OPINION

The molecular basis for public T-cell responses?

Vanessa Venturi, David A. Price, Daniel C. Douek and Miles P. Davenport

Abstract | Public T-cell responses, in which T cells bearing identical T-cell receptors (TCRs) are observed to dominate the response to the same antigenic epitope in multiple individuals, have long been a focus of immune T-cell repertoire studies. However, the mechanism that enables the survival of a specific TCR from the diverse repertoire produced in the thymus through to its involvement in a public immune response remains unclear. In this Opinion article, we propose that the frequency of production of T cells bearing different TCRs during recombination has an important role in the sharing of TCRs in an immune response, with variable levels of 'convergent recombination' driving production frequencies.

The adaptive immune response has evolved to recognize a variety of pathogen-derived molecules. This ability to respond to diverse molecular 'shapes' is conferred by the process of recombination of the immunoglobulin and T-cell receptor (TCR) genes, generating a random 'repertoire' of antigen-binding proteins. The randomness and diversity of this recognition is evident in some T-cell responses, in which the TCR repertoires responding to a particular antigenic epitope consist of many different TCRs. In most T-cell responses, the responding TCR repertoire consists of some TCRs with a private specificity[1,2], that is, TCRs which are observed in only one individual. In some T-cell responses, almost all TCRs are observed to have a private specificity, owing to the diversity of the responding TCR pool, and these are often referred to as private T-cell responses (see Glossary). However, in other responses there is an apparent loss of randomness and diversity, with the response being both very focused (dominated by one or a few TCRs) and highly shared (the same TCR is present in multiple individuals). Public TCR amino-acid sequences[1], which are clonally dominant and shared between different individuals, have often been regarded as an unusual phenomenon, owing to the apparent low probability of the same TCR being observed in multiple individuals responding to the same antigenic epitope. However, recent studies have highlighted the important role of public TCRs in a range of public T-cell responses; these include responses to both acute and persistent pathogens, as well as autoimmune and alloreactive responses.

Public $CD8^+$ T-cell responses to cytomegalovirus (CMV) and Epstein–Barr virus (EBV), which are persistent viruses that infect a large proportion of the population and can be potentially life-threatening to immunocompromised hosts, have been the focus of many structural[3–10] and TCR-repertoire[11–20] studies that are aimed at understanding both the cause of public T-cell responses and the role of public TCRs in these infections. Public TCRs have also been detected in $CD8^+$ T-cell responses to HIV[21,22] and simian immunodeficiency virus (SIV)[23]; in the setting of such antigenically variable pathogens, the highly focused nature of a public TCR repertoire can facilitate immune escape under certain conditions[23,24]. Recent studies have also reported a strong association between public $CD4^+$ T cells and experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis[25–27]. Furthermore, public $CD8^+$ T cells have been implicated in alloreactive responses[28–30]. Understanding the cause of public T-cell responses, the distinguishing features of these responses and their role both in immunity to infection and during adverse immune reactions is important for the design of immunotherapies and vaccines[24,31,32]. The frequency and diversity of immune responses in which public TCRs are observed (TABLE 1) suggests that they may arise from some fundamental feature of the TCR repertoire. In this Opinion article, we discuss the molecular mechanisms that might underlie the phenomenon of public T-cell responses and propose that the variable production frequencies of T cells that bear different TCRs, which are enabled by a process of 'convergent recombination', have an important role in the sharing of TCRs between different individuals.

The potential TCR repertoire

The survival and selection from a vast T-cell repertoire of a TCR that is identical in multiple individuals requires many formative steps and this makes public T-cell responses unexpected. That is, to contribute to a public T-cell response, the public TCR must: be produced by genetic recombination from among the enormous possible diversity of TCRs generated within the thymus; survive thymic selection; survive in the periphery; and have sufficient precursor frequency and avidity to compete effectively with the available TCR repertoire specific for a given antigenic epitope. The recombination of the variable (V), diversity (D) and joining (J) gene segments, which involves the random deletion of nucleotides from, and random addition of nucleotides to, the ends of the gene segments, has the potential to generate an αβ T-cell repertoire with a diversity of $>10^{15}$ different TCRs for mice[33] and $>10^{18}$ different TCRs for humans. However, taking into account that only ~3% of T cells survive thymic selection, the potential peripheral TCR diversity is $\sim10^{13}$ for mice and $\sim10^{16}$ for humans[34]. These estimates are at least several orders of magnitude larger than the estimated number of T cells in a mouse ($\sim10^8$) (REF. 35) or human ($\sim10^{12}$) (REF. 36) and many orders of magnitude larger than estimates of lower limits for the total number of unique T-cell clonotypes

Table 1 | **Examples and proposed explanations for public T-cell responses**

Disease	Antigen	MHC restriction	T-cell response	Refs	Proposed explanations
Mouse					
Influenza virus	NP (366–374)	H2-D^b	Acute CD8$^+$	45,46	Featureless ('vanilla') peptide–MHC structure[49] and near-germline TCR[54]
Experimental autoimmune encephalomyelitis	Myelin protein		Autoimmune CD4$^+$	25–27	
Macaque					
Simian immunodeficiency virus	Tat (28–35)	Mamu-A*01	Persistent CD8$^+$	23	
Human					
Antiphospholipid syndrome	β_2-glycoprotein I (276–290)		Autoimmune CD4$^+$	42	
Cytomegalovirus	pp65 (495–503)	HLA-A*0201	Persistent CD8$^+$	14,17,77	
Epstein–Barr virus	EBNA3A (339–347)	HLA-B*0801	Persistent CD8$^+$	11,78	Binding-induced conformational changes to the peptide–MHC[9] and TCR[10]
	BZLF1 (52–64)	HLA-B*3508	Persistent CD8$^+$	4	Prominent ('hot and spicy') peptide–MHC structure[4]
	BZLF1 (54–64)	HLA-B*3501	Persistent CD8$^+$	3	Prominent ('hot and spicy') peptide–MHC structure[3] and binding-induced conformational changes to both the peptide–MHC and TCR[8]
	BMLF1 (259–267)	HLA-A*0201	Persistent CD8$^+$	12,13,16,17	
Influenza virus	MP (58–66)	HLA-A*0201	Acute CD8$^+$	39,79	Featureless ('vanilla') peptide–MHC structure[48]

EBNA3A, Epstein–Barr virus nuclear antigen 3A; MP, matrix proteins; NP, nucleoprotein; TCR, T-cell receptor.

of ~10^6 for mice[37] and 10^7 for humans[36] (reviewed in REF. 38). Thus, if there were an equal probability of producing each of the 10^{15} or 10^{18} different possible TCRs, we would only rarely expect the same TCRs to be present in the repertoire of many individuals, let alone be selected in response to a particular antigenic epitope in many individuals. However, public TCRs have been observed in a variety of T-cell responses in many different species[1,11–18,21–23,25–30,39–47].

