Annu. Rev. Immunol. 1993. 11:637–85

GAMMA/DELTA CELLS

Werner Haas

Hoffman-LaRoche, Inc., Nutley, New Jersey 07110

Pablo Pereira and Susumu Tonegawa

Howard Hughes Medical Institute at the Center for Cancer Research, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

KEY WORDS: $\gamma\delta$ T cells, T cell subsets, thymic selection, T cell development, nonclassical MHC antigens, heat shock proteins, T cell

Abstract

Before TCR rearrangements, T cell progenitors are committed not only to the $\alpha\beta$ and $\gamma\delta$ T cell lineage but also to various subsets of both lineages. In the mouse, distinct $\gamma\delta$ T cell subsets can develop in the fetal thymus, the adult thymus, or independently of a thymus, probably in intestinal epithelia. The two subsets that develop in the fetal thymus home to and are maintained throughout adult life in the skin and the mucosa of the uterus, vagina, and tongue. They are monospecific. This unusual restriction in receptor repertoires is the result of severe limitations in the generation of diversity in the fetal progenitors of these subsets and the thymic selection. After birth, one $\gamma\delta$ T cell subset appears in the blood, spleen, and lymph nodes and one in the intestinal epithelia. The receptor repertoires of these subsets are characterized by the preferential usage of particular Vγ gene segments and extensive junctional diversity. Several murine and human $\gamma\delta$ T cell clones have been shown to recognize classical MHC class I and class II proteins or MHC class I–like proteins, and in very few cases the presented peptides are known. We suspect that the various murine $\gamma\delta$ T cell subsets interact with different antigen presenting cells which utilize different antigen presenting proteins and reside in different tissues. The function of $\gamma\delta$ T cells remains unknown. Preliminary results of experiments

0732–0582/93/0410–0637$02.00

with gene knock out mice which lack either $\alpha\beta$ T cells or $\gamma\delta$ T cells or both suggest that $\gamma\delta$ T cells do not function as helper cells in humoral immune responses but may complement $\alpha\beta$ T cells in the defense against various microorganisms.

INTRODUCTION

The long odyssey of immunologists searching for the T cell receptor for antigen (TCR) came to an end in 1984 when clonotypic antibodies were raised against T cell clones, and genes rearranging in T cells but not in B cells were identified and cloned. Because the clonotypic antibodies that were likely to recognize idiotypic determinants of the TCR precipitated an $\alpha\beta$ heterodimer (1–5), it came as a surprise when the third rearranging gene called γ was found (6, 7). Antibodies raised against peptides that were synthesized according to the sequence of the γ gene revealed a second TCR heterodimer, $\gamma\delta$ (8). The δ gene was cloned owing to its location within the TCR α locus (9). Further studies showed that cells expressing $\gamma\delta$ heterodimers did indeed exist and represented a new T cell class (10–13). Thus the immunology of $\gamma\delta$ T cells has been progressing in a "reversed direction" i. e. from genes to the TCR and from the TCR to a new class of lymphocytes. At present many laboratories are attempting to elucidate the functions of these cells.

Previous reviews have focused on the structure and organization of γ and δ genes as well as on the development and specificity of $\gamma\delta$ T cells in mice (14–18), human (17–21), and other species (22). In the present review we focus on the specificity and function of $\gamma\delta$ T cells.

MOUSE $\gamma\delta$ T-CELLS

Segregation of $\alpha\beta$ and $\gamma\delta$ Lineages

In the fetal thymus, rearrangements and surface expression of γ and δ genes precede those of α and β genes (23, 24). This and the finding that nonproductive rearrangements of γ genes are common in $\alpha\beta$ T cells (25) led to the belief that $\alpha\beta$ T cells are derived from T cell progenitors that failed to express $\gamma\delta$ TCRs (24). If this was correct $\alpha\beta$ T cell development should be impaired in transgenic mice expressing rearranged γ and δ transgenes. However, in the first $\gamma\delta$ TCR transgenic animals $\alpha\beta$ T cells developed normally (26). No transgenic transcripts were found in the $\alpha\beta$ T cells of these mice. Silencing of in-frame and out-of-frame rearranged γ genes was also observed in $\alpha\beta$ T cells of normal mice (27). A second set of $\gamma\delta$ TCR transgenic mice was generated with shorter transgenes which

apparently lacked the silencer element (28). In these mice αβ T cell development was severely retarded. These findings suggest that it is the expression of a γ silencer that determines the commitment to the αβ T cell lineage.

A similar silencing element is associated with the TCR α gene (29). Since the γ gene rearranges before the α gene, the α gene silencer cannot be primarily involved in the αβ versus γδ lineage commitment. Perhaps it determines the temporal order of β and α gene rearrangements in cells that have already been committed to the αβ lineage by the previous expression of the γ silencer.

According to another model the deletion of the δ locus by a novel recombination is a prerequisite of αβ T cell development (30, 31). However the normal development of αβ T cells in γδ TCR transgenic mice is not readily compatible with this proposition.

γδ T Cell Subsets

In mice there are various subsets of γδ T cells, which differ from each other by parameters such as time of appearance in ontogeny, anatomical location, TCR repertoires, and thymus dependence (see Table 1). According to the Vγ segments used preferentially or exclusively, we refer to these subsets as the V5, V6, V4 and V7 subsets. Each subset must express unique adhesion proteins that are responsible for the differences in their migratory behaviour. Two monospecific subsets are disseminated in epithelia, the V5 subset in the epidermis of the skin (32) and the V6 subset in the mucosal surfaces of the uterus, vagina, and tongue (33). They are both derived from the γδ T cells which appear first in the fetal thymus (34–37). Soon after birth most of the γδ T cells in the thymus express the Vγ4 and Vγ1 gene segments and a few of them express Vγ2 and Vγ7 (36, 38, 39). These γ chains pair with many different δ chains, and both chains exhibit great junctional diversity (38, 40, 41). Like αβ T cells V4 subset cells circulate through blood and lymphoid organs such as spleen and lymph nodes (39). It is not clear, however, whether γδ T cells recirculate from blood to lymph in lymph nodes. Indeed a histological study of sheep lymph nodes suggests that γδ T cells do not recirculate from blood to lymph and that they have no functional role in lymph nodes (22, 42).

One subset of γδ T cells is generated outside the thymus, probably somewhere in the intestinal epithelia (43–46). These cells appear during the first weeks of life (43). Unlike thymus dependent lymphocytes but similar to thymus independent αβ T cells, most of these cells do not express Thy1 and do express CD8α homodimers (43, 46, 47). Their TCR repertoire is characterized by the predominant usage of Vγ7 and Vγ1 chains, expression of multiple Vδ chains, and high junctional diversity (48–50; P.

Table 1 Mouse γδ T cells

Subset	Location	TCR usage	Diversity	Characteristics
V5	Skin	V5J1C1-γ V1D2J1C-δ	None	Generated in 14–17 day-old fetal thymus Generation depends on fetal progenitors and fetal thymus Positive selection of monospecific cells in the thymus Homing to and maintenance in epidermis Recognizes cultured keratinocytes
V6	Vagina, uterus, tongue	V6J1C1-γ V1D2J1C-δ	None	Generated in late fetal and newborn thymus Positive selection of monospecific cells in the thymus Homing to and maintenance in mucosal epithelia (vagina, uterus, tongue)
V1	Spleen, intestine, skin	V1J4C4-γ V6, 4, 5, 7-δ	High	Abundant in newborn thymus and in spleen 1–2 week after birth Autoreactive, spontaneous IL2 production Respond also to mycobacterial Hsp60 and Hsp60 peptide 180–196 Autoreactivity and response to exogenous Hsp is blocked by mAb to γδ TCR, VNR but not class I or II MHC proteins Various effects on hemopoesis in transgenic mice
V4	Blood, lymph nodes, spleen	V4J1C1-γ V5, 4, 6, 7-δ	High	Generated in postnatal thymus Major γδ cell population in adult thymus, lymph nodes and spleen
V7	Intestine	V7J1C1-γ V, 4, 5, 6, 7-δ	High	Highly diversified Thymus independent Expression of CD8α homodimers
	Lung	Vγ4 Vδ6	High	8–20% of resident pulmonary lymphocytes are γδ T cells
	Liver	V1, 2-γ Vδ6	High	Number increases with age Express CD8α homodimers
	Mammary gland	V4, 5-γ Vδ4	High	Fourfold increase of number in lactating mammary gland

Pereira, unpublished observations). In Table 1 we included subset V1 because of its unique autoreactivity even though V1 is probably not a distinct subset, i.e. it probably does not have a distinct progenitor but is rather a population derived from different progenitors but with common properties and Vγ usage. The V1 population has a thymus dependent and independent component.

The γδ T cell populations in the liver, lung, and mammary gland also cannot readily be assigned to one or the other of the above described subsets (51–53). They also may represent mixtures of cells from different subsets.

Human γδ T cell subsets are listed in Table 2. They are described in a later section.

Heterogeneity of Subset Progenitors

We assume that all the γδ T cell subsets described above are derived from different progenitor cells that are committed to give rise to distinct sublineages before any TCR gene rearrangements have taken place. This belief is based mainly on two sets of data.

First, γδ T cell subset progenitors differ in their requirements to generate mature progeny. One requires a fetal thymus, one requires an adult thymus, and one does not require any thymus to generate mature progeny. The V7 subset is thymus independent because it is found in the intestines of athymic nude mice and in thymectomized mice that have been lethally irradiated and reconstituted with syngeneic bone marrow cells (43, 46). A fetal thymus is required for the generation of the V5 and V6 subsets. An adult thymus fails to support the generation of the fetal subsets but is sufficient for the generation of the V4 and V1 subset (54, 55).

Table 2 Human γδ T cells

Subset	Location	TCR usage	Diversity	Characteristics
Vδ1	Thymus	VIC2-γ Vδ1 most non S-S	High	Predominant in thymus Rare in blood Proportion in blood decreases with age Most cells remain CD45RA
Vδ2	Blood	V2C1-γ Vδ3 most S-S	High	Rare in thymus Predominant in blood Proportion in blood increases with age Most cells become CD45RO

Second, $\gamma\delta$ T cell subset progenitors are committed to different modes of TCR rearrangements. Rearrangments may be "targeted" to different variable gene segments in different progenitors. Thus, a limited analysis of nonproductive rearrangements in mature cells expressing either Vγ4 (56, 57) or Vγ5 (32) chains revealed a preference for rearrangements of Vγ4 or Vγ5, respectively. Similarly, PCR-aided Southern blot analysis of Cγ1 cells colonizing the intestinal epithelia showed a strong bias for the rearrangement of Vγ7, both in the expressed and in the nonexpressed chromosome (49). Furthermore, in cultures of day–13 fetal liver cells with day–14 fetal thymus stromal cells, the temporal order of Vγ gene rearrangements corresponded to the temporal order of the appearance of the Vγ5 and Vγ6 expressing cells during thymic ontogeny (58). It should be noted that in one study (59), PCR analysis of Vγ gene rearrangements in early fetal thymocytes did not reveal any restricted use of particular Vγ gene segments. However, the data presented in this report are not quantitative. The demonstration that fetal precursors have the potential to rearrange any Vγ gene does not argue against the notion of "targeted rearrangements" i.e. preferential rearrangements of defined Vγ genes. Moreover, the rearrangements observed in this study may have occured not only in $\gamma\delta$ but also in $\alpha\beta$ T cell progenitors in which no particular $\gamma\delta$ T cell differentiation program is established.

In fetal progenitor cells the rearrangements are not only limited by a restricted usage of variable gene segments but also by the preferential joinings of segments with short sequence homologies and by the lack of N-region additions. The genes that are assembled in fetal progenitor cells appear to encode receptors that mediate "the conservative view of the immune system" with particular recognition of "old" self and microbial antigens. A very similar distinction can be made between fetal and adult subsets in the other two major classes of lymphocytes, B-cells (60–64) and $\alpha\beta$ T cells (65–67).

The different modes of rearrangement in different $\gamma\delta$ progenitor cells are part of a coordinated differentiation program in which the expression of a particular TCR-repertoire is linked to functional properties such as homing to and maintenance in different peripheral tissues. The homing to different epithelia appears to be independent of the TCR. This has been demonstrated for two $\gamma\delta$ T cell subsets in TCR transgenic mice in which T cells expressing "wrong" TCR's were found in the skin and the intestine (68). However, detailed studies of the lifespan and turnover of $\gamma\delta$ T cell populations in normal and $\gamma\delta$ TCR transgenic mice are necessary to examine the role of the $\gamma\delta$ TCR in the maintenance of the subsets in their "home" tissues. In the case of the fetal subsets, it is conceivable that continuous recognition of a self-antigen is required at least for their main-

tenance in the epithelia of the skin and the mucosae of uterus, vagina, and tongue.

Thymic Selection

The finding that the junctional sequences of rearranged Vγ5, Vγ6 and Vδ1 genes in PCR amplified DNA of fetal thymocytes and epidermal γδ T cells showed a limited junctional diversity in nonproductive rearrangements but almost none in productive rearrangements suggested that the accumulation of cells expressing the invariant Vγ5Vδ1 and Vγ6Vδ1 TCRs was due to TCR-mediated positive selection (32, 37). The monospecificity of the fetal subsets also could be the result of molecular constraints at the level of rearrangements and/or assembly of the heterodimeric TCR molecules. Several efforts were made to determine whether the "cellular selection model" or the "molecular constraint model" or both were correct. Receptor-mediated positive selection is best demonstrated by changing or removing the selecting ligand. Thus, several different mouse strains were analyzed in the hope of finding a polymorphism of the putative selecting ligand and consequently a different canonical sequence. The canonical sequences were the same in all strains tested (J. Lafaille, S. Tonegawa, unpublished). In an attempt to artificially alter the selection process Itohara & Tonegawa added antibodies against a constant region of the γδ TCR to fetal thymus organ cultures in which the monospecific fetal γδ T cell subsets are normally generated (58). The addition of the antibodies led to an increase in the frequency of productive Vγ5, Vγ6, and Vδ1 rearrangements with noncanonical junctional sequences. This finding supports the selection model because it shows that the molecular constraint model alone cannot explain the TCR homogeneity of the two fetal subsets.

Recently the same investigators produced mutant mice with a large deletion of the Cδ gene (S. Itohara, P. Mombaerts, J. Lafaille, A. Nelson, A. Farr, S. Tonegawa, submitted). Since these mutant mice do not express γδ TCR on their surface but do undergo Vγ-Jγ and Vδ-D-Jδ rearrangements, they are ideal to address the molecular constraint vs the cellular selection model. Surprisingly the canonical TCR genes that were assembled in mutant mice in the absence of TCR-mediated selection were as homogenous as those assembled in wild type mice. Indeed the preferred joins seem to be generated by using short sequence homologies present at the borders of the gene segments or in the so-called P nucleotides (37). This finding strongly supports the molecular constraint model. It also suggests that the effect of the anti-γδ TCR antibodies on the junctional diversity of the canonical TCRs in the fetal organ cultures was not due to inhibition of positive selection. We assume that the antibody led to the expansion of very rare cells expressing noncanonical TCRs while, for reasons which we

do not understand, it had little or no effect on cells expressing canonical TCRs, which presumably encountered endogenous ligands in the cultures.

Thus the unusual homogeneity of the TCR of the Vγ5 and Vγ6 subsets appears to result from three processes, namely, rearrangement of specific V segments (i.e. targeted rearrangements), rearrangements guided by short homologous regions at the break points (molecular constraint model) and by positive selection (cellular selection model).

The analysis of γδ TCR transgenic mice provided evidence for positive and negative selection of cells belonging to the adult V4 subset. Negative selection was demonstrated in two studies (69, 70). In the first study the γδ TCR transgenes were derived from the KN6 hybridoma which recognizes the T22 gene product (71, 72) expressed by spleen cells from H–2^b mice but not H–2^d mice (which carry a nonfunctional T22 gene) (72). The number of cells expressing KN6 TCR was similar in the thymus of transgenic H–2^b and of H–2^d mice, but 10 times lower in the spleens of H–2^d mice. Thymocytes and spleen cells from KN6 TCR ligand-positive H–2^b mice were anergic in that irradiated H–2^b spleen cells failed to induce them to produce IL–2 but did induce them to proliferate if exogenous IL–2 was added (69).

In the second study the γδ transgenes were derived from the G8 γδ T cell clone that was obtained from BALB/c nude mice and that is specific for a TL region encoded protein similar if not identical to the KN6 TCR ligand (73, 74). Transgenic TCR expressing cells were found in the intestines of TCR transgenic H–2^b mice, but not in their peripheral lymphoid organs such as lymph nodes and spleen (70, 75). The intestinal cells were unresponsive to H–2^b stimulator cells even in the presence of exogenous IL–2. The anergic state was suspected to be followed soon by apoptosis, but this remains to be demonstrated (75).

Evidence for positive selection of γδ T cells was obtained when the two TCR transgenic mice described above were crossed with β2m deficient mice (76, 77). Cells expressing the transgenic TCR at high levels were abundant in the thymus of β2m-deficient H–2^b and H–2^d TCR transgenic mice but did not exit to peripheral lymphoid tissues and did not give a strong proliferative response to H–2^b spleen cells even when exogenous IL–2 was added. The proportion of transgenic TCR expressing thymocytes that are stained with J11d antibodies was nearly 100% in mice with the β2m defect but only 50% in mice without this defect. These findings suggest that the maturation of transgenic γδ TCR expressing cells is arrested in the thymus of β2m deficient mice. J11d appears to be a marker for immature thymocytes not only in the αβ but also in the γδ T cell lineage. After emigration from the thymus the expression of J11d appears to be lost in both lineages (K. A. Kelly, M. Pearse, L. Lefrancois, R. Scollay, unpublished observations).

Not all γδ T cells require positive selection by β2m dependent proteins since no gross abnormalities of γδ T cells were observed in β2m deficient mice that were not transgenic for a particular γδ TCR (78). This finding does not exclude the possibility that most γδ T cells have β2m related specificities and depend on selection by β2m-associated proteins since a few γδ T cell clones with β2m unrelated specificities could expand in the β2m deficient mice to fill up the γδ T cell compartment.

The data obtained with the KN6 TCR transgenic mice and their crosses with the β2m-deficient mice suggest that positive and negative selection are mediated by the recognition of different ligands because only the former is seen in H–2^d mice (72). We propose that the positively selecting ligand in H–2^b mice is the $T22^b$ protein and in H–2^d mice the product of the T10 gene, a highly homologous duplicate of the T22 gene. The $T22^d$ allele is known to be defective. According to this hypothesis, induction of anergy and activation of mature cells requires recognition of the $T22^b$ protein plus a peptide that cannot be presented by the T10 protein.

Extrathymic Selection of γδ T Cells

Two groups found that the frequency of cells expressing γ or δ chains with particular sequence motifs varied greatly in different strains of mice. Thus, Sim & Augustin have shown that two TCR sequences named BID and GxYS were expressed by many pulmonary resident lymphocytes from BALB/c mice and BALB.B mice but not from C57BL/6 mice (79–81). The same sequences were also found in (BALB/c × C57BL/6) F1 hybrids and in athymic BALB/c mice. The lack of cells expressing BID TCRs and GxYS TCRs in the lungs of C57Bl/6 mice is not due to a failure of these mice to generate the corresponding γ and δ chain genes, because these genes were found in the thymus of all mouse strains (80). These results suggest that the cells expressing BID TCRs were positively selected by strain specific polymorphic ligands that are encoded outside of the classical H–2 region. The selection can take place in the absence of a thymus.

