac{7}{2}$ *Immunol* 162 4163–4170 CTL precursor frequency induced by
correlation with protective immunity :
challenge. *J. Immunol.* **162**, 4163–4170.
pulder P. I. (and 11 others) 1997 I ate correlation with protective immunity against influenza virus
challenge. J. Immunol. 162, 4163-4170.
Goulder, P. J. (and 11 others) 1997 Late escape from an immu-
nodominant cytotoxic T-lymphocyte response associated with
- challenge. *J. Immunol.* **162**, 4163–4170.
pulder, P. J. (and 11 others) 1997 Late escape from an immu-
nodominant cytotoxic T-lymphocyte response associated with
progression to AIDS. *Nature Med* 3, 212–217 pulder, P. J. (and 11 others) 1997 Late escape
nodominant cytotoxic T-lymphocyte response
progression to AIDS. *Nature Med.* 3, 212–217.
anke T. (and 11 others) 1999 Effective indu progressionto AIDS. Nature Med. 3, 212-217.
Hanke, T. (and 11 others) 1999 Effective induction of simian
- progression to AIDS. *Nature Med.* 3, 212–217.
anke, T. (and 11 others) 1999 Effective induction of simian
immunodeficiency virus-specific cytotoxic T lymphocytes in
macaques by using a multienitone gene and DNA primeanke, T. (and 11 others) 1999 Effective induction of simian
immunodeficiency virus-specific cytotoxic T lymphocytes in
macaques by using a multiepitope gene and DNA prime-
modified vaccinia virus Ankara boost vaccination macaques by using a multiepitope gene and DNA prime-
modified vaccinia virus Ankara boost vaccination regimen. *J.*
Virol. **73**, 7524–7532. modified vaccinia virus Ankara boost vaccination regimen. \tilde{J} .
- Jin, X. (and 13 others) 1999 Dramatic rise in plasma viremia a, X. (and 13 others) 1999 Dramatic rise in plasma viremia
after CD8(⁺) T cell depletion in simian immunodeficiency
virus-infected macagues $\frac{7}{100}$ Kth Med 189 991-998 viewel, N. (and 13 others) 1999 Dramatic rise in plasmate after CD8(⁺) T cell depletion in simian immunod virus-infected macaques. *J. Exp. Med.* **189**, 991–998.

Put S. J. Zhao A. Best S. J. Chandler J. D. Boyle virus-infectedmacaques. *J. Exp. Med.* **189**, 991–998.
Kent, S. J., Zhao, A., Best, S. J., Chandler, J. D., Boyle, D. B. &
- virus-infected macaques. J. Exp. Med. 189, 991–998.
ent, S. J., Zhao, A., Best, S. J., Chandler, J. D., Boyle, D. B. &
Ramshaw, I. A. 1998 Enhanced T-cell immunogenicity and
protective efficacy of a human immunodeficiency ent, S. J., Zhao, A., Best, S. J., Chandler, J. D., Boyle, D. B. & Ramshaw, I. A. 1998 Enhanced T-cell immunogenicity and protective efficacy of a human immunodeficiency virus type 1 vaccine regimen consisting of consecuti protective efficacy of a human immunodeficiency virus type 1 vaccine regimen consisting of consecutive primi[ng with DNA](http://matilde.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0022-538X^28^2972L.10[aid=535930]) and boosting with recombinant fowlpox virus. *J. Virol.* **⁷²**, 10 180^10188. andboosting with recombinant fowlpox virus. \tilde{J} . Virol. 72,
10 180–10188.
Koup, R. A., Safrit, J. T., Cao, Y., Andrews, C. A., McLeod,
G. Borkowsky W. Farthing C. & Ho. D. D. 1994 Temporal
- 10180–10188.

bup, R. A., Safrit, J. T., Cao, Y., Andrews, C. A., McLeod, G., Borkowsky, W., Farthing, C. & Ho, D. D. 1994 Temporal