Explanations for public T-cell responses

Proposed structural explanations. A variety of structural explanations have been put forward to explain different public T-cell responses and these are discussed in a recent Review on the structural determinants of T-cell selection[31]. Several studies[3,4,9,48,49] have suggested that the 'shape' of a peptide–MHC complex can lead to a biased TCR repertoire in a CD8$^+$ T-cell response, thereby giving rise to public TCRs. For some public T-cell responses, a 'bulged' peptide conformation has been observed; it has been argued that a protruding peptide ('hot and spicy') restricts TCR access[3,4,9], and thereby allows only a limited subset of TCRs to make effective contact with the peptide–MHC complex. Other public TCRs have been observed responding to very flat and featureless peptide–MHC complex conformations ('vanilla peptides')[48–50]. Alternatively, some studies have suggested that the nature of the public TCR itself, rather than the nature of the peptide–MHC complex, determines whether a T-cell response is public. Observations of binding-induced structural changes in public TCRs[8,10] have raised suggestions that the unusual structural features of the public TCR and its interactions with the peptide–MHC complex may provide an antigen-specificity advantage[10] that drives the public nature of the response.

Thus, although many different explanations that rely on unique structural features of the TCR or peptide–MHC complex have been proposed to account for TCR bias in the selected T-cell response, there is no general rule that could account for the variety of public T-cell responses observed (TABLE 1). Furthermore, although these structural features may appear to explain the recruitment of identical TCRs in multiple immune responses, they cannot account for the presence of these TCRs in the naive repertoires of a majority of individuals.

Before any of the immune response factors come into play, the first prerequisite is that the TCR be present in the peripheral repertoire of most individuals. Unless this is the case, no matter how high the affinity of the TCR for the peptide–MHC complex, the TCR will only be present in the repertoire of one or a few individuals.

Proposed sequence-based explanations. The nucleotide sequence of public TCRs has also been proposed as a possible reason for the public nature of the response. Some public TCR β-chains are found to be made from near-germline recombination of the TCR Vβ, Dβ and Jβ segments, involving some deletion of nucleotides from the ends of these germline gene segments but no or minimal random nucleotide additions[1,11]. Some studies have suggested that public T-cell responses may represent some primordial germline-encoded TCR specificities that are more degenerate in their peptide-binding specificity, have higher affinity for MHC or are somehow different from 'normal' T-cell responses[51,52]. However, studies of other public T-cell responses have revealed public TCR sequences that include a substantial number of nucleotide additions[13,18,53], thus making it unlikely that the near-germline nature of TCRs alone defines their public nature.

Other studies have suggested that biased recombination could lead to some sequences being generated more frequently than others. The observation of some public TCR sequences in mice that lack the gene

encoding terminal deoxynucleotidyltransferase, which is required for nucleotide addition during V(D)J recombination[51,54], has led to suggestions that public TCRs may be easier to generate because they do not require random nucleotide addition[54]. Indeed, a recombination event that involves few random nucleotide additions is likely to occur more often than an event requiring many nucleotide additions. Other observed recombinational biases include: germline gene segment usage in V(D)J recombination[55–59]; the extent of the removal of nucleotides from the germline gene segments (for example, there are differences between the various V and J genes in the numbers of nucleotides removed from the 3′ ends of the V and 5′ end of the J gene segments[55]); and additions of specific 'random' nucleotides (for example, single guanines and strings of guanines are frequently generated[60]). These sequence-based explanations rely on the frequent production of a particular TCR nucleotide sequence by the re-occurrence of a particular recombination event, which is not consistent with the observations of many studies[13,17,19,21–23,27,45,46,53,61] showing that a given public TCR amino-acid sequence may be encoded by many different nucleotide sequences both within the same individual and in different individuals.

A new proposal: convergent recombination?

Our recent study[53] suggests that public TCRs tend to be made more frequently than other TCRs but this does not require biases in the V(D)J recombination process[55–57,59,60] or that they be made without random nucleotide additions[54]. Whereas a small number of nucleotide additions can enable a particular recombination event to occur more frequently, the variety of different ways that a TCR sequence can be made also has an important role. That is, many different V(D)J recombination events 'converge' to produce the same nucleotide sequence and many different nucleotide sequences 'converge' to encode the same amino-acid sequence. Multiple nucleotide sequences have often been observed encoding public TCR amino-acid sequences[13,17,19,21–23,27,45,46,53,61]. Furthermore, the V(D)J recombination process can also facilitate the frequent production of TCR sequences that are characterized by distinct patterns of amino-acid usage, or amino-acid sequence motifs, which are also often associated with public T-cell responses[23,39,45] (FIG. 1). Amino-acid motifs usually consist of a predominantly germline-encoded consensus