Lefrancois et al (45) reported that the frequency of lymphocytes expressing the Vδ4 chain in the intestinal γδ T cell population varies from 20% to 50% in different strains of mice. F1 hybrids between Vδ4 high and low expressors were Vδ4 high expressors. The analysis of normal and thymectomized F1 into parent bone marrow chimeras showed that the Vδ4 high expressors were selected by host cells and that a thymus was not required for the selection. Further analysis of recombinant inbred strains and of mice recombinant within H–2 suggested that the Vδ4 high phenotype was controlled by a gene linked to the class II MHC genes and required I-E expression.

In these examples of extrathymic selection it is not clear whether exo-

genous antigens are involved nor whether the selection acts upon immature or mature cells. The most likely explanation seems to us to be antigen driven expansion of mature cells.

Figure 1 gives an overview of $\alpha\beta$ and $\gamma\delta$ T cell development.

$\gamma\delta$ T-CELLS IN OTHER SPECIES

$\gamma\delta$ T cells have been found in all vertebrates examined so far, including humans (12, 13), chickens (82, 83), rats (84, 85), sheep (22), cattle (42),

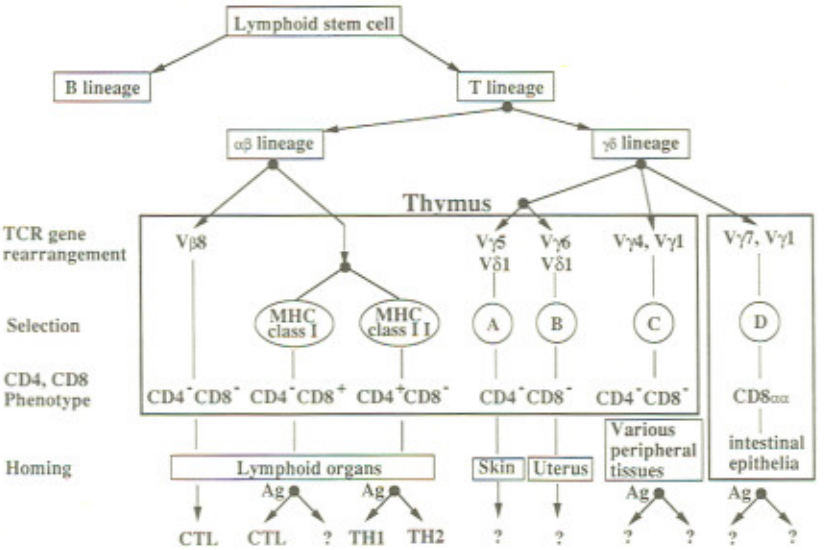

Figure 1 The commitment to functionally distinct subsets (marked by a black dot) may occur at all stages of differentiation, namely before TCR expression, after TCR expression but before maturation, and after maturation. Before TCR expression commitment is made not only to $\alpha\beta$ T-cells and $\gamma\delta$ T cells but also to subsets of both classes, namely, fetal subsets with restricted V segment usage (targeted rearrangements) and very limited junctional diversity and adult subsets with extensive combinatorial and junctional diversity. Positive selection of immature $\alpha\beta$ T cells in the thymus is associated with the commitment to the functionally distinct CD4 and CD8 $\alpha\beta$ T cell subsets that is most likely instructed by TCR recognition of class II and class I MHC proteins, respectively. There is also evidence for positive selection of $\gamma\delta$ T cells in the thymus. We assume that the selecting ligands of the various subsets are nonpolymorphic proteins such as TL region encoded proteins which we arbitrarily call A, B, C and D. Some $\gamma\delta$ T cells may also be selected by classical MHC proteins. After maturation different modes of antigenic stimulation can induce functionally distinct $\alpha\beta$ CD4 T cell subsets, namely TH1 and TH2 cells. Mature $\gamma\delta$ T cells resemble mature $\alpha\beta$ T cells in that they can lyse target cells and secrete the same lymphokines. The functions of the various $\gamma\delta$ T cell subsets remain to be elucidated.

and pigs (86, 87). (Table 3). A preferential localization to epithelia has been noticed in all these species, but there are differences in the abundance of cells and tissue distribution. Ruminants for example have more γδ T cells than αβ T cells in the blood (22, 42). In human (88, 89) and chicken (83), there seems to be no special γδ T cell population in the epidermis.

Human γδ T cells have been studied extensively with regard to TCR repertoire and putative sublineages. Rearrangements at the human TCR γ and δ loci also appear to occur in a developmentally ordered fashion (90, 91). The γδ TCR repertoire that is initially generated in the fetal thymus is small because of the targeting of rearrangements to a limited number of variable gene segments and because of very limited junctional diversity. In the thymuses of 8.5- to 15-week-old human embryos, rearrangements involve joinings of Vδ2 to Dδ3 and of Vγ1.8 or Vγ9 to the Jγ1 cluster (90, 91). The cells which express these TCR chains may be referred to as the Vδ2 subset. From 4 to 6 months after birth, rearrangements involve joinings of other Vδ segments, in particular Vδ1 to Dδ1 and Dδ2 and joinings of upstream Vγ gene segments in the Vγ1 family including Vγ2, 3, 5 and 8 to the Jγ2 cluster (90, 91). The cells which express these TCR chains may be referred to as the Vδ1 subset. The TCR chains of this subset exhibit extensive junctional diversity.

The two human γδ T cell subsets can be distinguished by monoclonal antibodies such as δTCS1 which recognizes Vδ1Jδ1 and Vδ1Jδ2 but not Vδ1Jδ3 (92), BB3 which recognizes Vδ2 (93) or TiγA which recognizes Vγ9 (94). In the postnatal thymus the Vδ2 subset represents about 15% and the Vδ1 subset about 80% of all γδ T cells (95, 96). These proportions of γδ TCR expressing thymocytes remain relatively constant throughout adult life (96). In the blood, however, the Vδ2 subset increases with age from about 25% in cord blood to more than 70% in the blood of most adults. The Vδ1 subset decreases from about 50% in cord blood to less

Table 3 Distribution of γδ T cells (% of lymphocytes in each organ). Data compiled from: humans (88, 89); mice (33, 36); rat (84, 85); chicken (82, 83); sheep (22) and cattle (42)

	Humans	Mice	Rat	Chicken	Sheep	Cattle
Blood	0.5–16	0.5–2	2	15	15–50	15–40
Thymus		0.5–1.5		10	1–4	1–5
Spleen	2–30	0.5–2	2	25	5–7	
Lymph node	5	0.5–3	4		1–6	1–3
Intestine	10	50	–	+	+	+
Skin (epidermis)	–	+		–	–/+	+
Other epithelia (tongue, etc.)		+			+	+

than 30% in the blood of adults (95–99). Most Vδ2 subset cells become positive for CD45RO, a probable marker for memory cells, while most Vδ1 subset cells remain CD45RO negative (100–102). The accumulation of CD45RO positive Vδ2 cells in the blood is thought to be the result of stimulation of mature cells by common ligands for Vδ2/Vγ9 TCRs, many of which are suspected to be superantigens (96). Selection of the predominant γδ T cell subset in adult human blood by superantigens is consistent with the extensive junctional diversity of their TCR (103).

γδ T-CELL SPECIFICITY

Self-Antigens

The murine V5 subset recognizes cultured keratinocytes or fibroblasts treated with tryptic digests of keratinocytes (104). Since the third complementarity determining regions of the canonical TCR of the V6 and V5 subset are identical one might speculate on the basis of current models of TCR/antigen/MHC protein interactions that the two TCRs recognize the same endogenous peptide in the context of different tissue specific peptide presenting proteins. The presenting proteins appear not to be classical MHC proteins.

The V1 population also appears to recognize an endogenous antigen that is expressed by lymphocytes and probably other hemopoietic cells. Since most autoreactive cells of the V1 subset also recognize heat shock proteins they will be described below.

Cultured human γδ T cells often lyse autologous target cells. However, this killing does not involve the γδ TCR. In most cases it is due to IL–2 induced promiscous killing activity that has also been observed with many IL–2 dependent αβ T cell clones. The biological significance of this undiscriminating lytic activity in vitro is questionable.

Classical MHC Proteins

A few murine and human γδ T cell clones have been shown to be specific for class I and class II proteins (Table 4). MHC class I and class II protein specific γδ T cell clones were obtained from nude mice after immunization or repeated in vitro stimulation with allogeneic spleen cells (74, 105, 106). The specificity of these clones was unusual in that it was broadly cross-reactive for the products of different alleles. Several human γδ T cell clones were shown to recognize HLA-A2, HLA-A24, HLA-DR7, HLA-DR3 (107–110) or HLA DQA1/DQB1 heterodimers (111).

Recognition of MHC proteins by γδ T cells probably involves recognition of presented peptides. In one recent study four human clones have been shown to recognize HLA DRw53 and tetanus toxin peptide 1235–

Table 4 Recognition of classical MHC proteins by γδ T cells

Origin of γδ T cells	Specificity	References
$CD4^-$ $CD8^-$ γδ T cell line obtained from draining lymph node cells of C57Bl/10 mice 7 days after immunization with B10.BR spleen cells in CFA in footpat	H-2 D^k (+peptide?)	Bluestone et al (1988) *J. Exp. Med.* 168, 1899
Lymph node cells from C57Bl/10 nude mice were repeatedly restimulated in vitro with B10.BR spleen cells, cloned and fused with BW5147 thymoma cells; hybridoma LBK.5F3	E^k, E^b, E^s, E^p (+peptide?)	Matis et al (1989) *Science* 245, 746
γδ T cell clones were obtained from cultures containing purified $CD4^-$ $CD8^-$ PBL from healthy donors and allogeneic stimulator cells; Clone 40.1(Vδ1)	HLA-A24 (+peptide?) lysis of P815 cells transfected with A24 cDNA	Ciccone et al (1989) *Eur. J. Immunol.* 19, 1267
γδ T cell clones were obtained from cultures containing purified $CD4^-$ $CD8^-$ PBL from healthy donors and allogeneic stimulator cells; Clones ES-204 (Vδ3) and ES-443 (Vδ1)	HLA-A2 (+peptide?) recognition of P815 cells transfected with A2 cDNA	Spits et al (1990) *J. Immunol.* 144, 4156
γδ T cell clones were obtained from cultures containing purified $CD4^-$ $CD8^-$ PBL from healthy donors and allogeneic stimulator cells after repeated restimulations and cell separations	HLA-DR1 (0501)/HLA DQB1 (0301) *cis* or *trans* encoded heterodimer (+peptide?)	Bosnes et al (1990) *Eur. J. Immunol.* 20, 1429
Two donor specific γδ T cell clones from mitogen stimulated PBL of a patient with a HLA mismatched kidney graft; clone 21 and 40	HLA-DQw6 HLA-A24	Vandekerckhove et al (1990) *J. Immunol.* 144, 1288
Four γδ T cell clones isolated from cultures containing the synovial fluid of T cells of rheumatoid arthritis patients that were repeatedly restimulated with AP-MT in the presence of autologous PBMC	HLA-DRw53+ tetanus toxin peptide (1235–1246); also reactive to AP-MT without DR restriction	Holoshits et al (1992) *J. Clin. Invest.* 89, 308
γδ T cells were isolated from blood and clones were established by stimulation with irradiated allogeneic PBMC, EBV-B cell line, PHA and IL2; clone N2A11	HLA-DR7 (+peptide?)	Jitsukawa et al (1988) *Eur. J. Immunol.* 18, 1671

1246 (112). These examples of $\gamma\delta$ T cell specificity for classical MHC proteins are exceptions. In many cases $\gamma\delta$ T cell responses could not be inhibited by antibodies against the classical MHC proteins that serve as restriction elements for $\alpha\beta$ T cells. Moreover, large numbers of murine $\gamma\delta$ T cell hybridomas failed to recognize classical H–2 proteins (113), and the vast majority of human $\gamma\delta$ T cell clones that were activated in limiting dilution cultures were not specific for the HLA proteins of the stimulator cells (114). Clearly, $\gamma\delta$ T cells do not have the bias for classical class I or class II MHC proteins that is characteristic for $\alpha\beta$ T cells.

MHC-Like Proteins

TL region encoded proteins are not only expressed by thymocytes and leukemic T cells but also by epithelial cells in the intestine. The $T3^b$ gene of C57Bl/6 mice and the $T3^d$ and $T18^d$ genes of BALB/c mice are highly expressed in the epithelium of the small intestine (115). A $T3^b$ product-specific antibody binds to columnar epithelial cells (116) which are in close contact with intestinal $\gamma\delta$ T cells (117). Two other TL region genes of C57BL/6 mice, $T9^b$ and $T21^b$ are also expressed almost exclusively by intestinal epithelial cells (116). The various murine $\gamma\delta$ T cell subsets may possibly recognize antigens that are presented by different tissue-specific TL region–encoded proteins (72, 118). However, thus far only a very few murine $\gamma\delta$ T cell clones have been shown to recognize TL region–encoded proteins (Table 5). The hybridoma KN6 mentioned previously is specific for the $T22^b$ gene product (72, 119). TL region–encoded proteins may serve as antigen-presenting molecules. Indeed, recently Imani et al (120, 121) have been able to show the binding of two peptides to the $T23^b$ (Qa–1^b) protein and one hybridoma recognizes the $T23^b$ protein and one of these peptides, namely the synthetic copolymer Glu: Tyr (122).

The human MHC class I family includes at least 15 loci other than the classical transplantation antigens HLA-A, B, and C (123), many of which may be located telomeric of the HLA-A locus (124). Some of these genes encode class I like proteins which may be the human equivalents of the murine TL region encoded proteins (125). Recognition of these proteins by $\gamma\delta$ T cells has not been described. However, a hint for the recognition of human MHC class I–like proteins was obtained when $\gamma\delta$ T cells from peripheral blood were stimulated with a HLA loss variant cell line (126). Cytolytic T cells were generated in this culture that specifically lysed the HLA loss variant cells. The killing was inhibited by anti-$\gamma\delta$ TCR antibodies and by antibodies against HLA-B and C even though HLA-B and C proteins were not expressed. A similar inhibition pattern was also shown for a $\gamma\delta$ T cell clone, the specificity of which could not be mapped to classical class I MHC genes (127). These findings were interpreted to mean

Table 5 Recognition of MHC like proteins by γδ T cells

Origin of γδ T cells	Specificity	References
γδ T cell clones obtained from draining lymph node cells of Balb/c nudes 7 days after immunization with B10.BR spleen cells in CFA in foot pat; clones FY and G8	TLa[a]? (+peptide?)	Bluestone et al (1988) *J. Exp. Med.* 168, 1899
γδ T cell hybridoma obtained by fusion of $CD4^-$ $CD8^-$ thymocytes of adult C57B1/6 mice with BW 5417	H-2 T22[b] (+peptide?)	Bonneville et al (1989) *PNAS* 86, 5928 Itoh et al (1990) *Cell* 62, 549 van Kaer et al (1991) *Immunol Rev.* 120, 8
γδ T cell hybridoma obtained by fusion of BW5147 with draining lymph node cells from DBA/2 mice immunized 7 days previously with the synthetic copolymer Glu:Tyr (GT)	H-2 T23[b](Qa-1[b], 37)+GT	Vidovic et al (1989) *Nature* 340, 646
Intestinal γδ IEL	T3?	Kronenberg, pers. commun.
γδ T cell line (IPD2), Vγ9/Vδ1 obtained from immunodeficient patient	CD1c (+peptide?) lysis of human rhabdomyosarcoma cell line transfected with CD1c cDNA	Porcelli et al (1989) *Nature* 341, 447
γδ T cell line (J287), Vγ3 or 4/Vδ1 isolated from blood of healthy donor	CD1c (+peptide?) (rare specificity)	Faure et al (1990) *Eur. J. Immunol.* 20, 703
γδ T cell clones were obtained from PBL of two healthy donors (E and G) stimulated with allogeneic B-LCL	T cell target 1 (TCT.1 = Blast-1 = CD48) (+peptide?) CD48 is a member of Ig superfamily and is encoded in the same band of chromosome 1 as the CD1 gene cluster	Mami-Chouaib et al (1990) *J. Exp. Med.* 172, 1071 Del Porto et al (1991) *J. Exp. Med.* 173, 1339 Mami-Chouaib et al (1991) *J. Immunol.* 147, 2869
One clone isolated from PBL after stimulation with allogeneic B-LCL and IL-4	Class I like MHC antigen	Spits et al (1989) *J. Immunol.* 143, 1506
Two clones isolated from PBL after stimulation with HLA class I loss variants	MHC class I like protein reactive with anti-HLA B and HLA-C antibodies (+peptide?)	Lam et al (1990) *J. Immunol.* 145, 36

that the $\gamma\delta$ T cells recognized a peptide presented by MHC class I like proteins that crossreact with antibodies against HLA-B and C proteins.

Two human $\gamma\delta$ T cell clones were found to recognize CD1c (128, 129), which is encoded by one gene of a cluster of five closely related MHC class I–like genes on chromosome 1 (130). However, the frequency of CD1 protein-specific $\gamma\delta$ T cells appears to be very low and in the same order of magnitude as the frequency of CD1 protein-specific $\alpha\beta$ T cells (129).

Several human $\gamma\delta$ T cell clones recognize a cell surface protein referred to as *T cell target antigen* 1 (TCT.1 or CD48), a member of the Ig superfamily (131–133) encoded by a gene that is located in the same band of chromosome 1 as the CD1 gene cluster (132). CD48 may be an antigen presenting protein or a ligand for a surface protein involved in $\gamma\delta$ T cell activation.

We favor the view that $\gamma\delta$ T cells recognize peptides and perhaps other small molecules such as carbohydrates in association with nonpolymorphic antigen presenting proteins. So far there are only a few well-documented cases of $\gamma\delta$ T cell specificities for such proteins. In contrast $\alpha\beta$ T cells specific for allogeneic MHC proteins are readily detectable even in very small $\alpha\beta$ T cell population samples. The high alloreactivity of $\alpha\beta$ T cells is due to crossreactions of $\alpha\beta$ TCRs with a + 1 and b or a + 1 and b + 2, where letters are products of MHC alleles and numbers are presented antigens. Such cross-reactions are not expected for TCRs which recognize non-polymorphic antigen presenting proteins.