association of cellular immune responses with the initial oup, R. A., Safrit, J. T., Cao, Y., Andrews, C. A., McLeod, G., Borkowsky, W., Farthing, C. & Ho, D. D. 1994 Temporal association of cellular immune responses with the initial control of viremia in primary human immunodefi G., Borkowsky, W., Farthing, C. & Ho, D. D. 1994 Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type I syndrome $\frac{7 \text{ V} \text{mol} \cdot 68.4650 - 465$ control of viremia in primary human immunodeficiency virus
type 1 syndrome. *J. Virol.* **68**, 4650-4655. controlof viremia in primary human immunodeficiency virus
type I syndrome. J. Virol. 68, 4650–4655.
Kuroda, M. J., Schmitz, J. E., Charini, W. A., Nickerson, C. E.,
Lifton, M. A., Lord, C. J. Forman, M. A. & Letvin, N. L.
- type 1 syndrome. *J. Virol.* **68**, 4650–4655.
aroda, M. J., Schmitz, J. E., Charini, W. A., Nickerson, C. E.,
Lifton, M. A., Lord, C. I., Forman, M. A. & Letvin, N. L.
1999 Emergence of CTL coincides with clearance of viru Lifton, M. A., Lord, C. I., Forman, M. A. & Letvin, N. L.
1999 Emergence of CTL coincides with clearance of virus
during primary simian immunodeficiency virus infection in 1999 Emergence of CTL coincides with clearance of virus rhesus monkeys. *J. Immunol.* **¹⁶²**, 5127^5133.
- Lalvani, A., Brookes, R., Hambleton, S., Britton, W. J., Hill, rhesus monkeys. *J. Immunol.* **162**, 5127–5133.
Ilvani, A., Brookes, R., Hambleton, S., Britton, W. J., Hill,
A.V. & McMichael, A. J. 1997 Rapid effector function in
CD^{8†} memoryTcells, 7 *Exh. Med* 186, 859–865 dvani, A., Brookes, R., Hambleton, S., Britton, V.
A.V. & McMichael, A. J. 1997 Rapid effector f
CD8⁺ memoryTcells. *J. Exp. Med.* **186**, 859–865.
cMichael A. J. & O'Callaghan. C. A. 1998. A new A.V.& McMichael, A. J. 1997 Rapid effector function in
CD8⁺ memory T cells. *J. Exp. Med.* **186**, 859–865.
McMichael, A. J. & O'Callaghan, C. A. 1998 A new look at T
cells. $\frac{7}{2}$ *Exp. Med* **187** 1367–1371
- CD8⁺ memoryTcells. *J. Exp. Med.* **186**, 859–865.
McMichael, A. J. & O'Callaghan, C. A. 1998 A new look at T
cells. *J. Exp. Med.* **187**, 1367–1371. McMichael,A. J. & O'Callaghan, C. A. 1998 A new look at T
cells. J. Exp. Med. 187, 1367–1371.
McMichael, A. J., Ogg, G., Wilson, J., Callan, M., Hambleton,
S. Appay V. Kelleber, A. & Rowland-Jones, S. 2000.
- cells. *J. Exp. Med.* **187**, 1367–1371.
cMichael, A. J., Ogg, G., Wilson, J., Callan, M., Hambleton,
S., Appay, V., Kelleher, A. & Rowland-Jones, S. 2000
Memory CD8⁺ T cells in HIV infection. *Phil Trans, R. Soc* S., Appay, V., Kelleher, A. & Rowland-Jones, S. 2000
Memory CD8⁺ T cells in HIV infection. *[Phil. Trans. R. Soc.](http://matilde.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0962-8436^28^29355L.363[aid=535932,csa=0962-8436^26vol=355^26iss=1395^26firstpage=363,cw=1,doi=10.1098/rstb.2000.0575,nlm=10794056])*
Lond. B 355, 363-367. *Memory* CD8⁺ T cells in HIV infection. *Phil. Trans. R. Soc.* MemoryCD8⁺ T cells in HIV infection. *Phil. Trans. R. Soc.*
 Lond. B 355, 363–367.

Murali-Krishna, K., Altman, J. D., Suresh, M., Sourdive, D. J.,
 Zajac A. J. Miller, J. D. Slansky, J. & Ahmed, R. 1998.
- *Lond.* B 355, 363–367.
urali-Krishna, K., Altman, J. D., Suresh, M., Sourdive, D. J.,
Zajac, A. J., Miller, J. D., Slansky, J. & Ahmed, R. 1998
Counting, antigen-specific, CD8, T. cells: a reevaluation of urali-Krishna, K., Altman, J. D., Suresh, M., Sourdive, D. J., Zajac, A. J., Miller, J. D., Slansky, J. & Ahmed, R. 1998
Counting antigen-specific CD8 T cells: a reevaluation of
bystander activation during viral infection Zajac, A. J., Miller, J. D., Slansky, J. & Ahmed, R. 1998
Counting antigen-specific CD8 T cells: a reevaluation of
bystander activation during viral infection. *Immunity* **8**,
177–187. bystander activation during viral infection. *Immunity* 8, 177–187.
Ogg, G. S. (and 14 others) 1998 Quantitation of HIV-1-specific extotoxic T lymphocytes and plasma load of viral RNA
- 177–187.
gg, G. S. (and 14 others) 1998 Quantitation of HIV-1-specific
cytotoxic T lymphocytes and plasma load of viral RNA.
Science 279 2103–2106 cytotoxic T lymphocytes and plasma load of viral RNA.
Science 279, 2103-2106. cytotoxicT lymphocytes and plasma load of viral RNA.
 Science 279, 2103-2106.