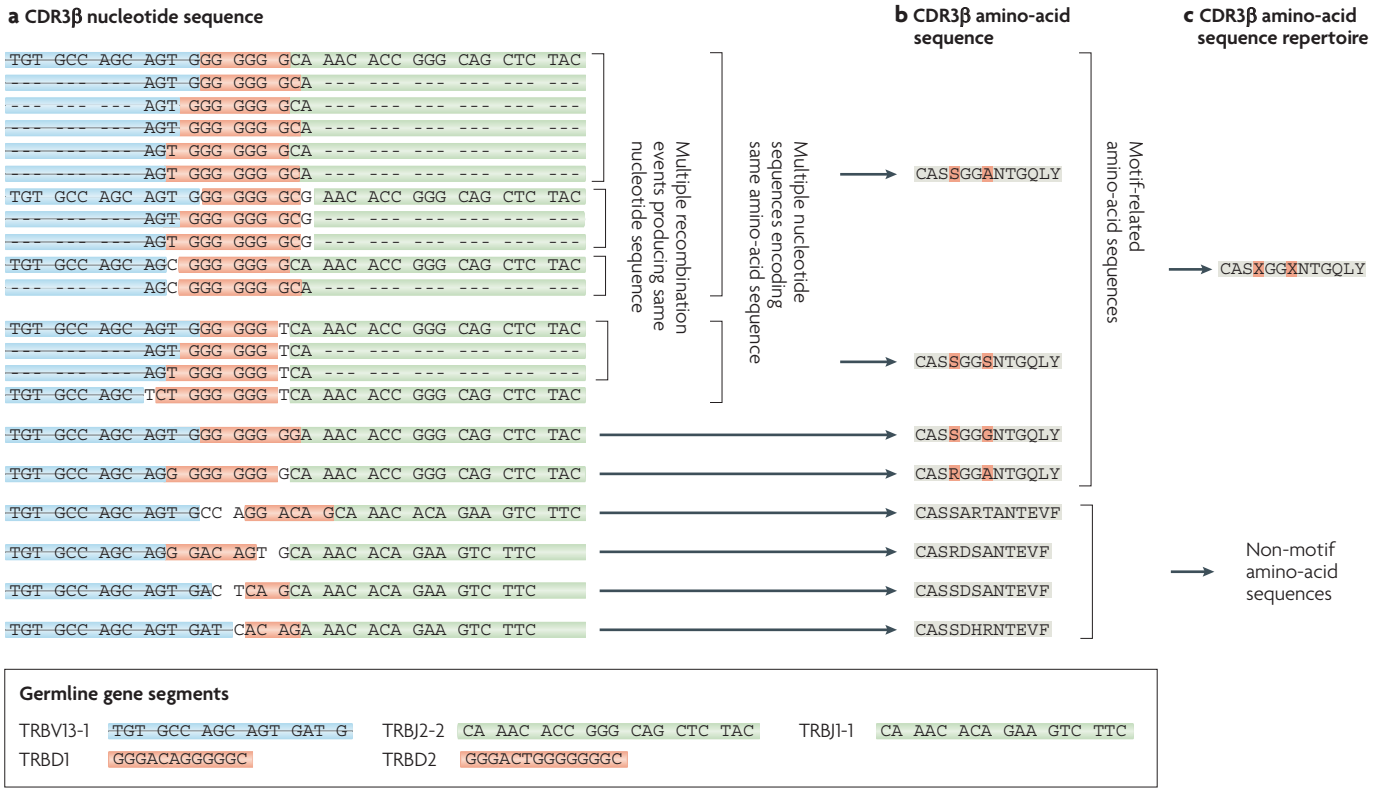

Figure 1 | **Schematic illustration of convergent recombination.** Convergent recombination is illustrated by T-cell receptor (TCR) β-chain sequences that are generated in influenza virus infection in response to H2-D^b complexed with the nucleoprotein (NP)$_{366–374}$ epitope[62,63]. **a** | The first level of convergent recombination is multiple recombination events, involving different splicings of the germline V (variable; highlighted in blue), J (joining; highlighted in green) and D (diversity; highlighted in red) β-chain gene segments and random nucleotide additions (no highlight), produce the same nucleotide sequences. Strings of multiple guanines can also be spliced many different ways from the inappropriately named 'diversity' gene segments of the β-chain[53]. ImMunoGeneTics (IMGT) nomenclature[76] is used for the germline gene segments; the corresponding Arden nomenclature is 8S3 for the mouse Vβ gene. **b** | The second level of convergent recombination involves multiple nucleotide sequences encoding the same amino-acid sequence. Protein sequences with amino acids in the V(D)J junction that are encoded by many codons can be encoded by many different nucleotide sequences. **c** | The third level of convergent recombination is at the level of the TCR repertoire, where some of the amino-acid sequences conform to an amino-acid motif. In this particular case, the 'XGGX' amino-acid motif (where X denotes any amino acid) is facilitated by strings of guanines encoding the two glycines, which can be spliced, often in multiple ways, from the Dβ gene segments. In most T-cell responses, some TCR sequences will also be observed responding to the epitope that do not conform to an amino-acid motif. These sequences are represented by the four non-motif amino-acid sequences. CDR3, complementarity-determining region 3.

Glossary

Clonal dominance
The dominance of a particular clonotype over others involved in an immune response to a specific epitope. This clonotype will be found at a higher copy number in the responding T-cell receptor (TCR) repertoire than other clonotypes.

Convergent recombination
The process whereby multiple recombination events 'converge' to produce the same nucleotide sequence and multiple nucleotide sequences 'converge' to encode the same amino-acid sequence. This process enables some TCR sequences to be produced more frequently than others.

Private T-cell response
An immune response to a specific epitope involving predominantly T cells bearing TCRs that are rarely observed in multiple individuals.

Public TCR
A TCR that is present and dominant in immune responses to a specific epitope in a majority of individuals.

Public T-cell response
An immune response to a specific epitope involving predominantly T cells bearing TCRs that are frequently observed in multiple individuals.

TCR recurrence
A measure of the average production frequency of a TCR. That is, the average number of copies of a TCR sequence per individual produced by V(D)J recombination.

sequence and one, or a few, positions in the TCR sequence with amino acids varying between sequences. These non-consensus amino acids usually appear at the Vβ–Dβ and Dβ–Jβ (or Vα–Jα) gene junctions but multiple splicing events of the germline gene segments, and the encoding of amino acids by multiple codons, often provide many different ways for both the consensus amino acids and non-consensus amino acids at the V(D)J junctions to be produced. We propose that the variety of different ways in which a TCR amino-acid sequence can be made by germline recombination is an important determinant of TCR sharing, and we term this process 'convergent recombination'.

That public TCRs are produced more frequently than other TCRs by convergent recombination is, we believe, the only proposed explanation that can potentially explain both the variety of public T-cell responses and account for the presence of identical TCR sequences in multiple individuals. In the following section, we discuss convergent recombination in more detail and describe how the variable production frequency of TCRs in the thymus can lead to a public T-cell response.

Convergent recombination and public TCRs

The various levels of convergent recombination are demonstrated in FIG. 1 using published data for TCR β-chain nucleotide and amino-acid sequences that were generated in response to an epitope of influenza A virus nucleoprotein (NP) bound to H2-D^b (H2-D^{b}NP$_{366–374}$) in mice[62,63]. An additional example of TCR β-chain sequences produced in response to the Mamu-A*01-restricted SIV Tat epitope 28–35 (TL8) in rhesus macaques is provided in Supplementary Information S1 (figure). The production frequency of different TCR nucleotide sequences depends on both the number of random nucleotide additions and the number of different recombination events (that is, different splicings at the 3′ end of the Vβ, 3′ and 5′ ends of the Dβ and 5′ end of the Jβ gene segments, as well as different random nucleotide additions) converging to produce the same nucleotide sequence (FIG. 1a). Frequently produced nucleotide sequences are often observed in the responding TCR repertoires of multiple individuals. Similarly, the frequency at which different amino-acid sequences are produced depends on both the number of different nucleotide sequences that can encode the particular amino-acid sequence (FIG. 1b), which is dependent on the codon usage of the amino acids at the V(D)J junction, and the production frequency of each nucleotide sequence that encodes the amino-acid sequence. Additionally, recombination events converge to produce amino-acid sequences that frequently conform to an amino-acid motif, in which the non-consensus amino acids are encoded by nucleotides at the junctions between the V, D and J germline gene segments (FIG. 1c). Convergent recombination has a role in the frequency of production of both TCR β-chains, which are most commonly observed as public, and TCR α-chains. The production frequency of a TCRαβ also depends on the pairing between the α-chains and β-chains (BOX 1).