Mycobacteria and Heat Shock Proteins

Both murine (Table 6) and human (Table 7) $\gamma\delta$ T cells mount strong proliferative responses to killed mycobacteria in the presence of antigen presenting cells. Initially a few $\gamma\delta$ T cell lines and clones were obtained from the blood of a BCG immune donor (134), blood or biopsy material from a lepromin skin test of patients with tuberculoid leprosy (135), or synovial fluid of rheumatoid arthritis patients (136). Several of these lines responded to recombinant mycobacterial heat shock proteins. It soon became clear that $\gamma\delta$ T cells from healthy donors with negative tuberculin tests and no history of mycobacterial infections also vigorously responded to killed mycobacteria or mycobacterial extracts in the presence of antigen presenting cells and that mycobacterial heat shock proteins were not the major stimulating components (132–139). Every second $\gamma\delta$ T cell in the circulating blood of some donors responded to killed mycobacteria, but only a few of the mycobacteria reactive clones also responded to PPD or mycobacterial Hsp65 (137). The major $\gamma\delta$ T cell stimulatory components of mycobacteria were found in a small molecular weight fraction (2–10 kd) of extracts, were resistant to proteolytic enzymes, and were shown to

Table 6 Recognition of mycobacteria and/or Hsp by murine γδ T cells

Origin of γδ T cells	Specificity	References
B10.A mice were immunized with M.t. in limb; draining lymph node cells were analyzed and restimulated in vitro	*in vivo*: increase in γδ T cells in draining lymph nodes from 1.5% to 10.4% after immunization *in vitro*: proliferation and IL-2 production in response to M.t.; not blocked by anti-class II MHC antibodies	Janis et al (1989) *Science* 244, 713
BALB/c mice were immunized with aerosol containing M.t. antigen of tuberculin (PPD) or with CFA at the base of the tail	*in vivo*: increase in γδ T cells in draining lymph nodes *in vitro*: response to heat shocked cells. Specificity for Hsp?	Augustin et al (1989) *Nature* 340, 239 Rajasekar et al (1990) *PNAS* 87, 1767
Thymocytes of B10 newborn mice were fused with BW 5417	Autoreactive γδ T cell hybridomas (IL-2 production) Additional response to PPD and less well to Hsp65 (BCG) in the presence of spleen cells	O'Brien et al (1989) *Cell* 57, 667
	25 of 26 Vγ1/Vδ6 hybridomas react with PPD Most PPD reactive hybridomas respond to Hsp65 peptide (180–196) No inhibition by anti-class I or II MHC antibodies	Happ et al (1989) *Nature* 342, 696 Born et al (1990) *Science* 249, 67
Spleen cells from adult B10 mice were fused with BW5417	10–20% of hybridomas respond to Hsp60 M.t. and Hsp60 M.t. peptide (180–196); all Vγ1/Vδ6; extensive junctional diversity of both TCR chains All Vγ1/Vδ6 cells are also autoreactive	O'Brien et al (1992) *PNAS* 89: 4348

Table 7 Recognition of mycobacteria and/or Hsp by human γδ T cells

Origin of γδ T cells	Specificity	References
γδ T cell line (GD) was established from PBL of a BCG immune donor after stimulation with PPD and autologous PBMC	Autologous APC + PPD or + rHsp60 (M.t.) Allogeneic APC work less well	Hargewoin et al (1989) *Nature* 340, 309
Four γδ T cell clones were isolated from cultures, containing the synovial fluid T cells of rheumatoid arthritis patients that were repeatedly restimulated with AP-MT	Autologous or allogeneic APC + AP-MT or + purified HSP64 (M. bovis)	Holoshitz et al (1989) *Nature* 339, 226
PBMC (line 1) or skin biopsy cells (line 2) of patients with tuberculoid leprosy were stimulated with M. leprae cell wall antigen and IL2 in the presence of partially HLA matched allogeneic PBMC as APC; long term γδ T cell lines were established after depletion of αβ T cells	Autologous APC + M. leprae PPD (line 1 and 2) or M. leprae cell wall (line 1 and 2) or rHsp65 (BCG) (line 1)* rHsp18 (M. leprae) (line 1)* Tetanus toxin (line 8)* * very weak response	Modlin et al (1989) *Nature* 338, 544
PBL from donors with negative tuberculin test were stimulated with killed M.t. and PBMC as APC in bulk and limiting dilution cultures	Autologous APC + killed M.t. recognized by 1 in 2 to 23 γδ T cells in the blood; only very few of them recognize PPD or Hsp65	Kabelitz et al (1990) *J. Exp. Med.* 171, 667
	All M.t. responsive γδ T cells use Vγ9/Vδ2 TCR	Kabelitz et al (1991) *J. Exp. Med.* 173, 1331
PBL from healthy donors were stimulated with various preparations from mycobacterial lysates and PBMC as APC in bulk and limiting dilution cultures	Autologous APC + protolytic digest (2–10k) of mycobacterial lysates recognized by 1 in 50 to 100 γδ T cells	Pfeffer et al (1990) *Eur. J. Immunol.* 20, 1175
PBL of 22 PPD positive, 2 PPD negative donor and cord blood from 4 neonates were stimulated with killed M.t. and PBMC as APC	Autologous APC + killed M.t. All responding γδ T cells use Vγ9/Vδ2 Vδ2 chains show extensive junctional diversity	Panchamoerty et al (1991) *J. Immunol.* 147, 3360

PBMC and pleural fluid cells of patients with tuberculous pleuritis were stimulated with killed M.t.	Autologous APC + killed M.t. All responding $\gamma\delta$ T cells use Vγ9/Vδ2 Extensive junctional diversity of both TCR chains	Ohmen et al (1991) *J. Immunol.* 147, 3353
Large panel of Vγ9/Vδ2 T cell clones from blood	Autologous APC + killed M.t. Recognized by almost all Vγ9/Vδ2 cells All M.t. specific clones also recognize MOLT-4 cells, some recognize also Listeria and E. coli No class I or II MHC restriction	de Libero et al (1991) *J. Exp. Med.* 173, 1311
T cells from peripheral blood of 5 PPD positive and 3 PPD negative healthy donors were cultured with monocytes either infected with live M.t. or pulsed with killed M.t.	Monocytes infected with M.t. induced expansion of $\gamma\delta$ T cells from all but one donor Monocytes pulsed with killed M.t. induced a lower $\gamma\delta$ T cell response	Havlir et al (1991) *J. Clin. Invest.* 87, 729
$\gamma\delta$ T cells were obtained from peritoneal cavity of mice infected 3 days previously with Listeria monocytogenes	CD4$^-$ CD8$^-$ $\gamma\delta$ T cells produce IFNγ and macrophage chemotactic factor in response to PPD or Hsp65 and irradiated syngeneic spleen cells	Hiromatsu et al (1992) *J. Exp. Med.* 173, 49
$\gamma\delta$ T cells were obtained from the lung of mice primed intranasally with influenza virus and challenged intranasally	$\gamma\delta$ T cells obtained 7 days after challenge express mRNA for IL-2, IL-10, IFNγ, IFNβ, GM-CSF; the frequency of cells producing IL-10 was higher in $\gamma\delta$ than in $\alpha\beta$ T cells	Eichelberger (1991) *J. Immunol.* 147, 2069
$\gamma\delta$ T cell subsets were isolated from intestinal IEL	CD8$^+$ $\gamma\delta$ IEL produce either IFNγ or IL-5 or both; stimulation by anti-$\gamma\delta$ TCR or anti-CD8 mab result in enhanced production of these lymphokines	Taguchi et al (1991) *J. Immunol.* 147, 3736
Splenic and intestinal $\gamma\delta$ T cells were stimulated with anti-CD3 mab	Produce IL-2, IL-3, IFNγ, GM-CSF, IFNα, TGFβ (no IL-4)	Bluestone et al (1991) *Immunol. Rev.* 120, 5

bind to some lectins (138, 139). The chemical nature of this material remains to be elucidated. It also remains to be worked out whether the ligand that is recognized by mycobacteria reactive $\gamma\delta$ T cells is of mycobacterial origin or whether it is an endogenous ligand that is induced by mycobacterial components in antigen presenting host cells. Havlir et al (140) found that $\gamma\delta$ T cells from human blood responded not only to monocytes exposed to dead mycobacteria or PPD but even better to monocytes that were infected with live mycobacteria. This interesting observation needs to be confirmed.

The human $\gamma\delta$ T cells that respond to mycobacteria all use Vγ9 and Vδ2 chains, both of which exhibit considerable junctional diversity (141–144). This suggests that mycobacteria contain or induce a superantigen for human Vγ9/Vδ2 cells.

In mice $\gamma\delta$ T cells accumulated in the draining lymph nodes a few days after immunization with killed mycobacteria in the limb. In vitro these $\gamma\delta$ T cells responded to killed mycobacteria with proliferation and IL–2 production (145). The response was not blocked by antibodies against class II MHC proteins of the host (145). As in humans a high frequency of mycobacteria reactive $\gamma\delta$ T cells was also found in mice. Thus many hybridomas obtained by fusion of BW5147 thymoma cells with thymocytes from newborn mice or spleen cells from adult mice were found to produce IL–2 in response to purified protein derivative (PPD) from mycobacteria (113, 146). Most PPD reactive hybridomas also responded to spleen cells pulsed with recombinant mycobacterial Hsp65 or peptide 180–196 from mycobacterial Hsp65, and less well to the corresponding peptide of murine Hsp63 that is identical in sequence with the corresponding chinese hamster and human Hsp65 peptides (113, 147). The reactivity of these hybridomas with Hsp is not readily demonstrable because of a very high level of spontanous IL–2 production. The response to the exogenous antigens can only be seen when the hybridoma cells are cultured at low density and in the presence of spleen cells. The spontanous production as well as the response to exogenous antigen is inhibitable by antibodies against the $\gamma\delta$ TCR and against the vitronectin receptor but not against MHC class I or class II proteins (113, 148, 149). The endogenous ligand that is responsible for the autoreactivity of the V1 population remains to be defined. It may or may not be a Hsp. So far hybridomas were used to study the specificity of the V1 cells. The autoreactivity of the hybridomas is revealed only in the presence of ligands for the vitronectin receptor (VNR). It is not known whether freshly isolated V1 cells are also autoreactive and whether they express VNRs.

All Hsp responsive $\gamma\delta$ T cell hybridomas were derived from V1 cells and use Vγ1 and Vδ6 TCR chains, both exhibiting extensive junctional diversity

(146, 150, 151). These findings suggest that mycobacterial Hsp peptide 180–196 is a superantigen for V1 cells. The same peptide is recognized by two rat αβ T cell clones one transferring experimental acute encephalitis (EAE) and one protecting against EAE (152).

Superantigens

Staphylococcal enterotoxin A (SEA) is a superantigen for both αβ T cells and γδ T cells (153–155). SEA coated cells are lysed by all human γδ T cells expressing Vγ9 chains. In contrast to αβ T cells the γδ T cells do not proliferate in vitro in response to SEA coated cells. SEA binds on the T cell site to Vγ9 and Vβ and on the antigen presenting site to a non-polymorphic region of MHC class II proteins.

Many of the γδ T cell stimulating cells or agents such as Daudi cells, Molt4 cells, microbial extracts, or heat shock proteins are also suspected to represent or contain superantigens. This suspicion is based on the finding that the TCRs of the responding cells are composed of δ and/or γ chains that use the same variable region gene segments but exhibit extensive junctional diversity. However, the molecular nature of putative superantigens for γδ T cells and their interactions with presenting molecules, as well as with the γδ TCR, remain to be elucidated.

γδ T-Cell Function

γδ T cells have not been noticed by cellular immunologists in innumerable studies of humoral and cell mediated immune responses. It was the discovery of rearranging genes other than Ig and TCRαβ genes rather than the observation of a new function that led to their discovery. Extensive analysis of these cells over the last several years revealed only a few phenotypic differences from αβ T cells.

First, γδ T cells do share many cell surface proteins with αβ T cells such as CD2, CD3, CD4, CD5, CD7, CD8, CD11b, CD16, CD25, CD28 or CD45, although the frequency of cells expressing a particular protein and the level of expression vary widely not only between αβ T cells and γδ T cells but also between subsets of γδ T cells and γδ T cells of different species (88, 100–102, 156–162). Besides the γδ TCR, a protein named T19 (also referred to as WC1) is the only unique surface protein of γδ T cells known so far. T19 was discovered by Mackay et al at the surface of γδ T cells from sheep (163). Anti-T19 antibodies stain γδ T cells from other ruminants but not from mice or humans. Recently WC1 cDNA was cloned. It encodes a transmembrane protein of 1436 amino acids with a large extracellular domain that contains 11 repeats that are typical for a family of proteins which includes CD5, CD6, the scavenger receptor, and probably additional WC1 like proteins (164).

Second, like $\alpha\beta$ T cells, $\gamma\delta$ T cells can be stimulated to secrete many lymphokines. The production of different combinations of lymphokines by different $\gamma\delta$ T cell clones has been noticed by several authors (Table 8) (39, 90, 165–176). We do not yet know whether functionally distinct $\gamma\delta$ T cell subsets analogous to the TH1 and TH2 subsets of the $\alpha\beta$ T cell lineage exist.

Third, $\gamma\delta$ T cells resemble $\alpha\beta$ T cells, NK cells and lymphokine activated killer cells (LAK cells) in that they can lyse target cells (177–179) and express the same granule mediators of cytotoxicity such as perforin and serine esterase 1 and 2 (180–182). Cytolytic activity is upregulated by IL–2 as in the other cytolytic cell types mentioned above. Freshly isolated intestinal $\gamma\delta$ T cells from some but not all mouse strains resemble NK cells in that they appear to constitutively express cytolytic activity (180, 183, 184; H. Ishikawa, Y. Li, A. Abeliovich, S. Yamamoto, S. H. E. Kaufmann, S. Tonegawa, submitted).

It is interesting that $\gamma\delta$ T cells isolated from murine skin and human blood share with NK cells the expression of Fc-receptors (murine FcγRα and human FcγRIII also named CD16) which mediate antibody dependent cellular cytotoxicity (ADCC) (185, 186). Because the homogeneous TCR on epidermal $\gamma\delta$ T cells in mice severely restricts antigen recognition, the FcR on these cells may broaden their scope for antigen recognition via aggregated IgG (185).

Like all other lymphocytes, $\gamma\delta$ T cells are under strict control of their antigen receptors. Ligand binding to $\gamma\delta$ TCRs leads to transmission of signal 1 by the CD3 complex (177), which appears to have the same subunit composition as the CD3 complex in $\alpha\beta$ T cells (186a). One or more additional signals mediated by other T cell surface antigens must accompany signal 1 to induce a response such as high affinity IL–2 receptor expression, proliferation, cytolytic activity, or secretion of lymphokines (187–189). The functional role of the various proteins at the $\gamma\delta$ T cell surface remains to be elucidated.

While most mature $\alpha\beta$ T cell express either CD4 or CD8, most $\gamma\delta$ T cells lack both markers (13, 36, 88, 161, 179). However a few $\gamma\delta$ T cells do express either CD8 (36, 88, 89) or CD4 (88, 167, 168, 190, 191), and most intestinal $\gamma\delta$ T cells express CD8α homodimers (46, 192). Analysis of human $\gamma\delta$ T cell clones indicated that CD4 $\gamma\delta$ T cells resemble CD4 $\alpha\beta$ T cells in that activated cells produce lymphokines at high levels but express little or no cytolytic activity (167, 168). The reverse is true for CD8 positive $\alpha\beta$ and $\gamma\delta$ T cells. We conclude that $\gamma\delta$ T cells and $\alpha\beta$ T cells do use the same "tools."

$\gamma\delta$ T cell research has emerged from molecular studies and remains heavily dominated by molecular studies. At the present time functional

studies in vivo are only beginning to address the putative role of γδ T cells in the defense against infections or in various pathological immune responses. The classical method to define the function of a particular cell type is to see what happens if it is eliminated. Recent studies investigate mice (193) and rats (194) depleted of αβ T cells by treatment from birth on with anti-αβ TCR antibodies. The spleens and lymph nodes of these animals contained normal numbers of γδ T cells. A few αβ T cells expressed the αβ TCR at 5 to 10 times lower levels-than αβ T cells from untreated mice. αβ T cell–deficient mice were also obtained from embryonal stem cells (ES cells) in which the α or β TCR locus was disrupted by homologous gene recombination (195, 196). These αβ TCR knock out mice have no αβ T cells at all but normal numbers of γδ T cells. Initial results obtained with αβ T cell–depleted mice and rats and with αβ TCR knock out mice are described in the following sections, together with observations that were made in normal mice and in patients with various immunological disorders.

Role of γδ T-Cells in Humoral Immune Responses

γδ T cells have been found to induce Ig secretion in B cell lines (197) and to induce autoantibody production in blood cells of patients with lupus erythematosus (198). A small fraction of human γδ T cells that express the CD4 marker could provide help for antibody responses in vitro (167, 168). The latter study showed that the γδ TCR was not involved in the interaction with B cells (168). The biological significance of this in vitro observation is questionable. Indeed no antibody responses to T cell–dependent antigens were obtained in αβ T cell–depleted mice and rats (193, 194) nor in αβ TCR knock out mice (196; P. Mombaerts, J. Iacomini, S. Tonegawa, unpublished), while antibody responses to type I and type II T cell–independent antigens were the same as in normal mice. These findings suggest that γδ T cells do not normally function as helper cells for B cells. Whether they can suppress B cell responses remains to be seen.

Role of γδ T-Cells in Graft Rejection

The vigorous rejection of grafts from MHC-mismatched donors is due to the high frequency of αβ T cells that recognize allogeneic MHC proteins. As pointed out above γδ T cell populations do not seem to contain many cells that recognize allogeneic MHC proteins or any other polymorphic proteins. No proliferative response was observed in mixed leukocyte cultures containing responder cells from αβ T cell–depleted mice or rats and stimulator cells from MHC disparate strains (193, 194). Even when exogenous IL–2 was added, no response to the allogeneic stimulator cell was seen. Moreover αβ T cell depleted rats failed to reject skin grafts from MHC-disparate donors (194).