Phillips, R. E. (and 10 others) 1991 Human immunodeficiency

virus genetic variation that can escape cytotoxic T cell recog-
- Science 279, 2103-2106.
illips, R. E. (and 10 others) 1991 Human immunodeficiency
virus genetic variation that can escape cytotoxic T cell recog-
nition (see comments). Nature 354, 453-459. nillips, R. E. (and 10 others) 1991 Human in
virus genetic variation that can escape cytoto
nition (see comments). *Nature* **354**, 453–459.
Icher, C. I. Quittner, C. Peterson, D. M. virus genetic variation that can escape cytotoxic T cell recognition (see comments). *Nature* **354**, 453–459.
Pitcher, C. J., Quittner, C., Peterson, D. M., Connors, M., Koun R. A. Maino V. C. & Picker L. I 1999 HIV. Lanec
- nition (see comments). *Nature* **354**, 453–459.
tcher, C. J., Quittner, C., Peterson, D. M., Connors, M.,
Koup, R. A., Maino, V. C. & Picker, L. J. 1999 HIV-1-specific
CD4⁺ T cells are detectable in most individuals with tcher, C. J., Quittner, C., Peterson, D. M., Connors, M., Koup, R. A., Maino, V. C. & Picker, L. J. 1999 HIV-1-specific
CD4⁺ T cells are detectable in most individuals with active
HIV-1 infection but decline with prolong Koup, R. A., Maino, V. C. & Picker, L. J. 1999 HIV-1-specific CD4⁺ T cells are detectable in most individuals with active HIV-1 infection, but decline with prolonged viral suppression (see comments). *Nature Med.* 5, 518 HIV-1 infection, but decline with prolonged viral suppression
- Robinson, H. L.(and16others)1999Neutralizing antibody-(see comments). *Nature Med.* 5, 518–525.
bbinson, H. L. (and 16 others) 1999 Neutralizing antibody-
independent containment of immunodeficiency virus chal-
lenges by DNA priming and recombinant pox virus booster binson, H. L. (and 16 others) 1999 Neutralizing antibody-
independent containment of immunodeficiency virus chal-
lenges by DNA priming and recombinant pox virus booster
immunizations (see comments). Nature Med 5, 596–534. independent containment of immunodeficiency virus of
lenges by DNA priming and recombinant pox virus bo
immunizations (see comments). *Nature Med.* **5**, 526–534.
psepherg F S Billingsley J M Caliendo A lengesby DNA priming and recombinant pox virus booster
immunizations (see comments). Nature Med. 5, 526–534.
Rosenberg, E. S., Billingsley, J. M., Caliendo, A. M.,
- Boswell, S. L., Sax, P. E., Kalams, S. A. & Walker, B. D. 1997 Senberg, E. S., Billingsley, J. M., Caliendo, A. M., Boswell, S. L., Sax, P. E., Kalams, S. A. & Walker, B. D.
1997 Vigorous HIV-1-specific CD4⁺ T cell responses asso-
ciated with control of viremia (see comments). Boswell, S. L., Sax, P. E., Kalams, S. A. & Walker, B. D. 1997 Vigorous HIV-1-specific CD4⁺ T cell responses associated with control of viremia (see comments). *Science* 2**78**, 1447–1450. ciated with control of viremia (see comments). Science 278,
1447–1450.
Rowland-Jones, S. L. (and 14 others) 1999 Broadly cross-
reactive HIV-specific cytotoxic T-lymphocytes in highly-
- 1447–1450.

wland-Jones, S. L. (and 14 others) 1999 Broadly cross-

reactive HIV-specific cytotoxic T-lymphocytes in highly-

exposed persistently seronegative donors *Impunel Lett* 66 both Jones, S. L. (and 14 others) 1999 Broadly cross-
reactive HIV-specific cytotoxic T-lymphocytes in highly-
exposed persistently seronegative donors. *Immunol. Lett.* **66**,
9–14. exposed persistently seronegative donors. *Immunol. Lett.* **66**, 9–14.
Schmitz, J. E. (and 15 others) 1999 Control of viremia in simian
immunodeficiency, virus, infection, by CD^{gt} , lymphocytes
- 9–14.
hmitz, J. E. (and 15 others) 1999 Control of viremia in simian
immunodeficiency virus infection by $CD8^+$ lymphocytes.
Science 283, 857–860 **hmitz, J. E.** (and 15 oth

immunodeficiency vir
 Science **283**, 857–860.

hneider I. Gilbert immunodeficiencyvirus infection by CD8⁺ lymphocytes.