TCR recurrence: a measure of production and sharing. Our proposal that TCR production frequency is an important determinant of TCR sharing, and that convergent recombination facilitates variable frequencies of TCR production in the thymus, assumes that the TCRs that are frequently produced within an individual are more likely to be frequently produced in multiple individuals. It follows that a TCR present in many individuals should also be present many times within a single individual. This relationship is predicted by a standard probabilistic relationship between the occurrence of a TCR within individuals and between individuals (FIG. 2) and is supported by observed trends that public TCR amino-acid sequences are often encoded by several nucleotide sequences within an individual[13,17,19,23,27,45,46,53]. We propose TCR recurrence as a measure that encompasses the frequency of production of a TCR and the sharing of a TCR between individuals, where TCR recurrence indicates the average frequency of production by V(D)J recombination of a given TCR amino-acid sequence present in the periphery of an individual. Thus, highly recurrent TCRs are made frequently both within an individual and across multiple individuals, whereas 'scarce' TCRs are rarely found in a single individual.

Box 1 | **What about the α-chain?**

'Public' T-cell receptor (TCR) α-chain amino-acid sequences have also been observed, in which an identical or near identical TCR α-chain is found at high frequency in multiple individuals[4,44]. It seems likely that similar mechanisms to those described for the TCR β-chain may drive this clonal dominance of recurrent TCR α-chains. However, an important question relates to the requirement for correct pairing of the TCR α-chains and β-chains. That is, if both the TCR α- and β-chains contribute to peptide–MHC complex recognition, simply generating the correct TCR β-chain sequence is not sufficient to ensure a high affinity for antigen; the correct TCR α-chain must also be chosen. As some degree of clonal expansion occurs between recombination of the TCR β-chain and the subsequent multiple TCR α-chain recombinations, each of the TCR β-chain sequences is likely to be paired with approximately one hundred different random TCR α-chain sequences[69], although only some of these paired combinations will survive thymic selection. Thus, if a highly specific TCR α/β-chain combination is required for peptide–MHC complex recognition, there is a low probability that this correct pairing will occur. By contrast, a TCR β-chain that is relatively promiscuous in its pairings with TCR α-chains while still maintaining a high affinity for peptide–MHC will be highly represented in the repertoire. As each TCR β-chain recombination results in ~100 TCR α-chain pairings, a 'fully promiscuous' TCR β-chain would have a precursor frequency 100 times that of a TCR β-chain that could only pair with on average 1 in 100 TCR α-chains. Thus, for a particular TCR β-chain sequence to contribute to a public T-cell response, it must not only be highly recurrent but it must also either be promiscuous with respect to its TCR α-chain pairing and/or be able to combine with highly recurrent TCR α-chains[44].

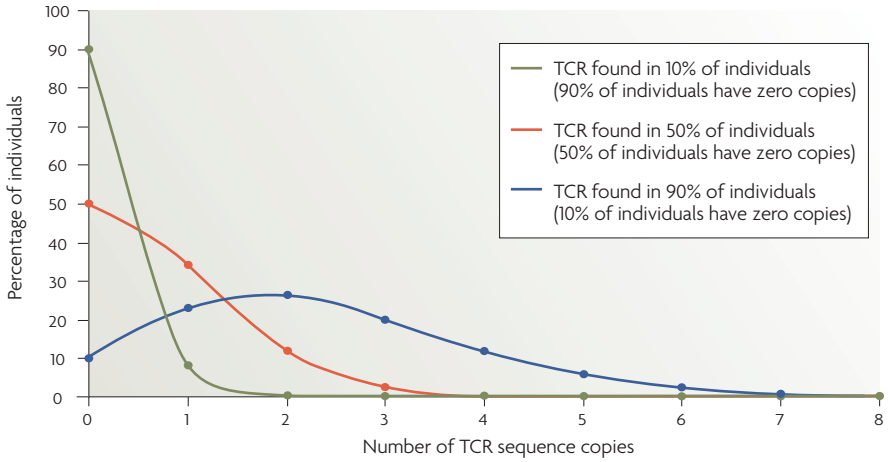

Figure 2 | **The relationship between the number of individuals in which a T-cell receptor (TCR) sequence is present and the number of copies of that TCR sequence in the individuals.** We use the Poisson distribution, which is a standard probabilistic model for describing random occurrences, to demonstrate the relationship between TCR sharing and the precursor frequency of a TCR within individuals. The Poisson distribution depends on only one parameter, which was varied to produce curves for TCRs with different percentages (for example, 10%, 50% and 90%) of individuals with zero copies of the TCR sequence. A TCR sequence found in ~90% of individuals (that is, ~10% of individuals have zero copies of the sequence; shown by the blue plot) is predicted by a Poisson distribution to be found in one copy in ~23% of individuals, in two copies in ~27% of individuals and in ≥ three copies in ~40% of individuals. Thus, we would expect to see multiple copies of highly shared TCR sequences in many individuals. A TCR sequence that is found in only ~10% of individuals (that is, ~90% of individuals have zero copies of the sequence; shown by the green plot) will mostly be found in only one copy, with only ~0.5% of individuals found with multiple copies of the sequence. As an intermediate case, we show the Poisson distribution for a TCR found in ~50% of individuals (shown by the red plot), where ~34% of individuals will be found with one copy of the sequence and ~15% of individuals will be found with multiple copies of the sequence. The higher precursor frequency of the TCR found in 90% of individuals will have a role in the sharing and clonal dominance of the TCR.

Public–private dichotomy of T-cell responses versus spectrum of TCR sharing. Convergent recombination will result in a range of production frequencies, with some TCRs being rarely produced, some TCRs being produced at an intermediate frequency and other TCRs being frequently produced. If production frequency is a determinant of the number of individuals in which an antigenic-epitope-specific TCR will be observed, why do many studies observe only public and private T-cell responses and not a range in the number of individuals in whom TCRs are found? It appears that when more extensive studies are undertaken (that is, many individuals and many sequences per individual are considered), there is indeed a range of TCR sharing, with sequences found in numbers of individuals ranging from one up to the majority of individuals in the group tested[17,23,45,53]. Thus, public TCRs and private TCRs are at the extremes of this range and many TCRs involved in immune responses fall between these extremes of TCR sharing. Moreover, a strong relationship between the number of individuals in which both antigenic-epitope-specific TCR amino-acid and nucleotide sequences are observed and the estimated relative frequency of TCR production has been demonstrated[53].

The competitive edge of public TCRs. Another feature that characterizes public TCRs is their clonal dominance within the immune response. The clonal dominance of individual T-cell clonotypes in the response may be determined by several factors including: the precursor frequency of individual TCRs; TCR avidity[64] (which is related to TCR–peptide–MHC interactions[3–6,8–10,48,49]); competition between T-cell clonotypes[65]; and stochastic events, such as the timing of the encounter with antigen[66]. The precursor frequency of an individual TCR in the naive repertoire is determined by both the production frequency in the thymus and post-thymic expansion. As discussed in the previous sections, TCR production frequency is also a determinant of sharing. Thus, if precursor frequency is a determinant of clonal dominance in the immune response, then TCR sharing and clonal dominance are intimately linked (BOX 2).