Table 8 Lymphokine production by γδ T cells

Origin of γδ T cell	Species	Lymphokine	References
Various T cell subpopulations were obtained from blood and stimulated with PPD or PHA	Human	γδ T cell clones were heterogeneous with regard to lymphokine production, high production of IL-4, IL-5 (clone HD 109), IFNγ (clone IPD2.4) IL-2, IL-4 IFNγ (clone LG.C6) correlation seen only for IL-2 and TBFα Only CD4 γδ T cell clones produce high levels of IL-2 and GM-CSF	Morita et al (1991) *Eur. J. Immunol.* 21, 2999
Various γδ T cell clones were established from blood by stimulation with irradiated Jy cells and IL-2 or IL-4	Human	IFNγ and GM-CSF production High by $CD4^+$ $CD28^+$ $CD11b^-$ γδ T cells Low by $CD8^+$ $CD28^{+/-}$ $CD11b^+$ γδ T cells	Spits et al (1991) *J. Immunol.* 147, 1180
HLA-A2 specific γδ T cell clones obtained stimulation of $CD4^-$ $CD8^-$ PBL with irradiated Jy cells and IL-2 or IL-4	Human	γδ clones product IL-2, IFNγ, GM-CSF Only some produce IL-4	Spits et al (1990) *J. Immunol.* 144, 4150
γδ T cells were purified from blood of patients with schistosomiasis and carcinoma of the urinary bladder	Human	γδ T cells produce high levels of BCGF and BCDF but are deficient in IL-2 production	Raziuddin et al (1992) *Eur. J. Immunol.* 22, 309
Freshly isolated blood γδ T cells were stimulated with anti-CD3 or anti-γδ TCR mab	Human	IL-2, TNF, IFNγ production	Mingari et al (1987) *Int. J. Cancer* 40, 495 Ferrini et al (1987) *J. Exp. Med.* 166, 277
γδ T cell clones were stimulated with anti-CD3 or lectin	Human	IL-2, IL-4, IL-5, TNFα GM-CSF, IFNγ production IL-2 and IL-4 production low or undetectable in most clones	Porcelli et al (1991) *Immunol. Rev.* 120, 137

γδ T cells were obtained from early fetal (8–15 weeks) thymi and postnatal thymi (4–6 months)	Human	Early thymic γδ T cells produce IL-4, IL-5, GM-CSF, IFNγ Late thymic γδ T cells produce GM-CSF and IFNγ	Krangel et al (1990) *J. Exp. Med.* 172, 847
γδ T cell clones were isolated from fetal liver and thymus (14 weeks)	Human	Produce: IL-2, IL-4, IFNγ production (clone 12) IL-4 production (clone T6)	Carding et al (1990) *Eur. J. Immunol.* 20, 1327
γδ T cell lines PEER and Molt 13	Human	Anti-CD7 mab induce mRNA for TNFα and TNFβ (PEER) and GM-CSF (Molt 13)	Carrel et al (1991) *Eur. J. Immunol.* 21, 1195
γδ T cells were obtained from peritoneal cavity of mice infected 3 days previously with Listeria monocytogenes	Mouse	$CD4^-$ $CD8^-$ γδ T cells produce IFNγ and macrophage chemotactic factor in response to PPD or Hsp65 and irradiated syngeneic spleen cells	Hiromatsu et al (1992) *J. Exp. Med.* 173, 49
γδ T cells were obtained from the lung of mice primed intranasally with influenza virus and challenged intranasally	Mouse	γδ T cells obtained 7 days after challenge express mRNA for IL-2, IL-10, IFNγ, IFNβ, GM-CSF; the frequency of cells producing IL-10 was higher in γδ than in αβ T cells	Eichelberger (1991) *J. Immunol.* 147, 2069
γδ T cell subsets were isolated from intestinal IEL	Mouse	$CD8^+$ γδ IEL produce either IFNγ or IL-5 or both; stimulation by anti-γδ TCR or anti-CD8 mab result in enhanced of these lymphokines	Taguchi et al (1991) *J. Immunol.* 147, 3736
Splenic and intestinal γδ T cells were stimulated with anti-CD3 mab	Mouse	IL-2, IL-3, IFNγ, GM-CSF, IFNα, TGFβ production; no IL-4 production	Bluestone et al (1991) *Immunol. Rev.* 120, 5

About one third of all lymphocytes that were isolated from endomyocardial biopsies of human heart allografts more than 1 year after transplantation were $\gamma\delta$ T cells, while earlier biopsies contained less $\gamma\delta$ T cells (199). The biopsy derived $\gamma\delta$ T cells were not specific for the donor cells. They were suspected to downregulate immune responses to allogeneic cells.

$\gamma\delta$ T cells have also been studied in patients receiving bone marrow or fetal liver and thymus transplants for treatment of immunodeficiency or neoplastic diseases (200–204). The immune system of most reconstituted patients consists of a complex mixture of host and donor cells and often does not function well for many months after transplantation. Some patients had elevated numbers of circulating $\gamma\delta$ T cells early after the transplantation presumably because $\gamma\delta$ T cells that were present in the graft expanded in the host (200–204). Antidonor reactivity of $\gamma\delta$ T cells has been implicated in the poor function of the immune system in some cases (200). In other cases $\gamma\delta$ T cells from transplanted patients did not show any reactivity to donor or host cells (203).

Role of $\gamma\delta$ T-Cells in Infectious Diseases

In vitro responses of $\gamma\delta$ T cells to microrganism and microbial compounds and related in vivo observations in humans and mice are summarized in Table 9 (bacteria), Table 10 (viruses), and Table 11 (parasites).

$\gamma\delta$ T cells accumulate in the draining lymph nodes of mice infected in the footpad with mycobacteria (145), in the lungs of mice infected intranasally with influenza virus (175, 205), in the peritoneal cavity of mice infected with *Listeria monocygotenes* (174, 206), in the hepatic granulomas of Schistosome infected mice (207), and in the skin lesions of patients with the tuberculous form of leprosy or with cutaneous leishmaniasis (135, 208). Elevated numbers of $\gamma\delta$ T cells have been noticed in the spleens of mice infected with *Trypanosoma cruzi* and *Plasmodium chabaudi* (209), in the blood of patients during the acute and convalescent phases of malaria infections (210, 211). In the acute phase of Epstein Barr virus (EBV) infection, the number of circulating Vδ2 cells was increased (212) while in vitro EBV transformed cells mainly stimulated Vδ1 (213). Elevated numbers of circulating $\gamma\delta$ T cells were in the blood of HIV infected patients with AIDS (214–216). Two of 35 T cell clones obtained from cells in the cerebrospinal fluid of patients with measle virus mediated subacute, sclerosizing panencephalitis were $\gamma\delta$ T cells (217).

Interestingly little evidence suggests that the expansion or accumulation of $\gamma\delta$ T cell clones in the infected tissues is due to the recognition of microbial antigens. A single $\gamma\delta$ T cell clone specific for a viral protein was isolated from the draining lymph node of a mouse infected in the footpad

Table 9 Bacterial infections

Bacteria	Species	Observations	References
Mycobacteria	Mouse	Increase in number of $\gamma\delta$ T cells in draining lymph nodes of mice immunized with M.t. in limb	Janis et al (1989) *Science* 244, 713
	Human	$\gamma\delta$ T cells accumulate granulomatous skin lesions of patients with leprosy (reversal reaction and positive lepromin skin test) increased number of $\gamma\delta$ T cells in tuberculous lymphadenitis	Modlin et al (1989) *Nature* 338, 544 Falini et al (1989) *J. Immunol.* 143, 2480
Listeria monocytogenes (L.m.)	Mouse	Increased number of $\gamma\delta$ T cells in peritoneal cavity of mice 3 days after intraperitoneal infection with L.m.	Ohga et al (1990) *Eur. J. Immunol.* 20, 533
		The early appearing $\gamma\delta$ T cells proliferate and secrete IFNγ and macrophage chemotactic factor in response to PPD from M.t. or Hsp65 from *M. bovis* but not to killed Listeria	Hiromatsu et al (1992) *J. Exp. Med.* 175, 49
		Mice depleted of $\alpha\beta$ T cells by mAb treatment show resistance of early stage of infection only	Kaufmann et al pers. commun.
		Treatment with anti-$\gamma\delta$ TCR mAb leads to enhanced L.m. multiplication at an early stage of infection	
Various bacteria	Human	$\gamma\delta$ T cells from blood of healthy donors Proliferation induced by killed mycobacteria, group A streptococci; staphylococcus aureus or Listeria monocytogenes	Munk et al (1990) *J. Immunol.* 145, 2434
		Killing of antigen pulsed target cells reveals recognition of shared and nonshared microbial components	
		A large number of different bacteria, especially gram negative bacteria induce proliferation of $\gamma\delta$ T cells from adult blood or cord blood	Abo et al (1990) *Int. Immunol.* 2, 8
Staphylococcus	Human	All Vγ9 expressing cells lyse target cells pulsed with staphylococcal enterotoxin (SEA)	Rust et al (1990) *Nature* 346, 572

Table 10 Viral infections

Virus	Species	Observations	References
Influenza virus	Mice	Number of γδ T cells is increased in lung lavage cells 7 to 10 days after intranasal infection	Carding et al (1990) *J. Exp. Med.* 172, 1225
		γδ T cells may provide protective cover of the lung during the time that tissue repair is proceeding through the secretion of cytokines (IFNγ, IFNβ, GM-CSF) in response to hsp expressing macrophages	Eichelberger et al (1991) *J. Immunol.* 147, 2069
		Alternatively γδ T cells are passively recruited from blood and play no active part in the disease process	
Herpes simplex virus (HSV-1)	Mice	A γδ T cell clone was isolated from the draining lymph node of a mouse infected with HSV-1 in the foot pat; biological significance?	Johnson et al (1992) *J. Immunol.* 148, 983
Epstein Barr virus (EBV)	Human	Elevated number of Vγ9/Vδ2 cells in blood in acute phase of EBV infection	de Paoli et al (1990) *J. Infect. Dis.* 161, 1013
		Numbers remain high for 4 weeks	
		EBV transformed B cells selectively stimulate Vδ1 cells in vitro	Hacker et al (1992) *Eur. J. Immunol.* In press
Human immunodeficiency virus (HIV)	Human	Increased numbers of Vδ1 cells in blood of some HIV infected patients; increase is most marked in patients with AIDS	Autran et al (1989) *Clin. Exp. Immunol.* 75, 206
		Vδ1 increase may be due to diminished retention within the thymus that is damaged by HIV infection or to stimulation by activated autologous B cells	de Paoli et al (1991) *Clin. Exp. Immunol.* 83, 187
			Hacker et al (1992) *Eur. J. Immunol.* In press
Measles virus	Human	Subacute sclerosing panencephalitis (SSPE) is due to an immune response against measle virus in the central nervous system; 2 of 35 T cell clones from cerebrospinal fluid of a patient with SSPE were γδ T cells; no proliferative response to measle virus infected cells was obtained in vitro	Ang et al (1987) *J. Exp. Med.* 165, 1453

Table 11 Parasitic infections

Parasites	Species	Observations	References
Trypanosoma cruzi	Mouse	Selective increase of $\gamma\delta$ T cells in the spleen of C57B1/6 mice infected with *Trypanosoma cruzi*	Minoprio et al (1989) *Immunol. Rev.* 112, 183
Plasmodium chabaudii	Mouse	Increase in number of $\gamma\delta$ T cells in the spleen of BALB/c mice seven days after infection with *Plasmodium chabaudii*	Minoprio et al (1989) *Immunol. Rev.* 112, 183
Plasmodium falciparum	Human	Increase in number of $\gamma\delta$ T cells in blood during acute and convalescent phases of malaria infections	Roussilhon et al (1990) *J. Inf. Dis.* 162, 283 Ho et al (1990) *Immunol. Letters* 25, 139
	Mouse	Outgrowth of Vγ9 cells from peripheral blood stimulated in vitro with merozoites, schizont lysate or whole parasitized red blood cells	Goerlich et al (1991) *Eur. J. Immunol.* 21, 2613 Behr & Dubois (1992) *Int. Immunol.* 4, 361 Goddier et al (1992) *Int. Immunol.* 4, 33
Cutaneous Leishmaniasis	Human	Accumulation of $\gamma\delta$ T cells in granulomatous skin lesions	Modlin et al (1989) *Nature* 339, 544
Schistosomiasis	Human	Increased number of $CD4^+$ $CD8^-$ $\gamma\delta$ T cells in the blood	Raziuddin et al (1992) *Eur. J. Immunol.* 22, 309
	Mice	In hepatic granulomas of schistosome infected mice activated $\gamma\delta$ T cells are present and express high levels of IgA and IgM FcR and low levels of IgG FcR; ADCC by $\gamma\delta$ T cells?	Sandor et al (1992) *J. Immunol.* 148, 2363

with *Herpes simplex* virus (218). Recently Flynn found $\gamma\delta$ T cells specific for various trypanosome proteins in the blood of cattle following infection with *trypanosoma congolense*. Interestingly such responses were observed in West African N'Dama cattle which recover from trypanosoma infections but not in Boran cattle which succumbed to the infection (N. Flynn, personal communication).

We are not aware of any other case in which $\gamma\delta$ T cells were unequivocally shown to recognize and respond to defined microbial antigens in infected humans or animals. The $\gamma\delta$ T cells in the lungs of mice infected with influenza virus appear to recognize host cell components rather than viral antigens (175). Similarly the $\gamma\delta$ T cells that accumulate in the peritoneal cavity of mice 3 days after infection with *Listeria monocygotenes* proliferate and secrete IFNγ and macrophage chemotactic factor in response to putative mycobacterial superantigens but not to listerial antigens (174). Mice depleted of $\alpha\beta$ T cells by mab treatment show resistance to the infection by *Listeria monocygotenes* within the first few days after infection but cannot control the infection later (S. H. Kaufmann, P. Mombaerts, unpublished observation). This finding is consistent with the well-established protective role of *Listeria monozygotenes*-specific $\alpha\beta$ T cells. $\gamma\delta$ T cells appear to have a crucial function early after infection at a time when there is no protection by specific $\alpha\beta$ T cells. An exaggerated multiplication of Listeria microorganisms is seen in normal mice and $\alpha\beta$ TCR knock out mice that were treated with anti-$\gamma\delta$ TCR antibodies (S. H. Kaufmann, P. Mombaerts, unpublished observation). These findings are the first indication for complementary functions of $\alpha\beta$ and $\gamma\delta$ T cells. The protection by $\gamma\delta$ T cells is not Listeria specific. It is fast but incomplete. For survival $\alpha\beta$ T cells must recognize and respond to listerial antigens and mount an immune response that eliminates the pathogen. Recently similar observations were made in a mouse model of malaria (R. Nussenzweig, personal communication).

Immune Surveillance Against Cancer by $\gamma\delta$ T-Cells

$\gamma\delta$ T cells have been suspected to have a surveillance function against tumors. The following observations (summarized in Table 12) are cited to support this idea:

First, IL–2 activated $\gamma\delta$ T cells can kill many different tumor cells. The molecular basis of the distinction between normal cells and tumor cells by the lymphokine activated $\gamma\delta$ T cell cells is not known.

Second, a subset of human $\gamma\delta$ T cells appears to recognize a superantigen on the surface of some Burkitt lymphoma cells (219–223). Another subset recognizes Epstein Barr virus transformed B cells (213).

Third, some $\gamma\delta$ T cells that were isolated from patients with Burkitt

lymphomas or acute lymphoblastic leukemias (ALL) in complete remission were shown specifically to recognize autologous tumor cells (224).

Fourth, γδ T cell lines could be established from populations of tumor infiltrating lymphocytes (TIL) (225–227). The γδ TIL isolated from lung tumors lysed autologous tumor cells, and this lysis was inhibited by anti-class I MHC antibodies (227). No evidence for specific lytic activity was obtained with γδ TIL that were isolated from Wilms tumors, melanomas, and sarcomas (225). These observations are interesting but far from being convincing evidence for a role of γδ T cells in the defense against tumors.

Pathological Immune Responses by γδ T-Cell

γδ T cells have been suspected to contribute to pathological immune responses in several different diseases (Table 13). The synovial fluid from patients with rheumatoid arthritis was found by many investigators to contain γδ T cells of the V1 subset that represents a minor proportion of circulating γδ T cells in most healthy individuals (136, 228–238). Vδ1 cells also accumulate in the intestinal lesions of patients with coeliac disease (239–243) and were found increased in the blood of a patient with type I autoimmune polyglandular syndrome that was associated with aplastic anemia (244). Vδ2 cells were found in 10 of 10 brain autopsies from multiple sclerosis patients (238) and the number of Vδ2 cells was elevated in the blood of a patient with atopic dermatitis (245).

The analysis of junctional regions of TCR chains from γδ T cells of patients with rheumatoid arthritis (232, 236–238), multiple sclerosis (242) or coeliac disease (243) did not reveal any extensive expansion of particular γδ T cell clones. However large γδ T cell clones were found in the blood and the bronchoalveolar lavage of some patients with pulmonary sarcoidosis (246, 247).

These reports are interesting but do not document a pathogenic or protective role of γδ T cells.

γδ T-Cells in Immunodeficiency Diseases

Brenner et al were the first to identify peripheral blood T cells which were CD3 positive but αβ TCR negative (8). While the initial attempts to expand these cells from the blood of normal donors failed, since the cultures were quickly overgrown by αβ T cells, these investigators succeeded in obtaining two $CD3^+$, αβ TCR^- lines from one patient with bare lymphocyte syndrome (IDP1) and one patient with ectodermal dysplasia syndrome (IDP2) respectively. These were the first cells from which CD3 cross-linked γδ TCRs were precipitated (8). The two TCR chains of both lines were non-disulphide linked. Later several additional lines and clones expressing either non-disulfide linked or disulfide linked γδ TCRs were obtained from

Table 12 Recognition of neoplastic cells by γδ T cells

Cancer	Species	Observations	References
B cell lymphoma	Mouse	γδ T cells proliferate in response to CD5 positive B cell lymphomas and induce Ig secretion	Sperling & Wortis (1989) *Int. Immunol.* 1, 434
Burkitt's lymphoma and EBV transformed B-LCL	Human	γδ T cells from children with Burkitt lymphoma lyse autologous tumor cells; the γδ T cell tumor cell interaction involves the γδ TCR and surface Ig of the tumor	Wright et al (1989) *J. Exp. Med.* 169, 1557
		Daudi Burkitt lymphoma cells induce selective growth of Vγ9/Vδ2 T cells; EBV transformed B-LCL induce growth of Vγ1 T cells	Hacker et al (1992) *EJI.* Submitted
		Many of 356 γδ T cell clones lyse Daudi but not Raji Burkitt lymphoma cells while NK cell lyse both targets	Fisch et al (1990) *J. Exp. Med.* 171, 1567
		All γδ T cell clones which lyse Daudi cells express Vγ9 Vδ2 TCR; the Vδ2 chains show extensive junctional diversity	Sturm et al (1990) *J. Immunol.* 145, 3202
		Freshly isolated Vγ9/Vδ2 T cells from blood proliferate in response to Daudi cells	
		Lysis of Daudi cells by γδ T cells is inhibited by a rabbit antiserum against mammalian Hsp50	Fisch et al (1990) *Science* 250, 1269

		Most γδ T cells expressing Vγ9/Vδ1 TCR also recognize Daudi cells in cytotoxicity and proliferative assays	Fisch et al (1990) *J. Immunol.* 148, 2315
Lung carcinoma	Human	The majority of freshly isolated tumor infiltrating lymphocytes from 2 patients were γδ T cells; 100% and 40% respectively were Vδ1$^+$; the γδ T cells lysed autologous tumor cells; lysis was inhibited by anti-class I MHC antibodies	Zocchi et al (1990) *Eur. J. Immunol.* 20, 2685
Wilms tumor Sarcoma Melanoma	Human	γδ T cell lines obtained from tumor infiltrating lymphocytes by stimulation with autologous tumor cells and IL-2; no evidence for tumor specific lysis	Nanno et al (1992) *Eur. J. Immunol.* 22, 679
Localized pagetoid reticulosis (Woringer-Kolopp disease)	Human	γδ T cells are abundant in epidermal infiltrate	Alaibac (1992) *Int. J. Dermatol.* 31, 157
Langerhans cell histiocytosis	Human	γδ T cells are increased in number in the dermal and epidermal infiltrate in close association with Langerhans cells	Alaibac (1992) *Int. J. Dermatol.* 31, 157
Acute lymphoblastic leukemia (ALL)	Human	84 γδ T cell clones were isolated from blood of 3 ALL patients after complete remission was achieved; all clones express cytolytic activity but only 10 clones lysed autologous leukemia cells	Bensussan et al (1989) *Blood* 73, 2077