Science 283, 857-860.

Schneider, J., Gilbert, S. C., Blanchard, T. J., Hanke, T.,

Robson K. J. Hannan, C. M. Becker, M. Sinden, R.
- Science 283, 857-860.
Schneider, J., Gilbert, S. C., Blanchard, T. J., Hanke, T., Robson, K. J., Hannan, C. M., Becker, M., Sinden, R., Smith, G. L. & Hill, A. V. 1998 Enhanced immunogenicity Robson, K. J., Hannan, C. M., Becker, M., Sinden, R., Robson, K. J., Hannan, C. M., Becker, M., Sinden, R., Smith, G. L. & Hill, A. V. 1998 Enhanced immunogenicity for CD8⁺ T cell induction and complete protective efficacy of malaxia DNA vaccination by boosting with modifie Smith, G. L. & Hill, A. V. 1998 Enhanced immunogenicity
for $CD8^+$ T cell induction and complete protective efficacy of
malaria DNA vaccination by boosting with modified vaccinia
virus Ankara. *Mature Med A* 307–409 malaria DNA vaccination by boosting with modified vaccinia
virus Ankara. *Nature Med.* 4, 397-402.
- Tan, L. C., Gudgeon,N.,Annels, N. E., Hansasuta, P., O'Callaghan, C. A., Rowland-Jones, S., McMichael, A. J.,

BIOLOGICAL
SCIENCES

ALE

Rickinson, A. B. & Callan, M. F. 1999 A re-evaluation of the frequency of CD8⁺ T cells specific for EBV in healthy virus carriers. *J. Immunol.* **¹⁶²**, 1827^1835. frequency of $CD8^+$ T cells specific for EBV in healthy virus
carriers. J. *Immunol*. **162**, 1827–1835.
Tanchot, C., Guillaume, S., Delon, J., Bourgeois, C., Franzke,
A. Sarukhan, A. Trautmann, A. & Rocha, B. 1998.

- carriers. *J. Immunol.* **162**, 1827–1835.
nchot, C., Guillaume, S., Delon, J., Bourgeois, C., Franzke,
A., Sarukhan, A., Trautmann, A. & Rocha, B. 1998
Modifications of CD8⁺ T.cell function during *in vivo* memory nchot, C., Guillaume, S., Delon, J., Bourgeois, C., Franzke, A., Sarukhan, A., Trautmann, A. & Rocha, B. 1998
Modifications of CD8⁺ T cell function during *in vivo* memory
or tolerance induction *Immunity* **8** 581–590 A., Sarukhan, A., Trautmann, A. & R
Modifications of CD8⁺ T cell function during
or tolerance induction. *Immunity* **8**, 581-590.
- Wilson, J. D. (and 10 others) 2000 Direct visualization of HIV-1 ilson, J. D. (and 10 others) 2000 Direct visualization of HIV-1
specific cytotoxic T lymphocytes during primary infection.
AIDS 14 225–233 **ilson, J. D. (and 10 o**
specific cytotoxic T
AIDS **14**, 225–233.
uac A I Blattmay specific cytotoxic T lymphocytes during primary infection.
 AIDS **14**, 225–233.

Zajac, A. J., Blattman, J. N., Murali-Krishna, K., Sourdive,

D. J. Suresh M. Altman, J. D. & Ahmed, R. 1998 Viral
- *AIDS* **14**, 225–233.
jac, A. J., Blattman, J. N., Murali-Krishna, K., Sourdive,
D. J., Suresh, M., Altman, J. D. & Ahmed, R. 1998 Viral
immune evasion due to persistence of activated Tcells without D. J., Suresh, M., Altman, J. D. & Ahmed, R. 1998 Viral immune evasion due to persiste[nce of activated T cells withou](http://matilde.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0022-1007^28^29188L.2205[aid=533231,nlm=9858507])t effector function (see comments). $\tilde{\jmath}$. Exp. Med. 188, 2205–2213. immune evasion due to persistence of activated T cells without