Public TCRs: prominent peaks in the TCR landscape. The influence of TCR production frequencies on T-cell responses observed in different individuals can best be explained by considering the potential TCR amino-acid sequence repertoire as a recurrence landscape (FIG. 3). This landscape is uneven with 'peaks' of highly recurrent TCRs frequently produced by V(D)J recombination. A given peptide–MHC complex, placed at any point on the TCR recurrence landscape, can be thought of as stimulating a 'circle' of T cells

Box 2 | **The role of precursor frequency in public T-cell responses**

The precursor frequency of T cells in the naive repertoire that can respond to a given epitope is determined by both the number of different T-cell receptors (TCRs) and the number of copies of each different TCR. Precursor frequency is often considered an important factor in characterizing immune responses and thus estimations of the precursor frequency have been the focus of several studies[70–75]. The main determinants of the precursor frequency of T cells in the naive pool with sufficient avidity for a peptide–MHC complex to respond to a given epitope include: the frequency at which each TCR is produced in the thymus by V(D)J recombination; survival during thymic selection; peripheral survival; and post-thymic expansion (for example, a TCR that crossreacts with environmental antigens may undergo peripheral expansion and thus be found at a high precursor frequency in an individual). The precursor frequency of a particular TCR provides a kinetic advantage during an immune response because there are initially more T cells bearing that TCR to encounter the antigen and each of these T cells will proliferate in response to the antigen. We have found that TCRs that are highly shared will often tend to occur in multiple copies in individuals (that is, have a high precursor frequency) whereas TCRs that are unshared will tend to be found in only one copy in one individual[53]. The expected relationship between precursor frequency of an individual TCR sequence and sharing of the sequence between individuals is illustrated in FIG. 2. The relative contribution of each of the determinants of precursor frequency, together with the relative avidities of the different TCRs for a peptide–MHC complex and stochastic effects, rather than the overall frequency of antigenic-epitope-specific precursor cells, is also important in the observation of public TCRs. For example, a low recurrence TCR that has a high precursor number, due to substantial expansion in the periphery, is unlikely to yield identical TCRs observed in multiple individuals.

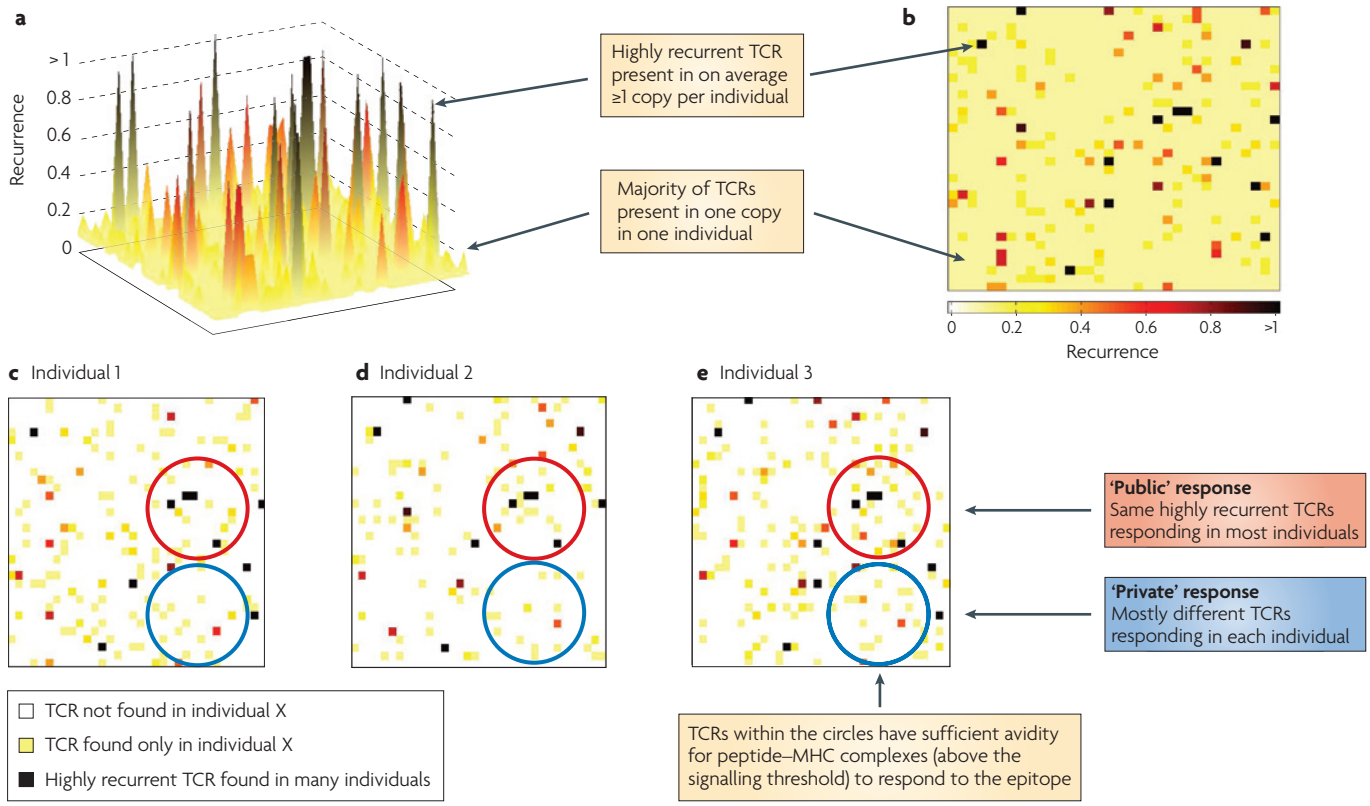

Figure 3 | **An illustration of the uneven landscape of T-cell receptor recurrence and how this leads to public and private T-cell responses.** The T-cell receptor (TCR) recurrence data used in the schematic is based on *in silico* TCR repertoires generated by simulations of the random recombination of the variable (V), diversity (D) and joining (J) germline gene segments[53]. Three-dimensional (**a**) and two-dimensional (**b**) representations of the expected frequency of recurrence of individual TCR amino-acid sequences per individual for all TCRs in 10 individuals. The colour indicates the recurrence (that is, average number of copies per individual) of each TCR and each pixel in panel **b** represents a TCR amino-acid sequence. A 'location' exists on the landscape where a given peptide–MHC complex will stimulate surrounding T cells to respond. The TCR landscapes for three of the 10 individuals are shown in parts **c**, **d** and **e**. Many of the highly recurrent sequences appear in all three individuals. The circles represent the TCR signalling threshold[67] within which TCRs have sufficient avidity to respond to peptide–MHC complexes. The 'public' or 'private' nature of the observed response depends on the recurrence of the TCRs responding to the peptide–MHC complex. The blue circles represent typically private responses, in which there are no highly recurrent TCRs with sufficient avidity to respond to the peptide–MHC complex in each individual. The red circles represent typically public responses, which involve several highly recurrent TCRs with sufficient avidity to respond to the peptide–MHC complex in all three individuals.

on the landscape (FIG. 3c–e). T cells within the 'circle' have sufficient avidity for the peptide–MHC complex (that is, an avidity at least as great as the signalling threshold[67]) and will be involved in the response. All peptide–MHC complexes will stimulate both scarce and recurrent TCRs. Whether the observed T-cell response is classed as public or private depends on the recurrence of the TCRs responding to the peptide–MHC complex. In a public T-cell response, the peptide–MHC complex is recognized by one or a few highly recurrent TCRs and thus most individuals will have at least one identical high-avidity TCR. A public T-cell response does not require that a recurrent TCR has the highest possible avidity for the peptide–MHC complex because the higher precursor frequency of these T cells (as a consequence of a higher production frequency in the thymus of most individuals) will provide them with a competitive edge[68]. In a private T-cell response, the peptide–MHC complex is mainly recognized by scarce or infrequently occurring TCRs. Thus, the TCR with the highest avidity (that is, the dominant TCR) will often vary from individual to individual and there is also sharing of subdominant TCRs.