Table 13 Pathological immune responses

Disease	Species	Observations	References
Rheumatoid arthritis (RA)	Human	10 of 202 T cell clones from synovial fluid of 4 juvenile arthritis patients are probably $\gamma\delta$ T cells	DeMaria et al (1987) *Eur. J. Immunol.* 17, 1815
		$\gamma\delta$ T cells are enriched in synovial fluid as compared to blood in some patients with RA	Brennan et al (1988) *J. Autoimmunity* 1, 319
		Coordinate expansion of $\gamma\delta$ T cells and $CD5^+$ B cells in blood of patients with RA and primary Sjogren's syndrome	Brennan et al (1989) *Clin. Exp. Immunol.* 77, 175
		4 $\gamma\delta$ T cell clones isolated from synovial fluid of a patient with RA respond to acetone precipitable fraction of M.t.	Holoshitz et al (1989) *Nature* 339, 226
		$\gamma\delta$ T cells in synovial fluid of RA patients preferentially use Vδ1	Sioud et al (1990) *Scand. J. Immunol.* 31, 415
		Vδ1 chains have diverse junctional sequences	Sioud et al (1991) *Eur. J. Immunol.* 21, 239
		$V\delta1^+$, $CD69^+$, $CD25^+$ $\gamma\delta$ T cells in synovial compartment of 6 juvenile RA patients	Kjeldsen-Kragh et al (1990) *Scand. J. Immunol.* 32, 651
		Lower numbers of $\gamma\delta$ T cells in blood of RA patients	Smith et al (1990) *Scand. J. Immunol.* 32, 585
		No consistent increase of $\gamma\delta$ T cells in synovial fluid or tissues of RA patients	Pope et al (1991) *Cell. Immunol.* 137, 127
		Increased number of $\gamma\delta$ T cells in synovial fluid of RA patients show extensive junctional diversity except in one patient	Keystone et al (1991) *Clin. Exp. Immunol.* 84, 78
		Vδ1 chains of $\gamma\delta$ T cells in synovial fluid of RA patients show extensive junctional diversity except in one patient	Bucht et al (1992) *Eur. J. Immunol.* 22, 567
Multiple sclerosis (MS)	Human	Identification of $\gamma\delta$ T cells in MS brain lesions by immunohistochemical techniques	Selmaj et al (1991) *PNAS* 88, 6425
		Evidence for clonal expansion of $\gamma\delta$ T cells in MS brain lesions	Wucherpfennig et al (1992) *PNAS*. In press
		γ and δ transcripts were found in 12 of 12 MS brains but only in 1 of 10 control brains junctional diversity of Vδ2 chains was limited	Huas et al (1992). Submitted

Coeliac disease	Human	Elevated number of $\gamma\delta$ T cells ($V\delta_1+$) in intestinal epithelia of patients with coeliac disease	Spencer et al (1989) *Eur. J. Immunol.* 19, 1335 Viney et al (1990) *Gut* 31, 841 Trejdosiewicz et al (1991) *Clin. Exp. Immunol.* 84, 440
		No evidence for oligoclonal $\gamma\delta$ T cell expansion	Rust et al (1992) *Scand. J. Immunol.* 35, 459 DeLibero et al 1992. Submitted
Polymyositis	Human	$\gamma\delta$ T cell infiltrates in nonnecrotic muscle fibres of one patient	Hohlfeld et al (1991) *New Eng. J. Med.* 324, 877
Kikuchi's lymphadenitis	Human	Hyperimmune response to unknown antigen massive $\gamma\delta$ T cell infiltrates	Falini et al (1989) *J. Immunol.* 143, 2480
Lupus nephritis	Human	7 of 59 autoantibody inducing TH lines obtained from blood were $\gamma\delta$ T cells	Rajagopalan et al (1990) *PNAS* 87, 7020
Discoid chronic lupus erythematosus	Human	$\gamma\delta$ T cells accumulate in dermis and basal keratinocyte layer of epidermis, frequently surrounding damaged keratinocytes	Platzer et al (1990) 20th Annual Meetg. Eur. Society of Dermatological Research
Type I Autoimmune polyglandular syndrome	Human	Increase in $V\delta1^+$ cells in blood associated with aplasic anemia	Hara et al (1990) *Blood* 75, 941
Atopic dermatitis	Human	$V\delta2^+$ cells expanded in blood of one patient	de Paoli et al (1990) *Immunol. Letters* 23, 195
Pulmonary sarcoidosis	Human	7 of 20 patients have elevated $\gamma\delta$ T cells in blood and bronchoalveolar lavage from lower respiratory tract	Balbi et al (1990) *J. Clin. Invest.* 85, 1353
		Expansion of a single clone (homogeneous junctional sequences) in blood and lung of one patient	Tamura et al (1990) *J. Exp. Med.* 172, 169

patients with different primary immunodeficiency diseases such as partial DiGeorge syndrome, common variable immunodeficiency (248), or Wiskott Aldrich syndrome (249). The studies published so far on $\gamma\delta$ T cells from patients with primary immunodeficiency syndroms are rather fragmentary, however.

Elevated numbers of $\gamma\delta$ T cell were also found in the blood of patients with Down's syndrome who are more prone to autoimmune diaseases, have a greatly increased susceptibility to viral and bacterial infections, and a 10- to 20-fold higher incidence of childhood leukemia (250). At least 5 of 10 patients with ataxia-teleangiectasia had an increased ratio of $\gamma\delta$ T cells to $\alpha\beta$ T cells. This finding is thought to reflect both a recombinational defect that interferes with Ig and TCR gene rearrangements and an inability to repair damage to the DNA (251).

CONCLUDING REMARKS

We do believe that $\gamma\delta$ T cells are as important for defense against microbes as B cells and $\alpha\beta$ T cells. There are many reasons why their function has not yet been recognized. One is certainly the preconception about T cells that is derived from our knowledge of $\alpha\beta$ T cells. Most investigators searching for $\gamma\delta$ T cell functions designed their experiments as if $\gamma\delta$ T cells were just other $\alpha\beta$ T cells. It was assumed that $\gamma\delta$ T cells recognize peptides presented by MHC or MHC-like proteins on the surface of macrophages or dendritic cells. Indeed, spleen cells appear to be appropriate antigen presenting cells, MHC and MHC like proteins are recognized at least by some $\gamma\delta$ T cells, and $\gamma\delta$ T cells responded to antigen recognition with proliferation, lymphokine production, expression of cytolytic activity or anergy—just like $\alpha\beta$ T cells. We do suspect that the observed responses were either mediated by rare $\gamma\delta$ T cells that are not representative for entire $\gamma\delta$ T cell subsets, or the responses were directed to superantigens that activate large fractions of cells irrespective of the junctional diversity of their receptors. The great diversity of $\gamma\delta$ T cells must be crucial for their function. Physiologically relevant responses of $\gamma\delta$ T cells may be directed to peptides with postranslational modifications that occur only in microbes or even to nonpeptidic antigens such as carbohydrates that are presented by novel antigen presenting proteins which coevolved with Vγ and Vδ gene segments. We suspect that there is a diverse set of antigen presenting cells that utilize different antigen presenting proteins in different tissues. This possibility has not been explored extensively. The analysis of these cells and of their mode of antigen presentation may be the key to the understanding of the unique functions of $\gamma\delta$ T cells.

ACKNOWLEDGMENTS

For helpful suggestions and/or for providing unpublished data, we thank C. Bernard, R. L. H. Bolhuis, M. Bonneville, J. Cihak, J. E. Coligan, G. De Libero, T. Hünig, J. Jacomini, F. Imani, C. Janeway, Jr., D. Kabelitz, K. A. Kelly, M. Kronenberg, B. Kyewski, C. Mackay, R. L. O'Brien, T. H. Rabbitts, R. Rajasekar, K. Shortman, H. Spits, E. Sturm, and J. E. de Vries. W. Haas is supported by Hoffman La Roche, P. Pereira by the Leukemia Society of America, and S. Tonegawa by Howard Hughes Medical Institute and grants from NIH.

Literature Cited

1. Allison, J. P., McIntyre, B. W., Bloch, D. 1982. Tumor specific antigen of murine T lymphoma defined with monoclonal antibody. *J. Immunol.* 129: 2293–97
2. Meuer, S. C., Fitzgerald, K. A., Hussey, R. E., Hogdon, J. C., Schlossman, S. F., Reinherz, E. L. 1983. Clonotypic structures involved in antigen-specific human T cell function. *J. Exp. Med.* 157: 705–19
3. Acuto, O., Hussey, R. E., Fitzgerald, K. A., Protentis, J. P., Meuer, S. C., Schlossman, S. F., Reinherz, E. L. 1983. The human T cell receptor: appearance in ontogeny and biochemical relationship of α and β subunits on IL-2 dependent clones and T cell tumors. *Cell* 34: 717–26
4. Haskins, K., Kubo, R., White, J., Pigeon, M., Kappler, J., Marrack, P. 1983. The major histocompatibility complex-restricted antigen receptor on T cells. I. Isolation with a monoclonal antibody. *J. Exp. Med.* 157: 1149–69
5. Kaye, J., Porcelli, S., Tite, J., Jones, B., Janeway, C. A. Jr. 1983. Both a monoclonal antibody and antisera specific for determinants unique to individual cloned helper T cell lines can substitute for the antigen and antigen presenting cells in the activation of T cells. *J. Exp. Med.* 158: 836–56
6. Saito, H., Kranz, D. M., Takagaki, Y., Hayday, A. C., Eisen, H. N., Tonegawa, S. 1984. Complete primary structure of a heterodimeric T-cell receptor deduced from cDNA sequences. *Nature* 309: 757–62
7. Kranz, D. M., Saito, H., Heller, M., Takagaki, Y., Haas, W., Eisen, H. N., Tonegawa, S. 1985. Limited diversity of the rearranged T cell gamma (γ) gene. *Nature* 313: 2752–55
8. Brenner, M. B., McLean, J., Dialynas, D. P. Strominger, J. L., Smith, J. A., Owen, F. L., Seidman, J. G., Ip, S., Rosen, F., Krangel, M. S. 1986. Identification of a putative second T-cell receptor. *Nature* 322: 145–49
9. Chien, Y. H., Iwashima, M., Kaplan, K. B., Elliott, J. F., David, M. M. 1987. A new T-cell receptor gene located within the alpha locus and expressed early in T-cell differentiation. *Nature* 327: 677–82
10. Bank, I., DePinho, R. A., Brenner, M. B., Cassimeris, J., Alt, F. W., Chess, L. 1986. A functional T3 molecule associated with a novel heterodimer on the surface of immature human thymocytes. *Nature* 322: 179–81
11. Lanier, L. L., Federspiel, N. A., Ruitenberg, J. J., Phillips, J. H., Allison, J. P., Littman, D., Weiss, A. 1987. The T cell antigen receptor complex expressed on normal peripheral blood $CD4^-$, $CD8^-$ T lymphocytes. *J. Exp. Med.* 165: 1076–94
12. Lew, A. M., Pardoll, D. M., Maloy, W. L., Fowlkes, B. J., Kruisbeek, A., Cheng, S-F., Germain, R. N., Bluestone, J. A., Schwartz, R. H., Coligan, J. E. 1986. Characterization of T cell receptor gamma chain expression in a subset of murine thymocytes. *Science* 234: 1401–5
13. Nakanishi, N., Maeda, K., Ito, K., Heller, M., Tonegawa, S. 1987. Tγ protein is expressed on murine fetal thymocytes as a disulfide-linked heterodimer. *Nature* 325: 720–23
14. Raulet, D. H. 1989. The structure, function, and molecular genetics of the γ/δ T cell receptor. *Annu. Rev. Immunol.* 7: 175–207
15. Allison, J. P., Havran, W. L. 1991. The immunobiology of T cells with in-

variant γδ antigen receptors. *Annu. Rev Immunol.* 9: 679–705
16. Doherty, P. C., Allan, W., Eichelberger, M., Cardig, S. R. 1992. Roles of αβ and γδ T cell subsets in viral immunity. *Annu. Rev Immunol.* 10: 123–52
17. Lefranc, M. P., Bonneville, M. 1990. 33rd forum in Immunology: γδ T cells. *Res. Immunol.* 141: 565–692
18. Moller, G. ed. 1991. γδ T cells. *Immunol. Rev.* 120: 1–204
19. Koning, F., Colligan, J. E. 1988. The γδ T cell receptors. In *The Year in Immunology* 1988, ed. J. M. Cruse, R. E. Lewis, 4: 94–109
20. Strominger, J. 1989. Developmental biology of T cell receptors. *Science* 244: 943–50
21. Spits, H. 1991. Human T cell receptor γδ T cells. *Semin. Immunol.* 3: 119–29
22. Hein, W. R., Mackay, C. R. 1991. Prominance of γδ T cells in the ruminant immune system. *Immunol. Today* 12: 30–34
23. Raulet, D. H., Garman, R. D., Saito, H. Y., Tonegawa, S. 1985. Developmental regulation of T-cell receptor gene expression. *Nature* 314: 103–7
24. Pardoll, D. M., Fowlkes, B. J., Bluestone, J. A., Kruisbeck, A., Maloy, W. L., Coligan, J. E., Schwartz, R. H. 1987. Differential expression of two distinct T-cell receptors during thymocyte development. *Nature* 326: 79–81
25. Heilig, J. S., Tonegawa, S. 1987. T-cell γ gene is allelically but not isotypically excluded and is not required in known functional T-cell subsets. *Proc. Natl. Acad. Sci. USA* 84: 8070–74
26. Ishida, I., Verbeck, S., Bonneville, M., Itohara, S., Berns, A., Tonegawa, S. 1990. T-cell receptor γδ and γ transgenic mice suggest a role of a γ gene silencer in the generation of αβ T-cells. *Proc. Natl. Acad. Sci. USA* 87: 3067–71
27. Heilig, J. S., Tonegawa, S. 1986. Diversity of murine gamma genes and expression in fetal and adult T lymphocytes. *Nature* 322: 836–40
28. Bonneville, M., Ishida, I., Mombaerts, P., Katsuki, M., Verbeek, S., Berns, A., Tonegawa, S. 1989. Blockade of αβ T cell development by TCR γδ transgenes. *Nature* 342: 931–32
29. Winoto, A., Baltimore, D. 1989. αβ lineage-specific expression of the a T-cell receptor gene by nearby silencers. *Cell* 59: 649–55
30. De Villartay, J. P., Cohen, D. L. 1990. Gene regulation within the TCR-γ/δ locus by specific deletion of the TCR-δ cluster. *Res. Immunol.* 141: 618–23
31. De Villartay, J. P., Mossalayi, D., De Chasseval, R., Dalloul, A., Debre, P. 1991. The differentiation of human pro-thymocytes along the TCR-α/β pathway in vitro is accompanied by the site-specific deletion of the TCR-δ locus. *Int. Immunol.* 3: 1301–5
32. Asarnow, D. M., Kuziel, W. A., Bonyhadi, M., Tigelaar, R. E., Tucker, P. W., Allison, J. P. 1988. Limited diversity of γ/δ antigen receptor genes of Thy-1$^+$ dendritic epidermal cells. *Cell* 55: 837–47
33. Itohara, S., Farr, A. G., Lafaille, J. J., Bonneville, M., Takagaki, Y., Haas, W., Tonegawa, S. 1990. Homing of a γ/δ thymocyte subset with homogenous T-cell receptors to mucosal epithelial. *Nature* 343: 754–57
34. Havran, W. L., Allison, J. P. 1988. Developmentally ordered appearance of thymocytes expressing different T-cell antigen receptors. *Nature* 335: 443–45
35. Ito, K., Bonneville, M., Takagaki, Y., Nakanishi, N., Kanagawa, O., Krecko, E., Tonegawa, S. 1989. Different γδ T-cell receptors are expressed on thymocytes at different stages of development. *Proc. Natl. Acad. Sci. USA* 86: 631–35
36. Itohara, S., Nakanishi, N., Kanagawa, O., Kubo, R., Tonegawa, S. 1989. Monoclonal antibodies specific to native murine T-cell receptor γ/δ: analysis of γ/δ T-cells during thymic ontogeny and in peripheral lymphoid organs. *Proc. Natl. Acad. Sci. USA* 86: 5094–98
37. Lafaille, J. L., Decloux, A., Bonneville, M., Takagaki, Y., Tonegawa, S. 1989. Junctional sequences of T cell receptor γδ genes: implications for γδ T cell lineages and for a novel intermediate of V-(D)-J joining. *Cell* 339: 857–70
38. Takagaki, Y., Nakanishi, N., Ishida, I., Kanagawa, O., Tonegawa, S. 1989. T-cell receptor γ and δ genes preferentially utilized by adult thymocytes for the surface expression. *J. Immunol.* 142: 2112–21
39. Bluestone, J. A., Cron, R. Q., Barrett, T. A., Houlden, B., Sperling, A. I., Dent, A., Hedrick, S., Rellahan, B., Matis, L. A. 1991. Repertoire development and ligand specificity of murine TCR γδ cells. *Immunol. Rev.* 120: 5–33
40. Elliott, J. F., Rock, E. P., Patten, P. A., Davis, M. M., Chien, Y-H. 1988. The adult T-cell receptor δ-chain is diverse and distinct from that of fetal thymocytes. *Nature* 331: 627–31

41. Ezquerra, A., Cron, R. Q., McConnell, T. J., Valas, R. B., Bluestone, J. A., Coligan, J. E. 1990. TCR δ gene expression and diversity in the mouse spleen. *J. Immunol.* 145: 1311–17
42. Mackay, C. R., Hein, W. R. 1989. A large proportion of bovine T cells express the γδ T cell receptor and show a distinct tissue distribution and surface phenotype. *Int. Immunol.* 1: 540–45
43. Bandeira, A., Itohara, S., Bonneville, M., Burlen-Defranoux, O., Mota-Santos, T., Coutinho, A., Tonegawa, S. 1991. Extrathymic origin of intestinal intraepithelial lymphocytes bearing T-cell antigen receptor γδ. *Proc. Natl. Acad. Sci. USA* 88: 43–47
44. Mosley, R. L., Styre, D., Klein, J. R 1990. Differentiation and functional maturation of bone marrow-derived intestinal epithelial T-cells expressing membrane T-cell receptor in athymic radiation chimeras. *J. Immunol.* 145: 1369–75
45. Lefrancois, L., Lecorre, R., Mayo, J., Bluestone, J. A., Goodman, T. 1990. Extrathymic selection of TCR $\gamma\delta^+$ cells by class II major histocompatibility complex molecules. *Cell* 63: 333–40
46. Guy-Grand, D., Cerf-Benussan, N., Malissen, B., Malassis-Seris, M., Briottet, C., Vassalli, P. 1991. Two gut intraepithelial $CD8^+$ lymphocyte populations with different T cell receptors: A role for the gut epithelium in T cell differentiation. *J. Exp. Med.* 173: 471–81
47. Lefrancois, L., Goodman, T. 1989. In vivo modulation of cytolytic activity and Thy-1 expression in TCR-$\gamma\delta^+$ intraepithelial lymphocytes. *Science* 243: 1716–18
48. Bonneville, M., Janeway, C. A. Jr., Ito, K., Haser, W., Ishida, I., Nakanishi, N., Tonegawa, S. 1988. Intestinal intraepithelial lymphocytes are a distinct set of γδ T-cells. *Nature* 336: 479–82
49. Takagaki, Y., Decloux, A., Bonneville, M., Tonegawa, S. 1989. Diversity of γδ T-cell receptors on murine intestinal intraepithelial lymphocytes. *Nature* 339: 712–14
50. Kyes, S., Carew, E., Carding, S. R., Janeway, C. A. Jr., Hayday, A. 1989. Diversity in T-cell receptor γ gene usage in intestinal epithelium. *Proc. Natl. Acad. Sci. USA* 86: 5527–31
51. Ohteki, T., Abo, T., Seki, S., Kobata, T., Yagita, H., Okumura, K., Kumagai, K. 1991. Predominant appearance of γδ T lymphocytes in the liver of mice after birth. *Eur. J. Immunol.* 21: 1733–40
52. Augustin, A., Kubo, R. T., Sim, G. K. 1989. Resident pulmonary lymphocytes expressing the γδ T-cell receptor. *Nature* 340: 239–41
53. Reardon, C., Lefrancois, L., Farr, A., Kubo, R., O'Brien, R., Born, W. 1990. Expression of γ/δ T-cell receptors on lymphocytes from the lactating mammary gland. *J. Exp. Med.* 172: 1263–66
54. Havran, W. L., Allison, J. P. 1990. Origin of Thy-1^+ dendritic epidermal cells of adult mice from fetal thymic precursors. *Nature* 344: 68–70
55. Ikuta, K., Kina, T., MacNeil, I., Uchida, N., Peault, B., Chien, Y., Weissman, I. L. 1990. A developmental switch in thymic lymphocyte maturation potential occurs at the level of hematopoietic stem cells. *Cell* 62: 863–74
56. Kranz, D. M., Saito, H., Heller, M., Takagahi, Y., Haas, W., Eisen, H. N., Tonegawa, S. 1985. Limited diversion of the rearranged T-cell γ gene. *Nature* 313: 752–55
57. Korman, A. J., Marusic-Galesic, S., Spencer, D., Kruisbeck, A., Raulet, D. H. 1988. Predominant variable region gene usage by γ/δ T cell receptor-bearing cells in the adult thymus. *J. Exp. Med* 168: 1021–40
58. Itohara, S., Tonegawa, S. 1990. Selection of γδ T cells with canonical T-cell antigen receptors in fetal thymus. *Proc. Natl. Acad. Sci. USA* 87: 7935–38
59. Carding, S. R., Kyes, S., Jenkinson, E. J., Kingston, R., Bottomly, K., Owen, J. J. T., Hayday, A. C. 1990. Developmentally regulated fetal thymic and extrathymic T cell receptor γδ gene expression. *Genes and Develop.* 4: 1304–15
60. Gu, H., Forster, I., Rajewsky, K. 1990. Sequence homologies, N sequence insertion and JH gene utilization in VHDJH joining: implications for the joining mechanism and the ontogenetic timing of Lyl B cell and B-CLL progenitor generation. *EMBO J* 9: 2133–40
61. Jeong, H. D., Teale, J. M. 1990. Contribution of the $CD5^+$ B cell to D-proximal VH family expression early in ontogeny. *J. Immunol.* 145: 2725–29
62. Carlsson, L. and Holmberg, D. 1990. Genetic basis of the neonatal antibody repertoire: germline V-gene expression and limited N-region diversity. *Int. Immunol.* 2: 639–45
63. Feeney, A. J. 1990. Lack of N regions in fetal and neonatal mouse immunoglobulin V-D-J junctional sequences. *J. Exp. Med.* 172: 1377–90

64. Meek, K. 1990. Analysis of junctional diversity during B lymphocyte development. *Science* 250: 820–23
65. Budd, R. C., Meischer, G. C., Howe, R. C., Less, R. K., Bron, C., Macdonald, H. R. 1987. Developmentally regulated expression of T cell receptor β chain variable domains in immature thymocytes. *J. Exp. Med.* 66: 577–82
66. Fowlkes, B. J., Kruisbeek, A. M., Ton-Hat, H., Weston, M. A., Coligan, J. E., Schwartz, R. H., Pardoll, D. M. 1987. A novel population of T-cell receptor $\alpha\beta$-bearing thymocytes which predominantly express a single Vβ family. *Nature* 329: 251–54
67. Crispe, I. M., Moore, M. W., Husmann, L. A., Smith, L. A., Bevan, M. J., Shimonkevitz, R. P. 1987. Differentiation potential of subsets of $CD4^-CD8^-$ thymocytes. *Nature* 329: 336–39
68. Bonneville, M., Itohara, S., Krecko, E. G., Mombaerts, P., Ishida, I., Katsuki, M., Berns, A., Farr, A. G., Janeway, C. A. Jr, Tonegawa, S. 1990. Transgenic mice demonstrate that epithelial homing of $\gamma\delta$ T cells is determined by cell lineages independent of T cell receptor specificity. *J. Exp. Med.* 171: 1015–26
69. Bonneville, M., Ishida, I., Itohara, S., Verbeek, S., Berns, A., Kanagawa, O., Haas, W., Tonegawa, S. 1990. Self-tolerance to transgenic $\gamma\delta$ T cells by intrathymic inactivation. *Nature* 344: 163–65
70. Dent, A. L., Matis, L. A., Hooshmand, F., Widacki, S. M., Bluestone, J. A., Hedrick, S. M. 1990. Self-reactive $\gamma\delta$ T cells are eliminated in the thymus. *Nature* 343: 714–19
71. Bonneville, M., Ito, K., Krecko, E. G., Itohara, S., Kappes, D., Ishida, I., Kanagawa, O., Janeway, D. A. Jr., Murphy, D. B., Tonegawa, S. 1989. Recognition of a self MHC TL region product by $\gamma\delta$ T cell receptors. *Proc. Natl. Acad. Sci. USA* 86: 5928–32
72. Ito, K., Van Kaer, L., Bonneville, M., Hau, S., Murphy, D. B., Tonegawa, S. 1990. Recognition of the product of a novel MHC TL region gene (27b) by a mouse $\gamma\delta$ T cell receptor. *Cell* 62: 549–56
73. Bluestone J. A., Cron, R. Q., Cotterman, M., Houlden, B. A., Matis, L. A. 1988. Structure and specificity of T cell receptor γ/δ on major histocompatibility complex antigen-specific $CD3^+$, $CD4^-$, $CD8^-$ T lymphocytes. *J. Exp. Med.* 168: 1899–1916
74. Houlden, B. A., Matis, L. A., Cron, R. Q., Widacki, S. M., Brown, D., Pampeno, C., Meruelo, D., Bluestone, J. A. 1990. A TCR gamma/delta cell recognizing a novel TL-encoded gene product. *Cold Spring Harbor Symp.* 54: 45–55
75. Barrett, T. A., Delvy, M. L., Kennedy, D. M., Lefrancois, L., Matis, L. A., Dent, A. L., Hedrick, S. M., Bluestone, J. A. 1992. Mechanism of self-tolerance of γ/δ T cells in epithelial tissue. *J. Exp. Med.* 175: 65–70
76. Pereira, P., Ziljstra, M., McMaster, J., Loring, J. M., Jaenisch, R., Tonegawa, S. 1992. Blockade of transgenic of $\gamma\delta$ T cell development in β2-microglobulin deficient mice. *EMBO J.* 11: 25–31
77. Wells, F. B., Gahm, S. J., Hedrick, S. M., Bluestone, J. A., Dent, A., Matis, L. A. 1991. Requirement for positive selection of $\gamma\delta$ receptor bearing T cells. *Science* 253: 903–5
78. Correa, I., Bix, M., Liao, N-S, Zijlstra, M., Jaenisch, R. 1992. Most $\gamma\delta$ T cells develop normally in β2-microglobulin-deficient mice. *Proc. Natl. Acad. Sci. USA* 89: 653–57
79. Sim, G. K., Augustin, A. 1990. Dominantly inherited expression of BID, an invariant undiversified T cell receptor δ chain. *Cell* 61: 397–405
80. Sim, G. K., Augustin, A. 1991. Dominant expression of the T cell receptor BALB invariant δ (BID) chain in resident pulmonary lymphocytes is due to selection. *Eur. J. Immunol.* 21: 859–61
81. Sim, G. K., Augustin, A. 1991. Extrathymic positive selection of $\gamma\delta$ T cells. *J. Immunol.* 146: 2439–45
82. Sowder, J. T., Chen, C. H., Lanier Ager, L., Chan, M. M., Cooper, M. D. 1988. A large subpopulation of avian T cells express a homologue of the mammalian T γ/δ receptor. *J. Exp. Med.* 167: 315–22
83. Bucy, R. P., Chen, C-L. H., Cihak, J., Losch, U., Cooper, M. D. 1988. Avian T cells expressing $\gamma\delta$ receptors localize in the splenic sinusoids and the intestinal epithelium. *J. Immunol.* 141: 2200–5
84. Lawetzky, A., Tiefenthaler, G., Kubo, R., Hunig, T. 1990. Identification and characterization of rat T cell subpopulations expressing T cell receptors $\alpha\beta$ and $\gamma\delta$. *Eur. J. Immunol.* 20: 343–47
85. Vaage, J. T., Dissen, E., Ager, A., Roberts, I., Fossum, S., Rolstad, B. 1990. T cell receptor–bearing cells among rat intestinal intraepithelial lymphocytes are mainly $\alpha\beta^+$ and are thymus dependent. *Eur. J. Immunol.* 20: 1193–96
86. Hirt, W., Saalmuller, A., Reddehase,

M. J. 1990. Distinct γ/δ T cell receptors define two subsets of circulating porcine CD2⁻CD4⁻CD8⁻ T lymphocytes. *Eur. J. Immunol.* 20: 265–69
87. Saalmuller, A., Hirt, W., Reddehase, M. J. 1990. Porcine γ/δ T lymphocyte subsets differing in their propensity to home to lymphoid tissue. *Eur. J. Immunol.* 20: 2343–46
88. Groh, V., Porcelli, S., Fabbi, M., Lanier, L. L., Picker, L. J., Anderson, T., Warnke, R. A., Bhan, A. K., Strominger, J. L., Brenner, M. B. 1989. Human lymphocytes bearing T cell receptor γ/δ are phenotypically diverse and evenly distributed throughout the lymphoid system. *J. Exp. Med.* 169: 1277–94
89. Bucy, R. P., Chen, C-L. H., Cooper, M. D. 1989. Tissue localization and CD8 accessory molecule expression of T γδ cells in humans. *J. Immunol.* 142: 3045–49
90. Krangel, M. S., Yssel, H., Brocklehurst, C., Spits, H. 1990. A distinct wave of human T cell receptor γδ lymphocytes in the early fetal thymus: Evidence for controlled gene rearrangement and cytokine production. *J. Exp. Med.* 172: 847–59
91. McVay, L. D., Cardig, S. R., Bottomly, K., Hayday, A. C. 1991. Regulated expression and structure of T cell receptor gamma delta transcripts in human thymic ontogeny. *EMBO J.* 10: 83–88
92. Wu, Y. J., Tian, W. T., Snider, R. M., Rittershaus, C., Rogers, P., LaManna, L., Ip, S. H. 1988. Signal transduction of γδ T cell antigen receptor with a novel mitogenic anti-delta antibody. *J. Immunol.* 141: 1476–79
93. Ciccone, E., Ferrini, S., Bottino, C., Viale, O., Prigione, I., Pantaleo, G., Tambussi, G., Moretta, A., Moretta, L. 1988. A monoclonal antibody specific for a common determinant of the human T cell receptor γδ directly activates CD3⁺WT31⁻ lymphocytes to express their functional program(s) *J. Exp. Med.* 169: 1–11
94. Jitsukawa, S., Faure,F., Lipinski, M., Triebel, F., Hercend, T. 1987. A novel subset of human lymphocytes with a T cell receptor-gamma complex. *J. Exp. Med.* 166: 1192–97
95. Casorati, G., De Libero, G., Lanzavecchia, A., Migone, N. 1989. Molecular analysis of human γδ clones from thymus and peripheral blood. *J. Exp. Med.* 170: 1521–35
96. Parker, C. M., Groh, V., Band, H., Porcelli, S., Morita, C., Fabbi, M., Glass, D., Strominger, J. L., Brenner, M. B. 1990. Evidence for extrathymic changes in the T cell receptor γ/δ repertoire. *J. Exp. Med.* 171: 1597–1612
97. Triebel, F., Faure, F., Graziani, M., Jitsukawa, S., FeFranc, M-P., Hercend, T. 1988. A unique V-J-C rearrangement gene encodes a gamma protein expressed on the majority of CD3⁺ T cell receptor αβ-circulating lymphocytes. *J. Exp. Med.* 167: 694–99
98. Borst, J., Wicherink, A., van Dongen, J. J., de Vries, E., Comans-Bitter, W. M., Wassenaar, F., Van der Elsen, P. 1989. Non-random expression of T cell receptor γ and δ variable gene segments in functional T lymphocyte clones from human peripheral blood. *Eur. J. Immunol.* 19: 1559–68
99. Bottino, C., Tambussi, G., Ferrini, S., Ciccone, E., Varese, P., Mingari, M-C., Moretta, L., Moretta, A. 1988. Two subsets of human T lymphocytes expressing γδ antigen receptor are identifiable by monoclonal antibodies directed to two distinct molecular forms of the receptor. *J. Exp. Med.* 168: 491–505
100. Hayward, A. R., Lee, J., Beverley, P. C. L. 1989. Ontogeny of expression of UCHL1 antigen on TCR–1⁺ (CD4/8) and TcRd⁺ T cells. *Eur. J. Immunol.* 19: 771–73
101. Miyawaki, T., Kasahara, Y., Taga, K., Yachie, A., Taniguchi, N. 1990. Differential expression of CD45RO (UCHL1) and its functional relevance in two subpopulations of circulating TCR-γ/δ⁺ lymphocytes. *J. Exp. Med.* 171: 1833–38
102. Braakman, E., Sturm, E., Vijverberg, K., van Krimpen, B. A., Gratama, J. W. Bolhuis, R. L. H. 1991. Expression of CD45 isoforms by fresh and activated human γδ T lymphocytes and natural killer cells. *Int. Immunol.* 3: 691–97
103. Tamura, N., Holroyd, K. J., Banks, T., Kirby, M., Okayama, H. Crystal, R. G. 1990. Diversity in junctional sequences associated with the human Vγ9 and Vδ2 gene segments in normal blood and lung compared with the limited diversity in a granulomatous disease. *J. Exp. Med.* 172: 169–81
104. Havran, W. L., Chien, Y. H., Allison, J. P. 1991. Recognition of self antigens by skin-derived T cells with invariant γδ antigen receptors. *Science* 252: 1430–32
105. Matis, L. A., Fry, A. M., Cron, R. Q., Cotterman, M. M., Dick, R. F., Bluestone, J. A. 1989. Structure and specificity of a class II MHC alloreactive

$\gamma\delta$ T cell receptor heterodimer. *Science* 245: 746–49
106. Rellahan, B. L., Bluestone, J. A., Houlden, B. A., Cotterman, M. M., Matis, L. A. 1991. Junctional sequences influence the specificity of γ/δ T cell receptors. *J. Exp. Med.* 173: 503–6
107. Ciccone, E., Viale, O., Pende, D., Malnati, M., Battista Ferrara, G., Barocci, S., Moretta, A., Moretta, L. 1989. Specificity of human T lymphocytes expressing a $\gamma\delta$ T cell antigen receptor. Recognition of a polymorphic determinant of HLA class I molecules by a $\gamma\delta$ T cell clone. *Eur. J. Immunol.* 19: 1267–71
108. Spits, H., Paliard, X., Engelhard, V. H., deVries, J. E. 1990. Cytotoxic activity and lymphokine production of T cell receptor (TCR)-$\alpha\beta^+$ and TCR-$\gamma\delta^+$ cytotoxic T lymphocyte (CTL) clones recognizing HLA-A2 and HLA-A2 mutants. *J. Immunol.* 144: 4156–62
109. Vandekerckhove, B. A. E., Datema, G., Koning, F., Goulmy, E., Persijn, G. G., Van Rood, J. J., Claas, F. H. J., De Vries, J. E. 1990. Analysis of the donor-specific cytotoxic T lymphocyte repertoire in a patient with a long-term surviving allograft. *J. Immunol.* 144: 1288–94
110. Jitsukawa, S., Triebel, F., Faure, F., Miossec, C., Hercend, T. 1988. Cloned $CD3^+$ TcR α/β^- $TiaA^-$ peripheral blood lymphocytes compared to the $TiaA^+$ counterparts: structural differences of the γ/δ receptor and functional heterogeneity. *Eur. J. Immunol.* 18: 1671–79
111. Bosnes, V., Qvigstad, E., Lundin, K. E. A., Thorsky, E. 1990. Recognition of a particular HLA-DQ heterodimer by a human $\gamma\delta$ T cell clone. *Eur. J. Immunol.* 20: 1429–33
112. Holoshitz, J., Vila, L. M., Keroack, B. J., McKinley, D. R., Bayne, N. K. 1992. Dual antigenic recognition of cloned human $\gamma\delta$ T-cells. *J. Clin. Invest.* 89: 308–14
113. O'Brien, R. L., Happ, M. P., Dallas, A., Palmer, E., Kubo, R., Born, W. K. 1989. Stimulation of a major subset of lymphocytes expressing T cell receptor $\gamma\delta$ by an antigen derived from mycobacterium tuberculosis. *Cell* 57: 667–74
114. Kabelitz, D., Bender, A., Schondelmaier, S., Da Silva Lobo, M. L., Janssen, O. 1990. Human cytotoxic lymphocytes V. Frequency and specificity of $\gamma\delta^+$ cytotoxic lymphocyte precursors activated by allogeneic or autologous stimulator cells. *J. Immunol.* 144: 1288–94
115. Hershberg, R., Eghtesady, P., Sydora, B., Brorson K., Cheroutre, H., Modlin, R., Kronenberg, M. 1990. Expression of the thymus leukemia antigen in mouse intestinal epithelium. *Proc. Natl. Acad. Sci. USA* 87: 9727–31
116. Wu, M., Van Kaer, L., Itohara, S., Tonegawa, S. 1991. Highly restricted expression of the thymus leukemia (TL) antigen on intestinal epithelial cells. *J. Exp. Med.* 174: 213–18
117. Tonegawa, S., Berns, A., Bonneville, M., Farr, A. G., Ishida, I., Ito, K., Itohara, S., Janeway, C. A. Jr., Kanagawa, W., Katsuki, M., Kubo, R., Lafaille, J. J., Mombaerts, P., Murphy, D., Nakanishi, N., Takagaki, Y., Van Kaer, L., Veebeek, S. 1989. Diversity, development, ligands, and probable functions of $\gamma\delta$ T cells. *Cold Spring Harbor Symp. Quant. Biol.* LIV: 31–44
118. Strominger, J. L. 1989. The $\gamma\delta$ T cell receptor and class Ib MHC- related proteins: Enigmatic molecules of immune recognition. *Cell* 57: 895–96
119. van Kaer, L., Wu, M., Ichikawa, Y., Ito, K., Bonneville, M., Ostrand-Rosenberg, S., Murphy, D. B., Tonegawa, S. 1991. Recognition of MHC TL gene products by $\gamma\delta$ T cells. *Immunol. Rev.* 120: 89–115
120. Imani, F., Soloski, M. J. 1991. Heat shock proteins can regulate expression of the Tla region-encoded class Ib molecule Qa–1. *Proc. Natl. Acad. Sci. USA* 88: 10475–79
121. Imani, F., Shinnick, T., Soloski, M. J. 1992. The interaction of peptides with the non-classical MHC molecule, Qa–1b. *J. Exp. Med.* In press
122. Vidovic, D., Roglic, M., McKune, K., Guerder, S., MacKay, C., Dembic, Z . 1989. Qa–1 restricted recognition of foreign antigen by a $\gamma\delta$ T-cell hybridoma. *Nature* 340: 646–50
123. Malissen, M., Damotte, M , Birnboum, D., Trucy, J., Jordan, E. R. 1982. HLA cosmid clones show complete, widely spaced human class I genes with occasional clusters. *Gene* 20: 485–93
124. Koller, B. H., Geraghty, D. E., DeMars, R., Duvick, L., Rich, S. S., Orr, H. T. 1989. Chromosomal organization of the human major histocompatibility complex class I gene family. *J. Exp. Med.* 169: 469–80
125. Shimizu, Y., Geraghty, D. E., Koller, B. H., Orr, H. T., DeMars, R. 1988. Transfer and expression of three cloned human non-HLA-A,B,C class I major histocompatibility complex genes in mutant lymphoblastoid cells. *Proc.*

Natl. Acad. Sci. USA 85: 227–31
126. Lam, V., DeMars, R., Chen, B. P., Hank, J. A., Kovats, S., Fisch, P., Sondel, P. M. 1990. Human T cell receptor γδ expressing T cell lines recognize MHC-controlled elements on autologous EBV-LCL that are HLA-A, -B, -C, -DR, -DQ, or -DP. *J. Immunol.* 145: 36–45
127. Spits, H., Paliard, X., de Vries, J. E. 1989. Antigen-specific, but not natural killer, activity of T cell receptor γδ cytotoxic T lymphocyte clones involves secretion of Na-benzyloxycarbonyl-L-lysine thiobenzyl ester serine esterase and influx of Ca^{2+} ions. *J. Immunol.* 143: 1506–11
128. Porcelli, S., Brenner, M. B., Greenstein, J. L., Balk, S. P., Terhorst, C., Bleicher, P. A. 1989. Recognition of cluster of differentiation 1 antigens by human $CD4^-CD8^-$ cytolytic T lymphocytes. *Nature* 341: 447–50
129. Faure, F., Jitsukawa, S., Miossec, C., Hercend, T. 1990. CD1c as a target recognition structure for human T lymphocytes: analysis with peripheral blood γ/δ cells. *Eur. J. Immunol.* 20: 703–6
130. Calabi, F., Milstein, C. 1986. A novel family of human major hystocompatibility complex–related genes not mapping to chromosome 6. *Nature* 323: 540–43
131. Mami-Chouaib, F., Miossec, C., Del Porto, P., Flament, C., Triebel, F., Hercend, T. 1990. T cell target 1 (TCT. 1): a novel target molecule for human non-major histocompatibility complex–restricted T lymphocytes. *J. Exp. Med.* 172: 1071–82
132. Del Porto, P., Mami-Chouaib, F., Bruneau, J. M., Jitsukawa, S., Dumas, J., Harnois, M., Hercend, T. 1991. TCT.1, a target molecule for γ/δ T cells is encoded by an immunoglobulin superfamily gene (Blast–1) located in the CD1 region of human chromosome 1. *J. Exp. Med.* 173: 1339–44
133. Mami-Chouaib, F., Del Porto, P., Delorme, D., Hercend, T. 1991. Further evidence for a γ/δ T cell receptor-mediated TCT. 1/CD48 recognition. *J. Immunol.* 1147: 2864–67
134. Haregewoin, A., Soman, G., Hom, R. C., Finberg, R. W. 1989. Human $γδ^+$ T cells respond to mycobacterial heat-shock protein. *Nature* 340: 309–12
135. Modlin, R. L., Pirmez, C., Hofman, F. M., Torigian, V., Uyemura, K., Rea, T. H., Bloom, B. R., Brenner, M. B. 1989. Lymphocytes bearing antigen-specific γδ T cell receptors accumulate in human infectious disease lesions. *Nature* 338: 544–48
136. Holoshitz, J., Koning, F., Coligan, J. E., De Bruyn, J., Strober, S. 1989. Isolation of $CD4^-CD8^-$ mycobacteria-reactive T lymphocyte clones from rheumatoid arthritis synovial fluid. *Nature* 339: 226–29
137. Kabelitz, D., Bender, A., Schondelmaier, S., Schoel, B., Kaufmann, S. H. E. 1990. A large fraction of human peripheral blood γδ T cells is activated by *Mycobacterium tuberculosis* but not by its 65-kD heat shock protein. *J. Exp. Med.* 171: 667–79
138. Pfeffer, K., Schoel, B., Gulle, H., Kaufmann, S. H. E., Wagner, H. 1990. Primary responses of human T cells to mycobacteria: a frequent set of γ/δ T cells are stimulated by protease-resistant ligands. *Eur. J. Immunol.* 20: 1175–79
139. Pfeffer, K., Schoel, B., Plesnila, N., Lipford, G. B., Kromer, S., Deusch, K., Wagner, H. 1992. A lectin-binding, protease-resistant mycobacterial ligand specifically activates $Vg9^+$ human γδ T cells. *J. Immunol.* 148: 575–83
140. Havlir, D. V., Ellner, J. J., Chervenak, K. A., Boom, W. H. 1991. Selective expansion of human γδ T cells by monocytes infected with live *Mycobacterium tuberculosis*. *J. Clin. Invest.* 87: 729–33
141. Kabelitz, D., Bender, A., Prospero, T., Wesselborg, S., Janssen, O., Pechhold, K. 1991. The primary response of human γδ T cells to *Mycobacterium tuberculosis* is restricted to Vγ9-bearing cells. *J. Exp. Med.* 173: 1331–38
142. Panchamoorthy, G., McLean, J., Modlin, R. L., Morita, C. T., Ishikawa, S., Brenner, M. B., Band, H. 1991. A predominance of the T cell receptor Vγ2/Vδ2 subset in human mycobacteria-responsive T cells suggests germline gene encoded recognition. *J. Immunol.* 147: 3360–69
143. Ohmen, J. D., Barnes, P. F., Uyemura, K., Lu, S., Grisso, C. L. Modlin, R. L. 1991. The T cell receptors of human γδ T cells reactive to *Mycobacterium tuberculosis* are encoded by specific V genes but diverse V-J junctions. *J. Immunol.* 147: 3353–59
144. De Libero, G., Casorati, G., Giachino, C., Carbonara, C., Migone, N., Matzinger, P., Lanzavecchia, A. 1991. Selection by two powerful antigens may account for the presence of the major population of human peripheral γ/δ T cells. *J. Exp. Med.* 173: 1311–22

145. Janis, E. M., Kaufmann, S. H. E., Schwartz, R. H., Pardoll, D. M. 1989. Activation of γδ T cells in the primary immune response to *Mycobacterium tuberculosis*. *Science* 244: 713–16
146. O'Brien, R. L., Fu, Y-X., Cranfill, R., Dallas, A., Ellis, C., Reardon, C., Lang, J., Carding, S. R., Kubo, R., Born, W. 1992. Heat shock protein Hsp60-reactive γδ cells: A large, diversified T-lymphocyte subset with highly focused specificity. *Proc. Natl. Acad. Sci. USA* 89: 4348–52
147. Born, W., Hall, L., Dallas, A., Boymel, J., Shinnick, T., Young, D., Brennan, P., O'Brien, R. 1990. Recognition of a peptide antigen by heat shock-reactive γδ T lymphocytes. *Science* 249: 67–69
148. Roberts, K., Yokoyama, W. M., Kehn, P. J., Shevach, E. M. 1991. The vitronectin receptor serves as an accessory molecule for the activation of a subset of γδ T cells. *J. Exp. Med.* 173: 231–40
149. Wilde, D. B., Roberts, K., Sturmhofel, K., Kikuchi, G., Coligan, J. E., Shevach, E. M. 1992. Mouse autoreactive γδ T cells I. Functional properties of autoreactive T cell hybridomas. *Eur. J. Immunol.* 22: 483–89
150. Happ, M. P., Kubo, R. T., Palmer, E., Born, W. K., O'Brien, R. L. 1989. Limited receptor repertoire in a mycobacteria-reactive subset of γδ T lymphocytes. *Nature* 342: 696–98
151. Ezquerra, A., Wilde, D. B., McConnell, T. J., Sturmhofel, K., Valas, R. B., Shevach, E. M., Coligan, J. E. 1992. Mouse autoreactive γδ T cells II. Molecular characterization of the T cell receptor. *Eur. J. Immunol.* 22: 491–98
152. van Eden, W., Thole, J. E. R., van der Zee, R., Noordzij, A., van Embden, J. D. A., Hensen, E. J., Cohen, I. R. 1988. Cloning of the mycobacterial epitope recognized by T lymphocytes in adjuvant arthritis. *Nature* 331: 171–73
153. Fleischer, B., Gerardy-Schahn, R., Metzroth, B., Carrel, S., Gerlach, D., Kohler, W. 1991. An evolutionary conserved mechanism of T cell activation by microbial toxins. Evidence for different affinities of T cell receptor-toxin interactions. *J. Immunol.* 146: 11–17
154. Abe, J., Forrester, J., Nakahara, T., Lafferty, J. A., Kotzing, B. L., Leung, D. Y. M. 1991. Selective stimulation of human T cells with streptococcal erythrogenic toxins A and B. *J. Immunol.* 146: 3747–50
155. Rust, C. J. J., Verreck, F., Vietor, H., Koning, F. 1990. Specific recognition of staphylococcal enterotoxin A by human T cells bearing receptors with the Vγ9 region. *Nature* 346: 572–74
156. Inghirami, G., Zhu, B. Y., Chess, L., Knoles, D. M. 1990. Flow cytometric and immunohistochemical characterization of the γ/δ T-lymphocyte population in normal human lymphoid tissue and peripheral blood. *Am. J. Pathol.* 136: 357–67
157. Kabelitz, D., Conradt, P., Schondelmaier, S., Wagner, H., Haars, R. 1989. A novel subset of $CD2^-$, $CD3^+$/T cell receptor α/β^+ human peripheral blood T cells. Phenotypic and functional characterization of interleukin 2-dependent $CD2^-$, $CD3^+$ T cell clones. *J. Exp. Med.* 170: 559–70
158. Faure, F., Jitsukawa, S., Meuer, S., Bohuon, C., Triebel, F., Hercend, T. 1989. Identification of a $CD2^-$ $CD3^+$ T cell receptor-γ peripheral blood. *J. Immunol.* 140: 2128–32
159. Poggi, A., Bottino, C., Zocchi, M. R., Pantaleo, G., Ciccone, E., Mingari, C., Moretta, L., Moretta, A. 1987. $CD3^-$ $WT31^-$ peripheral T lymphocytes lack T44 (CD28), a surface molecule involved in activation of T cells bearing the alpha/beta heterodimer. *Eur. J. Immunol.* 17: 1065–68
160. Testi, R., Lanier, L. L. 1989. Functional expression of CD28 on T cell antigen receptor γ/δ-bearing T lymphocytes. *Eur. J. Immunol.* 19: 185–88
161. Cron, R. Q., Gajewski, T. F., Sharrow, S. O., Fitch, F. W., Matis, L. A., Bluestone, J. A. 1989. Phenotype and functional analysis of murine $CD3^+$, $CD4^-$, $CD8^-$ TCR-γδ-expressing peripheral T cells. *J. Immunol.* 142: 3754–62
162. Lefrancois, L. 1991. Phenotypic complexity of intraepithelial lymphocytes of the small intestine. *J. Immunol.* 147: 1746–51
163. Mackay, C. R., Beya, M-F., Matzinger, P. 1989. γ/δ T cells express a unique surface molecule appearing late during thymic development. *Eur. J. Immunol.* 19: 1477–83
164. Wijngaard, P. L. J., MacHugh, N. D., Metzelaar, M. J., Morrisons, W. I., Davis, B. C., Clevers, H. C. 1992. A novel family of genes expressed exclusively on subsets of bovine $CD4^-CD8^-$ γδ T cells. Submitted
165. Porcelli, S., Brenner, B., Band, H. 1991. Biology of the human γδ T cell receptor. *Immunol. Rev.* 120: 137–83
166. Patel, S.S., Wacholtz, M. C., Duby, A. D., Thiele, D. L., Lipsky, P. E. 1989. Analysis of the functional capabilities of $CD3+CD4^-CD8^-$ and

CD3+CD4+CD8+ human T cell clones. *J. Immunol.* 143: 1108–17
167. Morita, C. T., Verma, S., Aparicio, P., Martinez-A., C., Spits, H., Brenner, M. B. 1991. Functionally distinct subsets of human γδ T cells. *Eur. J. Immunol.* 21: 2999–3007
168. Spits, H., Paliard, X, Vandekerckhove, Y., van Vlasselaer, P., de Vries, J. E. 1991. Functional and phenotypic differences between CD4+ and DC4− T cell receptor-γδ clones from peripheral blood. *J. Immunol.*147: 1180–88
169. Spits, H., Paliard, N., Engelhard, V. H., de Vries, J. E. 1990. Cytotoxic activity and lymphokine production of T cell receptor (TCR)-αβ+ and TCR-γδ+ cytotoxic T lymphocyte (CTL) clones recognizing HLA-A2 and HLA-A2 mutants. Recognition of TCR-γδ+ CTL clones is affected by mutations at positions 152 and 156. *J. Immunol.* 144: 4156–62
170. Raziuddin, S., Shetty, S., Ibrahim, A. 1992. Phenotype, activation and lymphokine secretion by γδ T lymphocytes from schistosomiasis and carcinoma of the urinary bladder. *Eur. J. Immunol.* 22: 309–31
171. Mingari, M. C., Ferrini, S., Pende, D., Bottino, C., Prigione, I., Moretta, A., Moretta, L. 1987. Phenotypic and functional analysis of human CD3+ and CD3− clones with "lymphokine activated killer" (LAK) activity. Frequent occurrence of CD3+ LAK clones which produce interleukin–2. *Int. J. Cancer* 40: 495–508
172. Ferrini, S., Bottino, C., Biassoni, Poggi, A., Sekaly, R. P., Moretta, L., Moretta, A. 1987. Characterization of CD3+ CD4− CD8− clones expressing the putative T cell receptor gamma-gene product. Analysis of the activation pathways leading to IL–2 production and triggering of the lytic machinery. *J. Exp. Med.* 166: 277–96
173. Carrel, S., Salvi, S., Rafti, F., Favrot, M., Rapin, C., Sekaly, R. P. 1991. Direct involvement of CD7 (gp40) in activation of TcRγ/δ+ T cells. *Eur. J. Immunol.* 21: 1195–200
174. Hiromatsu, K., Yoshikai, Y., Matsuzaki, G., Ohga, S., Muramori, K., Matsumoto, K., Bluestone, J. A., Nomoto, K. 1992. A protective role of γδ T cells in primary infection with *Listeria monocytogenes* in mice. *J. Exp. Med.* 175: 49–56
175. Eichelberger, M., Allan, W., Carding, S. R., Bottomly, K., Doherty, P. C. 1991. Activation status of the CD4−8− γδ-T cells recovered from mice with influenza pneumonia. *J. Immunol.* 147: 2069–74
176. Taguchi, T., Aicher, W. K., Fujihashi, K., Yamamoto, M., McGhee, J. R., Bluestone, J. A., Kiyono, H. 1991. Novel function for intestinal intraepithelial lymphocytes murine CD3+, γ/δ TCR+ T cells produce IFN-γ and IL–5. *J. Immunol.* 147: 3736–44
177. Borst, J., van de Griend, R. J., van Oostveen, J. W., Ang, S.-L., Melief, C. J., Seidman, J. G., Bolhuis, R. L. H. 1987. A T-cell receptor γ/CD3 complex found on cloned functional lymphocytes. *Nature* 325: 683–88
178. Brenner, M. B., McLean, J., Scheft, H., Riberdy, J., Ang, S.-L., Seidman, J. G., Devlin, P., Krangel, M. S. 1987. Two forms of the T-cell receptor γ protein found on peripheral blood cytotoxic T lymphocytes. *Nature* 325: 689–94
179. Lanier, L. L., Ruitenberg, J. J., Phillips, J. H. 1986. Human CD3+ T lymphocytes that express neither CD4 nor CD8 antigens. *J. Exp. Med.* 164: 339–44
180. Nakata, M., Smyth, M. J., Norihisa, Y., Kawasaki, A., Shinkai, Y., Okumura, K., Yagita, H. 1990. Constitutive expression of pore-forming protein in peripheral blood γ/δ T cells: Implication for their cytotoxic role in vivo. *J. Exp. Med.* 172: 1877–80
181. Koizumi, H., Liu, C., Zheng, L. M., Joag, S. V., Bayne, N. K., Holoshitz, J., Young, J. D. E. 1991. Expression of perforin and serine esterases by human γ/δ T cells. *J. Exp. Med.* 173: 499–502
182. Guy-Grand, D., Malassis-Seris, M., Briottet, C., Vassalli, P. 1991. Cytotoxic differentiation of mouse gut thymodependent and independent intraepithelial T lymphocytes is induced locally. Correlation between functional assays, presence of perforin and granzyme transcripts and cytoplasmic granules. *J. Exp. Med.* 173: 1549–52
183. Goodman, T., Lefrancois, L. 1988. Expression of the γ-δ T-cell receptor on intestinal CD8+ intraepithelial lymphocytes. *Nature* 333: 855–57
184. Viney, J. L., Kilshaw, P. J., MacDonald, T. T. 1990. Cytotoxic α/β+ and γ/δ+ T cells in murine intestinal epithelium. *Eur. J. Immunol.* 20: 1623–26
185. Kuziel, W. A., Lewis, J., Nixon-Fulton, J., Tigelaar, R. E. Tucker, P. W. 1991. Murine epidermal γδ T cells express Fcg receptor II encoded by the FcgRa gene. *Eur. J. Immunol.* 21: 1563–66
186. van de Griend, R. J., Tax, W. J. M., van Krimpen, B. A., Vreudgenhil, R.