The TCR recurrence landscape suggests that we should observe a range in the public nature of T-cell responses. That is, all T-cell responses will comprise some shared TCRs, but in some (public) responses these shared TCRs are clonally dominant and found in most individuals, whereas in other (private) responses there is a minor degree of sharing of subdominant TCRs. This range of TCR sharing has been observed in several TCR repertoire studies[17,23,53].

Concluding remarks

Despite the enormous potential diversity of the TCR repertoire, identical, clonally dominant TCRs are often observed responding to the same peptide–MHC antigenic epitope in different individuals. This apparent concentration of the immune response into a single 'solution' to the recognition requirements of the host has long presented a conundrum for immunologists. That public T-cell responses arise from highly recurrent TCRs that survive to the periphery provides the first consistent explanation for the variety of public T-cell responses observed. This mechanism leads to a range of TCR sharing[17,23,45,53] and encoding of highly shared amino-acid sequences by multiple nucleotide sequences, which is observed in T-cell responses in inbred mice[27,45,46], as well as in outbred monkey[23] and human

TCR repertoires[13,17,19,21,22,39,61]. Much is still to be learned about convergent recombination and TCR sharing and their effects on both viral escape and disease progression. Future investigation should be aimed at better understanding the role of the TCR repertoire in immune responses, autoimmunity and alloreactivity and thus unlocking the potential to optimize T-cell clonotype selection from the available repertoire for therapeutic benefit.

Vanessa Venturi and Miles P. Davenport are at the Complex Systems Biology Group, Centre for Vascular Research, University of New South Wales, Kensington New South Wales 2052, Australia.

Daniel C. Douek is at the Human Immunology Section, Vaccine Research Center, NIAID/NIH, Bethesda, Maryland 20892, USA.

David A. Price is at the Human Immunology Section, Vaccine Research Center, NIAID/NIH, Bethesda, Maryland 20892, USA, and the Department of Medical Biochemistry and Immunology, Cardiff University School of Medicine, Cardiff CF14 4XN, UK.

Correspondence to D.C.D. and M.P.D.
e-mails: ddouek@nih.gov; m.davenport@unsw.edu.au

1. Cibotti, R. *et al.* Public and private VβT cell receptor repertoires against hen egg white lysozyme (HEL) in nontransgenic versus HEL transgenic mice. *J. Exp. Med.* **180**, 861–872 (1994).
2. Kim, S. K. *et al.* Private specificities of CD8 T cell responses control patterns of heterologous immunity. *J. Exp. Med.* **201**, 523–533 (2005).
3. Miles, J. J. *et al.* CTL recognition of a bulged viral peptide involves biased TCR selection. *J. Immunol.* **175**, 3826–3834 (2005).
4. Tynan, F. E. *et al.* High resolution structures of highly bulged viral epitopes bound to major histocompatibility complex class, I. Implications for T-cell receptor engagement and T-cell immunodominance. *J. Biol. Chem.* **280**, 23900–23909 (2005).
5. Tynan, F. E. *et al.* T cell receptor recognition of a 'super-bulged' major histocompatibility complex class I-bound peptide. *Nature Immunol.* **6**, 1114–1122 (2005).
6. Tynan, F. E. *et al.* The immunogenicity of a viral cytotoxic T cell epitope is controlled by its MHC-bound conformation. *J. Exp. Med.* **202**, 1249–1260 (2005).
7. Miles, J. J. *et al.* TCRα genes direct MHC restriction in the potent human T cell response to a class I-bound viral epitope. *J. Immunol.* **177**, 6804–6814 (2006).
8. Tynan, F. E. *et al.* A T cell receptor flattens a bulged antigenic peptide presented by a major histocompatibility complex class I molecule. *Nature Immunol.* **8**, 268–276 (2007).
9. Kjer-Nielsen, L. *et al.* The structure of HLA-B8 complexed to an immunodominant viral determinant: peptide-induced conformational changes and a mode of MHC class I dimerization. *J. Immunol.* **169**, 5153–5160 (2002).
10. Kjer-Nielsen, L. *et al.* A structural basis for the selection of dominant αβ T cell receptors in antiviral immunity. *Immunity* **18**, 53–64 (2003).
11. Argaet, V. P. *et al.* Dominant selection of an invariant T cell antigen receptor in response to persistent infection by Epstein–Barr virus. *J. Exp. Med.* **180**, 2335–2340 (1994).
12. Annels, N. E., Callan, M. F., Tan, L. & Rickinson, A. B. Changing patterns of dominant TCR usage with maturation of an EBV-specific cytotoxic T cell response. *J. Immunol.* **165**, 4831–4841 (2000).
13. Lim, A. *et al.* Frequent contribution of T cell clonotypes with public TCR features to the chronic response against a dominant EBV-derived epitope: application to direct detection of their molecular imprint on the human peripheral T cell repertoire. *J. Immunol.* **165**, 2001–2011 (2000).
14. Khan, N., Cobbold, M., Keenan, R. & Moss, P. A. Comparative analysis of CD8+ T cell responses against human cytomegalovirus proteins pp65 and immediate early 1 shows similarities in precursor frequency, oligoclonality, and phenotype. *J. Infect. Dis.* **185**, 1025–1034 (2002).
15. Khan, N. *et al.* Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. *J. Immunol.* **169**, 1984–1992 (2002).
16. Trautmann, L. *et al.* Dominant TCR Vα usage by virus and tumor-reactive T cells with wide affinity ranges for their specific antigens. *Eur. J. Immunol.* **32**, 3181–3190 (2002).
17. Price, D. A. *et al.* Avidity for antigen shapes clonal dominance in CD8+ T cell populations specific for persistent DNA viruses. *J. Exp. Med.* **202**, 1349–1361 (2005).
18. Trautmann, L. *et al.* Selection of T cell clones expressing high-affinity public TCRs within human cytomegalovirus-specific CD8 T cell responses. *J. Immunol.* **175**, 6123–6132 (2005).
19. Brennan, R. M. *et al.* Predictable αβT-cell receptor selection toward an HLA-B*3501-restricted human cytomegalovirus epitope. *J. Virol.* **81**, 7269–7273 (2007).
20. Day, E. K. *et al.* Rapid CD8+ T cell repertoire focusing and selection of high-affinity clones into memory following primary infection with a persistent human virus: human cytomegalovirus. *J. Immunol.* **179**, 3203–3213 (2007).
21. Gillespie, G. M. *et al.* Strong TCR conservation and altered T cell cross-reactivity characterize a B*57-restricted immune response in HIV-1 infection. *J. Immunol.* **177**, 3893–3902 (2006).
22. Yu, X. G. *et al.* Mutually exclusive T-cell receptor induction and differential susceptibility to human immunodeficiency virus type 1 mutational escape associated with a two-amino-acid difference between HLA class I subtypes. *J. Virol.* **81**, 1619–1631 (2007).
23. Price, D. A. *et al.* T cell receptor recognition motifs govern immune escape patterns in acute SIV infection. *Immunity* **21**, 793–803 (2004).
24. Davenport, M. P., Price, D. A. & McMichael, A. J. The T cell repertoire in infection and vaccination: implications for control of persistent viruses. *Curr. Opin. Immunol.* **19**, 294–300 (2007).
25. Fazilleau, N. *et al.* Persistence of autoreactive myelin oligodendrocyte glycoprotein (MOG)-specific T cell repertoires in MOG-expressing mice. *Eur. J. Immunol.* **36**, 533–543 (2006).
26. Fazilleau, N. *et al.* T cell repertoire diversity is required for relapses in myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis. *J. Immunol.* **178**, 4865–4875 (2007).
27. Menezes, J. S. *et al.* A public T cell clonotype within a heterogeneous autoreactive repertoire is dominant in driving EAE. *J. Clin. Invest.* **117**, 2176–2185 (2007).
28. Battaglia, M. & Gorski, J. Overlap of direct and indirect alloreactive T-cell repertoires when MHC polymorphism is limited to the peptide binding groove. *Hum. Immunol.* **63**, 91–100 (2002).
29. O'Keefe, C. L. *et al.* Molecular TCR diagnostics can be used to identify shared clonotypes after allogeneic hematopoietic stem cell transplantation. *Exp. Hematol.* **32**, 1010–1022 (2004).
30. Ely, L. K. *et al.* Antagonism of antiviral and allogeneic activity of a human public CTL clonotype by a single altered peptide ligand: implications for allograft rejection. *J. Immunol.* **174**, 5593–5601 (2005).
31. Turner, S. J., Doherty, P. C., McCluskey, J. & Rossjohn, J. Structural determinants of T-cell receptor bias in immunity. *Nature Rev. Immunol.* **6**, 883–894 (2006).
32. Miles, J. J., Silins, S. L. & Burrows, S. R. Engineered T cell receptors and their potential in molecular medicine. *Curr. Med. Chem.* **13**, 2725–2736 (2006).
33. Davis, M. M. & Bjorkman, P. J. T-cell antigen receptor genes and T-cell recognition. *Nature* **334**, 395–402 (1988).
34. Shortman, K., Egerton, M., Spangrude, G. J. & Scollay, R. The generation and fate of thymocytes. *Semin. Immunol.* **2**, 3–12 (1990).
35. Doherty, P. C., Riberdy, J. M. & Belz, G. T. Quantitative analysis of the CD8+ T-cell response to readily eliminated and persistent viruses. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **355**, 1093–1101 (2000).
36. Arstila, T. P. *et al.* A direct estimate of the human αβT cell receptor diversity. *Science* **286**, 958–961 (1999).
37. Casrouge, A. *et al.* Size estimate of the αβTCR repertoire of naive mouse splenocytes. *J. Immunol.* **164**, 5782–5787 (2000).
38. Nikolich-Zugich, J., Slifka, M. K. & Messaoudi, I. The many important facets of T-cell repertoire diversity. *Nature Rev. Immunol.* **4**, 123–132 (2004).
39. Lehner, P. J. *et al.* Human HLA-A0201-restricted cytotoxic T lymphocyte recognition of influenza A is dominated by T cells bearing the Vβ17 gene segment. *J. Exp. Med.* **181**, 79–91 (1995).
40. Zeng, W., Maciejewski, J. P., Chen, G. & Young, N. S. Limited heterogeneity of T cell receptor BV usage in aplastic anemia. *J. Clin. Invest.* **108**, 765–773 (2001).
41. Boudinot, P., Boubekeur, S. & Benmansour, A. Rhabdovirus infection induces public and private T cell responses in teleost fish. *J. Immunol.* **167**, 6202–6209 (2001).
42. Yoshida, K. *et al.* Restricted T-cell receptor β-chain usage by T cells autoreactive to β_2-glycoprotein I in patients with antiphospholipid syndrome. *Blood* **99**, 2499–2504 (2002).
43. May, E. *et al.* Conserved TCR β chain usage in reactive arthritis; evidence for selection by a putative HLA-B27-associated autoantigen. *Tissue Antigens* **60**, 299–308 (2002).
44. Hamrouni, A., Aublin, A., Guillaume, P. & Maryanski, J. L. T cell receptor gene rearrangement lineage analysis reveals clues for the origin of highly restricted antigen-specific repertoires. *J. Exp. Med.* **197**, 601–614 (2003).
45. Kedzierska, K., Turner, S. J. & Doherty, P. C. Conserved T cell receptor usage in primary and recall responses to an immunodominant influenza virus nucleoprotein epitope. *Proc. Natl Acad. Sci. USA* **101**, 4942–4947 (2004).
46. Zhong, W. & Reinherz, E. L. *In vivo* selection of a TCR Vβ repertoire directed against an immunodominant influenza virus CTL epitope. *Int. Immunol.* **16**, 1549–1559 (2004).
47. Kasprowicz, V. *et al.* A highly restricted T-cell receptor dominates the CD8+ T-cell response to parvovirus B19 infection in HLA-A*2402-positive individuals. *J. Virol.* **80**, 6697–6701 (2006).
48. Stewart-Jones, G. B., McMichael, A. J., Bell, J. I., Stuart, D. I. & Jones, E. Y. A structural basis for immunodominant human T cell receptor recognition. *Nature Immunol.* **4**, 657–663 (2003).
49. Turner, S. J. *et al.* Lack of prominent peptide-major histocompatibility complex features limits repertoire diversity in virus-specific CD8+ T cell populations. *Nature Immunol.* **6**, 382–389 (2005).
50. Davis, M. M. The problem of plain vanilla peptides. *Nature Immunol.* **4**, 649–650 (2003).
51. Gavin, M. A. & Bevan, M. J. Increased peptide promiscuity provides a rationale for the lack of N regions in the neonatal T cell repertoire. *Immunity* **3**, 793–800 (1995).
52. Huseby, E. S. *et al.* How the T cell repertoire becomes peptide and MHC specific. *Cell* **122**, 247–260 (2005).
53. Venturi, V. *et al.* Sharing of T cell receptors in antigen-specific responses is driven by convergent recombination. *Proc. Natl Acad. Sci. USA* **103**, 18691–18696 (2006).
54. Fazilleau, N. *et al.* Vα and Vβ public repertoires are highly conserved in terminal deoxynucleotidyl transferase-deficient mice. *J. Immunol.* **174**, 345–355 (2005).
55. Candeias, S., Waltzinger, C., Benoist, C. & Mathis, D. The Vβ17+ T cell repertoire: skewed Jβ usage after thymic selection; dissimilar CDR3s in CD4+ versus CD8+ cells. *J. Exp. Med.* **174**, 989–1000 (1991).
56. Quiros Roldan, E. *et al.* Different TCRBV genes generate biased patterns of V-D-J diversity in human T cells. *Immunogenetics* **41**, 91–100 (1995).
57. Livak, F., Burtrum, D. B., Rowen, L., Schatz, D. G. & Petrie, H. T. Genetic modulation of T cell receptor gene segment usage during somatic recombination. *J. Exp. Med.* **192**, 1191–1196 (2000).
58. Wallace, M. E. *et al.* Junctional biases in the naive TCR repertoire control the CTL response to an immunodominant determinant of HSV-1. *Immunity* **12**, 547–556 (2000).
59. Fuschiotti, P. *et al.* Analysis of the TCR α-chain rearrangement profile in human T lymphocytes. *Mol. Immunol.* **44**, 3380–3388 (2007).
60. Gauss, G. H. & Lieber, M. R. Mechanistic constraints on diversity in human V(D)J recombination. *Mol. Cell Biol.* **16**, 258–269 (1996).
61. Naumov, Y. N., Hogan, K. T., Naumova, E. N., Pagel, J. T. & Gorski, J. A class I MHC-restricted recall response to a