J., Ronteltap, C. P. M., Bolhuis, R. L. H. 1987. Lysis of tumor cells by $CD3^+4^-8^-16^+$ T cell receptor $\alpha\beta^-$ clones, regulated via CD3 and CD16 activation sites, recombinant interleukin 2, and interferon β. *J. Immunol.* 138: 1627–33

186a. Van Neerven, J., Coligan, J. E., Koning, F. 1990. Structural comparison of α/β and γ/δ T cell receptor-CD3 complexes reveals identical subunit interactions but distinct cross-linking patterns of T cell receptor chains. *Eur. J. Immunol.* 20: 2105–11

187. Pantaleo, G., Ferrini, S., Zocchi, M. R., Bottino, C., Biassoni, R., Moretta, L., Moretta, A. 1987. Analysis of signal transduction mechanisms in $CD3^+$ $CD4^+CD8^+$ cells expressing the putative T cell receptor γ gene product. *J. Immunol.* 139: 3580–84

188. Moretta, A., Bottino, C., Ciccone, E., Tambussi, G., Mingari, M. C., Ferrini, S., Casorati, G., Varese, P., Viale, O., Migone, N., Moretta, L. 1988. Human peripheral blood lymphocytes bearing T cell receptor gamma/delta. Expression of CD8 differentiation antigen correlates with the expression of the 55 kD, Cγ2-encoded, γ-chain. *J. Exp. Med.* 168: 2349–54

189. Moretta, A., Ciccone, E., Pantaleo, G., Tambussi, G., Bottino, C., Melioli, G., Mingari, M. C., Moretta, L. 1989. Surface molecules involved in the activation and regulation of T or natural killer lymphocytes in humans. *Immunol. Rev.* 111: 145–75

190. Kabelitz, D., Conradt, P. 1988. Identification of $CD2^+/CD3^+$ T-cells in fetal human tissue. *J. Exp. Med.* 168: 1941–46

191. Aparicio, P., Alonoso, J. M., Toribio, M. L., Marcos, M. A. R., Pezzi, L., Martinez-A., C. 1989. Isolation and characterization of ($\gamma\delta$) $CD4^+$ T cell clones derived from human fetal liver cells. *J. Exp. Med.* 170: 1009–14

192. Parrott, D. W. V., Tait, R. C., MacKenzie, S. 1983. *Ann. N. Y. Acad. Sci.* 409: 307–20

193. Carbone, A., Harbeck, R., Dallas, A., Nemazee, D., Finkel, T., O'Brien, R., Kubo, R., Born, W. 1991. Alpha beta T-lymphocyte depleted mice, a model for $\gamma\delta$ T-lymphocyte functional studies. *Immunol. Rev.* 120: 35–50

194. Hunig, T., Tiefenthaler, G., Lawetzky, A., Kubo, R., Schlipkoter, E. 1989. T-cell subpopulations expressing distinct forms of the TCR in normal, athymic, and neonatally TCR ab-suppressed rats. *Cold Spring Harbor Symp. Quant. Biol.* 54: 61–68

195. Mombaerts, P., Clarke, A. R., Rudnicki, M. A., Iacomini, J., Shigeyoshi, I., Lafaille, J. J., Wang, L., Ishikawa, Y., Jaenisch, R., Hooper, M. L., Tonegawa, S. 1992. Mutations in T-cell receptor genes α and β block thymocyte development at different stages. *Nature* 360: 225–31

196. Philpott, K. L., Viney, J. L., Kay, G., Rastan, S., Gardiner, E. M., Chae, S., Hayday, A. C., Owen, M. J. 1992. Lymphoid development in mice congenitally lacking T cell receptor $\alpha\beta$-expressing cells. *Science* 256: 1448–52

197. Sperling, A. I., Wortis, H. H. 1989. $CD4^+$, $CD8^+$ γ/δ cells from normal mice respond to a syngeneic B cell lymphoma and can induce its differentiation. *Int. Immunol.* 1: 434–42

198. Rajagopalin, S., Zordan, T., Tsokos, G. C., Datta, S. K. 1990. Pathogenic anti-DNA autoantibody-inducing T helper cell lines from patients with active lupus nephritis: Isolation of $CD4^+CD8^+$ T helper cell lines that express the $\gamma\delta$ T cell antigen receptor. *Proc. Natl. Acad. Sci. USA* 87: 7020–24

199. Vaessen, L. M. B., Ouwehand, A. J., Baan, C. C., Jutte, N. H. P. M., Balk, A. H. M. M., Claas, F. H. J., Weimar, W. 1991. Phenotypic and functional analysis of T cell receptor $\gamma\delta$-bearing cells isolated from human heart allografts. *J. Immunol.* 147: 846–50

200. Vilmer, E., Guglieimi, P., David, V., Leca, G., Rabian, C., Degos, L., Boiron, M., Bensussan, A. 1988. Predominant expression of circulating $CD3^+$ lymphocytes bearing gamma T cell receptor in a prolonged immunodeficiency after allogeneic bone marrow transplantation. *J. Clin. Invest.* 82: 755–61

201. Vilmer, E., Triebel, F., David, V., Rabian, C., Schumpp, M., Leca, G., Degos, L., Hercend, T., Sigaux, F., Bensussan, A. 1988. Prominent expansion of circulating lymphocytes bearing γ T-cell receptors, with preferential expression of variable a genes after allogeneic bone marrow transplantation. *Blood* 72: 841–49

202. van der Harst, D., Brand, A., van Luxemburg-Heijs, S. A. P., Kooij-Winkelaar, Y. M. C., Zwaan, F. E., Koning, F. 1991. Selective outgrowth of $CD45RO^+$ $V\gamma9^+/V\delta2^+$ T-cell receptor γ/δ T cells early after bone marrow transplantation. *Blood* 78: 1875–81

203. Bacchetta, R., Vandekerckhove, B. A. E., Touraine, J. L., Bigler, M.,

Martino, S., de Vries, J. E., Spits, H., Roncarolo, M. G. 1992. Chimerism and tolerance to host and donor in severe combined immunodeficiencies transplanted with fetal liver stem cells. *J. Clin. Invest.* Submitted

204. Small, T. N., Keever, C. Al., O'Reilly, R. J., Flamenberg, N. 1983. Presence of circulating $CD3^+$ T cells expressing the gamma-delta T cell receptor following HLA-mismatched T-cell depleted BMT for severe combined immunodeficiency. *Blood* 72(Suppl 1): 408a
205. Carding, S. R., Allan, W., Kyes, S., Hayday, A., Bottomly, K., Doherty, P. C. 1990. Late dominance of the inflammatory process in murine influenza by $\gamma\delta^+$ T cells. *J. Exp. Med.* 172: 1225–31
206. Ohga, S., Yoshikai, Y., Takeda, Y., Hiromatsu, K., Nomoto, K. 1990. Sequential appearance of $\gamma\delta-$ and $\alpha\beta$-bearing T cells in the peritoneal cavity during an i.p. infection with Listeria monocytogenes. *Eur. J. Immunol.* 20: 533–38
207. Sandor, M., Houlden, B., Bluestone, J., Hedrick, S. M., Weinstock, J., Lynch, R. G. 1992. In vitro and in vivo activation of murine $\gamma\delta$ T cells induces the expression of IgA, IgM, and IgG Fc receptors. *J. Immunol.* 148: 2363–69
208. Falini, B., Flenghi, L., Pileri, S., Pelicci, P., Fagioli, M., Martelli, M. F., Moretta, L., Ciccone, E. 1989. Distribution of T cells bearing different forms of the T cell receptor γ/δ in normal and pathological human tissues. *J. Immunol.* 143: 2480–88
209. Minoprio, P., Itohara, S., Heusser, C., Tonegawa, S., Coutinho, A. 1989. Immunobiology of murine *T. cruzi* infection: The predominance of parasite-nonspecific responses and the activation of TCR1 T cells. *Immunol. Rev.* 112: 183–207
210. Roussilhon, C., Agrapart, M., Ballet, J-J., Bensussan, A. 1990. T lymphocytes bearing the $\gamma\delta$ T cell receptor in patients with acute *Plasmodium falciparum* malaria. *J. Infect. Dis.* 162: 283–85
211. Ho, M., Webster, K., Tongtawe, P., Pattanapanyasat, K., Weidanz, W. P. 1990. Increased $\gamma\delta$ T-cells in acute *Plasmodium falciparum* malaria. *Immunol. Lett.* 25: 139–45
212. De Paoli, P., Gennari, D., Martelli, P., Cavazerani, V., Comoretto, R., Santini, G. 1990. $\gamma\delta$ T-cell receptor–bearing lymphocytes during Epstein-Barr Virus infection. *J. Infect. Dis.* 161: 1013–16
213. Hacker, G., Kromer, S., Falk, M., Heeg, K., Wagner, H., Pfeffer, K. 1992. The Vδ1 positive subset of human $\gamma\delta$ T cells responds to ligands expressed by Epstein-Barr virus infected Burkitt lymphoma cells and transformed B-lymphocytes. *Eur. J. Immunol.* In press
214. Autran, B., Triebel, F., Katlama, C., Rozenbaum, W., Hercend, T., Debre, P. 1989. T-cell receptor $\gamma\delta^+$ lymphocyte subsets during HIV infection. *Clin. Exp. Immunol.* 75: 206–10
215. De Paoli, P., Gennari, D., Martelli, P., Basaglia, G., Grovatto, M., Battistin, S. 1991. A subset of lymphocytes is increased during HIV–1 infection. *Clin. Exp. Immunol.* 83: 187–91
216. Kabelitz, D., Pechold, K., Bender, A., Wesselborg, S., Wesch, D., Friese, K., Janssen, O. 1991. Activation and activation-driven death of human $\gamma\delta$ T cells. *Immunol. Rev.* 120: 71–88 *Clin. Exp. Immunol.* 83: 187
217. Ang, S-L., Seidman, J. G., Peterman, G. M., Duby, A. D., Benjamin, D., Lee, S. J., Hafler, D. A. 1987. Functional γ chain-associated T cell receptors on cerebrospinal fluid-derived natural killer-like T cell clones. *J. Exp. Med.* 165: 1453–58
218. Johnson, R. M., Lancki, D. W., Sperling, A. I., Dick, R. F., Spear, P. G., Fitch, Bluestone, J. A. 1992. A murine CD4-, CD8- T cell receptor-$\gamma\delta$ lymphocyte clone specific for herpes simplex virus glycoprotein. *J. Immunol.* 148: 983–88
219. Wright, A., Lee, J. E., Link, M. P., Smith, S. D., Carroll, W., Levy, R., Clayberger, C., Krensky, A. M. 1989. Cytotoxic T lymphocytes specific for self tumor immunoglobulin express T-cell receptor δ chain. *J. Exp. Med.* 169: 1557–64
220. Sturm, E., Braakman, E., Fisch, P., Vreudgenhil, R. J., Sondel, P., Bolhuis, R. L. H. Human Vγ9-Vδ2 T cell receptor-$\gamma\delta$ lymphocytes show specificity to Daudi Burkitt's lymphoma cells. *J. Immunol.*145: 3202–8
221. Fisch, P., Malkovsky, M., Braakman, E., Sturm, E., Bolhuis, R. L. H., Prieve, A., Sosman, J. A., Lam, V. A., Sondel, P. M. 1990. γ/δ T cell clones and natural killer cell clones mediate distinct patterns of non-major histocompatibility complex-restricted cytolysis. *J. Exp. Med.* 171: 1567–79
222. Fisch, P., Malkovsky, M., Kovats, S., Sturm, E., Braakman, E., Klein, B. S., Voss, S. D., Morrissey, L. W., DeMars, W., Welch, W. J., Bolhuis, R. L. H.,

Sondal, P. M. 1990. Recognition by human $V\gamma9^+/V\delta2^+$ T-cells of a GroEL homolog on Daudi Burkitt's lymphoma cells. *Science* 250: 1269–73
223. Fisch, P., Oettel, K., Fudim, N., Surfus, J. E., Malkovsky, M., Sondel, P. M. 1992. MHC-unrestricted cytotoxic and proliferative responses of two distinct human $\gamma\delta$ T cell subsets to Daudi cells. *J. Immunol.* 148: 2315–23
224. Bensussan, A., Lagabrielle, J., Degos, L. 1989. TCR $\gamma\delta$ bearing lymphocyte clones with lymphokine-activated killer activity against autologous leukemic cells. *Blood* 73: 2077–80
225. Nanno, M., Seki, H., Mathioudakis, G., Suzuki, R., Itoh, K., Ioannides, C. G., Suzuki, S., Chen, P., Platsoucas, C. D. 1992. γ/δ T cell antigen receptors expressed on tumor-infiltrating lymphocytes from patients with solid tumors. *Eur. J. Immunol.* 22: 679–87
226. Alaibac, M. 1992. $\gamma\delta$ T-lymphocytes: Relevance of the current studies to dermatology. *Int. J. Dermatol.* 31: 157–59
227. Zocchi, M. R., Ferrarini, M., Rugarli, C. 1990. Selective lysis of the autologous tumor by $\delta TCS1^+$ γ/δ^+ tumor-infiltrating lymphocytes from human lung carcinomas. *Eur. J. Immunol.* 20: 2685–89
228. De Maria, A., Malnati, M., Moretta, A., Pende, D., Bottino, C., Casorati, G., Cottafava, F., Meliolo, G., Mingari, M. C., Migone, N., Romagnani, S., Moretta, L. 1987. $CD3^+4^-8^-$ $WT31^-$ (T-cell receptor γ^+) cells and other unusual phenotypes are frequently detected among spontaneously interleukin 2-responsive T lymphocytes present in the joint fluid in juvenile rheumatoid arthritis. A clonal analysis. *Eur. J. Immunol.* 17: 1815–19
229. Brennan, F. M., Londei, M., Jackson, A. M., Hercend, T., Brenner, M. B., Maini, R. N., Feldmann, M. 1988. T-cell expressing $\gamma\delta$ chain receptors in rheumatoid arthritis. *J. Autoimmun.* 1: 319–26
230. Brennan, F., Plater-Zyvwek, X., Maini, R. N., Feldmann, M. 1989. Coordinate expansion of "fetal type" lymphocytes (TCR $\gamma\delta^+$ T and $CD5^+B$) in rheumatoid arthritis and primary Sjogren's syndrome. *Clin. Exp. Immunol.* 77: 175–78
231. Sioud, M., Kjeldsen-Kragh, J., Quayle, A., Kalvenes, C., Waalen, K., Forre, O., Natvig, J. B. 1990. The Vδ gene usage by freshly isolated T lymphocytes from synovial fluids in rheumatoid synovitis: a preliminary report. *Scand. J. Immunol.* 31: 415–21
232. Sioud, M., Forre, O., Natvig, J. B. 1991. T cell receptor δ diversity of fresh ly isolated T lymphocytes in rheumatoid synovitis. *Eur. J. Immunol.* 21: 239–41
233. Kjeldsen-Kragh, J., Quayle, A., Kalvenes, C., Forre, O., Sorskaar, D., Vinje, O., Thoen, J., Natvig. J. B. 1990. T$\gamma\delta$ cells in juvenile rheumatoid arthritis and rheumatoid arthritis. *Scand. J. Immunol.* .32: 651–60
234. Smith, M. D., Broker, B., Moretta, L., Ciccone, E., Grossi, C. E., Edwards, J. C. W., Yuksel, F., Colaco, B., Worman, C., Mackenzie, L., Kinne, R., Weseloh, G., Gluckert, K., Lydyard, P. M. 1990. T$\gamma\delta$ cells and their subsets in blood and synovial tissue from rheumatoid arthritis patients. *Scand. J. Immunol.* 32: 585–93
235. Pope, R. M., Landay, A., Modlin, R. L., Lessard, J., Koch, A. E. 1991. $\gamma\delta$ T cell receptor positive T cells in the inflammatory joint: Lack of association with response to soluble antigens. *Cell. Immunol.* 137: 127–38
236. Keystone, E. C., Rittershaus, C., Wood, N., Snow, K. M., Flatow, J., Purvis, J. C., Poplonski, L., Kung, P. C. 1991. Elevation of a $\gamma\delta$ T cell subset in peripheral blood and synovial fluid of patients with rheumatoid arthritis. *Clin. Exp. Immunol.* 84: 78–82
237. Bucht, A., Soderstrom, K., Hultman, T., Uhlen, M., Nilsson, E., Kiessling, R., Gronberg, A. 1992. T cell receptor diversity and activation markers in the Vδ1 subset of rheumatoid synovial fluid and peripheral blood T lymphocytes. *Eur. J. Immunol.* 22: 567–74
238. Hvas, J., Oksenberg, J., Fernando, R., Steinman, L., Bernard, C. C. A. 1992. $\gamma\delta$ T cell receptor repertoire in brain lesions of patients with multiple sclerosis. Submitted
239. Spencer, J., Isaacson, P. G., Diss, T. C., MacDonald, T. T. 1989. Expression of disulfide-linked and non-disulfide-linked forms of the T cell receptor γ/δ heterodimer in human intestinal intraepithelial lymphocytes. *Eur. J. Immunol.* 19: 1335–39
240. Viney, J., MacDonald, T. T. 1990. Gamma/delta T cells in the gut epithelium. *Gut* 31: 841–44
241. Trejdosiewicz, L. K., Calabrese, A., Smart, C. J., Oakes, J. J., Howdle, P. D., Crabtree, J. E., Losowsky, M. S., Lancaster, F., Boylston, A. W. 1991. $\gamma\delta$ T cell receptor-positive cells of the human gastrointestinal mucosa: occurrence and V region gene expression in *Heliobacter pylori*-associated gastritis,

coeliac disease and inflammatory bowel disease. *Clin. Exp. Immunol.* 84: 440–44

242. Rust, C., Kooy, Y., Pena, S., Mearins, M.-L., Kluin, P., Koning, F. 1992. Phenotypical and functional characterization of small intestinal TcRγδ$^+$ T cells in coeliac disease. *Scand. J. Immunol.* 35: 459–68
243. DeLibero, G., Rocci, M. P., Casorati, G., Giachino, C., Oderda, G., Tavassoli, K., Migone, N. 1992. T cell receptor heterogeneity in γδ T cell clones from intestinal biopsies of coeliac disease patients. *Eur. J. Immunol.* In press
244. Hara, T., Mizuno, Y., Nagata, M., Okabe, Y., Tanikguchi, S., Harada, M., Niho, Y., Pshimi, K., Ohga, S., Yoshikai, Y., Nomoto, K., Yumura, K., Kawa-Ha, K., Ueda, K. 1990. Human γδ T cell receptor-positive cell-mediated inhibition of erythropoiesis in vitro in a patient with type I autoimmune polyglandular syndrome and pure red blood cell aplasia. *Blood* 75: 941–50
245. de Paoli, P., Gennari, D., Basaglia, G., Martelli, P., Santini, G. 1990. Phenotypic analysis of CD2$^-$ CD3$^+$ T cell receptor gamma delta lymphocyte subset. *Immunol. Lett.* 23: 195–98
246. Balbi, B., Moller, D. R., Kirby, M., Holroyd, K. J., Crystal, R. G. 1990. Increased numbers of T lymphocytes with γδ-positive antigen receptors in a subgroup of individuals with pulmonary sarcoidosis. *J. Clin. Invest.* 85: 1353–61
247. Tamura, N., Holrolyd, J. J., Banks, T., Kirby, M., Okayama, H., Crystal, R. G. 1990. Diversity in junctional sequences associated with the common human Vγ9 and Vδ2 gene segments in normal blood and lung compared with the limited diversity in a granulomatous disease. *J. Exp. Med.* 172: 169–81
248. Seki, H., Nanno, M., Day, N. K., Good, R. A., Platsoucas, C. D. 1989. Disulfide-linked γδ T cell antigen receptors expressed on T cells derived from patients with primary immunodeficiency disorders. *J. Clin. Invest.* 84: 1679–82
249. Morio, T., Nagasawa, M., Nonoyama, S., Okawa, H., Yata, J-I. 1990. Phenotypic profile and functions of T cell receptor-γδ-bearing cells from patients with primary immunodeficiency syndrome. *J. Immunol.* 144: 1270–75
250. Bertotto, A., Scalise, F., Gerli, R., Castellucci, G., Fabietti, G. M., Spinozzi, F., Sensi, L., Vaccaro, R. 1992. Lymphocytes bearing the γ/δ T-cell receptors in Down's Syndrome. *Scan. J. Immunol.* 35: 275–78
251. Carbonari, M., Cherchi, M., Paganelli, R., Geannini, G., Galli, E., Gaetano, C., Papetti, C., Fiorilli, M. 1990. Relative increase of T cells expressing the gamma/delta rather than the alpha/beta receptor in ataxia-telangiectasia. *New Engl. J. Med.* 322: 73–76