viral peptide is highly polyclonal despite stringent CDR3 selection: implications for establishing memory T cell repertoires in "real-world" conditions. *J. Immunol.* **160**, 2842–2852 (1998).
62. Kedzierska, K., La Gruta, N. L., Davenport, M. P., Turner, S. J. & Doherty, P. C. Contribution of T cell receptor affinity to overall avidity for virus-specific CD8$^+$ T cell responses. *Proc. Natl Acad. Sci. USA* **102**, 11432–11437 (2005).
63. Kedzierska, K. *et al.* Early establishment of diverse T cell receptor profiles for influenza-specific CD8$^+$CD62L^{hi} memory T cells. *Proc. Natl Acad. Sci. USA* **103**, 9184–9189 (2006).
64. Gray, P. M., Parks, G. D. & Alexander-Miller, M. A. High avidity CD8$^+$ T cells are the initial population elicited following viral infection of the respiratory tract. *J. Immunol.* **170**, 174–181 (2003).
65. Kedl, R. M. *et al.* T cells compete for access to antigen-bearing antigen-presenting cells. *J. Exp. Med.* **192**, 1105–1113 (2000).
66. Bousso, P., Levraud, J. P., Kourilsky, P. & Abastado, J. P. The composition of a primary T cell response is largely determined by the timing of recruitment of individual T cell clones. *J. Exp. Med.* **189**, 1591–1600 (1999).
67. Malherbe, L., Hausl, C., Teyton, L. & McHeyzer-Williams, M. G. Clonal selection of helper T cells is determined by an affinity threshold with no further skewing of TCR binding properties. *Immunity* **21**, 669–679 (2004).
68. Moon, J. J. *et al.* Naive CD4$^+$ T cell frequency varies for different epitopes and predicts repertoire diversity and response magnitude. *Immunity* **27**, 203–213 (2007).
69. Dion, M. L. *et al.* HIV infection rapidly induces and maintains a substantial suppression of thymocyte proliferation. *Immunity* **21**, 757–768 (2004).
70. Bousso, P. *et al.* Individual variations in the murine T cell response to a specific peptide reflect variability in naive repertoires. *Immunity* **9**, 169–178 (1998).
71. Blattman, J. N. *et al.* Estimating the precursor frequency of naive antigen-specific CD8 T cells. *J. Exp. Med.* **195**, 657–664 (2002).
72. Pewe, L., Heard, S. B., Bergmann, C., Dailey, M. O. & Perlman, S. Selection of CTL escape mutants in mice infected with a neurotropic coronavirus: quantitative estimate of TCR diversity in the infected central nervous system. *J. Immunol.* **163**, 6106–6113 (1999).
73. Pewe, L. L., Netland, J. M., Heard, S. B. & Perlman, S. Very diverse CD8 T cell clonotypic responses after virus infections. *J. Immunol.* **172**, 3151–3156 (2004).
74. Kedzierska, K. *et al.* Quantification of repertoire diversity of influenza-specific epitopes with predominant public or private TCR usage. *J. Immunol.* **177**, 6705–6712 (2006).
75. Whitmire, J. K., Benning, N. & Whitton, J. L. Precursor frequency, nonlinear proliferation, and functional maturation of virus-specific CD4$^+$ T cells. *J. Immunol.* **176**, 3028–3036 (2006).
76. Lefranc, M. P. *et al.* IMGT, the international ImMunoGeneTics database. *Nucleic Acids Res.* **27**, 209–212 (1999).
77. Weekes, M. P., Wills, M. R., Mynard, K., Carmichael, A. J. & Sissons, J. G. The memory cytotoxic T-lymphocyte (CTL) response to human cytomegalovirus infection contains individual peptide-specific CTL clones that have undergone extensive expansion *in vivo*. *J. Virol.* **73**, 2099–2108 (1999).
78. Callan, M. F. *et al.* T cell selection during the evolution of CD8$^+$ T cell memory *in vivo*. *Eur. J. Immunol.* **28**, 4382–4390 (1998).
79. Moss, P. A. *et al.* Extensive conservation of α and β chains of the human T-cell antigen receptor recognizing HLA-A2 and influenza A matrix peptide. *Proc. Natl Acad. Sci. USA* **88**, 8987–8990 (1991).

Acknowledgements
We thank A. Collins and R. Ribeiro for reviewing the manuscript and for helpful discussions, and K. Kedzierska, S. Turner and P. Doherty for provision of the mouse TCR data, which initially motivated our interest in TCR sharing, and for helpful discussions. This work was supported by the James S. McDonnell Foundation 21st Century Research Award/Studying Complex Systems, the National Institutes of Health, the Australian National Health and Medical Research Council, and the Australian Research Council. M.P.D. is a Sylvia and Charles Viertel Senior Medical Research Fellow. D.A.P. is a Medical Research Council (UK) Senior Clinical Fellow.

FURTHER INFORMATION

Complex Systems in Biology Laboratory homepage:
http://www.cvr.net.au/research/complex.htm

SUPPLEMENTARY INFORMATION

See online article: S1 (figure)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF