MURINE T CELL RECEPTOR BETA CHAIN IS ENCODED ON CHROMOSOME 6

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Part of the controversy that for many years has complicated studies of the biochemistry and genetics of the T cell receptor for antigen has centered on persistent reports that the gene or genes encoding it are closely linked to the immunoglobulin heavy chain locus (IgH) on chromosome 12 of the mouse (1–4) or the major histocompatibility complex (MHC)[1] on chromosome 17 of the mouse (5, 6). The linkage to IgH is supported by data indicating that some antiidiotypic antisera can induce T cell specific responses (1–4) or, more recently, that serological determinants specific to different subsets of T cells map very closely to the IgH locus (7, 8). The genes for the latter surface markers have been referred to as "C_T" and postulated to encode receptor constant region determinants (7, 8). In addition, the linkage to IgH coincided with the prevailing view that T cell recognition was closely related to that of B cells and that the requirements for diversity are so similar that the formation of the T cell receptor must involve at least a portion of an Ig locus, in particular the large repertoire of variable region genes. Repeated attempts to detect receptor mRNAs using Ig probes have not been successful (9–13), however, suggesting that the T cell complex is encoded independently of the Ig genes. Evidence supporting the existence of an antigen-binding receptor on suppressor T cells has included the mapping of a determinant on the putative I-J molecule to the MHC locus of chromosome 17 (5, 6). However, recent studies (14–16) analyzing the I-J locus have virtually excluded the possibility that the MHC encodes a portion of a receptor molecule. Somatic cell genetic experiments using allele-specific chromosome markers have further appeared to rule out the involvement of any of the Ig- or MHC-bearing chromosomes; one study using Robertsonian fusions (17) argued against chromosomes 6, 16, and 17, which encode the kappa light chain locus (18, 19), lambda light chain (20), and the MHC locus (21), respectively, and another using restriction polymorphism mapping (22) argued against chromosome 12, which encodes the IgH locus (19, 23).

The development of monoclonal antibodies specific to clones of T cells which

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[1] *Abbreviations used in this paper:* C region, constant region; J region, joining region; MHC, major histocompatibility complex; V region, variable region.

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can block or stimulate T cell activation has made possible direct biochemical studies of the murine (24–26) and human (27) receptors. This work shows the receptor in both species to be a disulfide-linked heterodimer, with the α and β chains each being between 40 and 50 kD in size. Recently, Hedrick et al. (28, 29) isolated a T cell–specific murine cDNA clone from antigen-specific T helper hybridomas which exhibits variable (V), joining (J), and constant (C) region elements with substantial evolutionary homology to Ig (20–40% of the amino acid sequence). At the same time, Yanagi et al. (30) reported the isolation of a cDNA clone that appears to encode the human equivalent of this chain. The human cDNA clone and, by analogy, the mouse gene as well appear to correspond to the beta chain of the receptor molecule (31). The murine gene is almost invariably rearranged in T cell lines and hybridomas derived from helper and cytotoxic T cells, but not in most suppressor cell hybrids (28).[2] Antisera raised against a J region element effectively blocks IL-2 production by antigen-specific T helper hybrids.[3] DNA sequence analysis of the murine gene (32, 33) indicates that the organization of the gene segments and the pattern of rearrangement is very similar to that of Ig, even to the size of the V, D, and J region elements and to the presence of seven and nine nucleotide sequences thought to mediate rearrangement in Ig genes (as reviewed in 34).

Given the availability of probes for this gene, it becomes possible to directly determine to which chromosome this chain for the receptor maps and to resolve at least part of the controversy surrounding this molecule. The chromosome mapping presented here was accomplished using somatic cell hybrids formed from the fusion of mouse and Chinese hamster cells. Such hybrids have been widely used for mapping studies. By correlating lanes positive for hybridization with the presence of specific chromosomes, one can identify the chromosome on which a particular gene is located (for review, see 35).

Materials and Methods

Somatic cell hybrids were formed between E36 (a Chinese hamster cell line) and various primary mouse cells or mouse cell lines described before (18, 20, 36–38). These lines are listed in Table I. The murine chromosomes in each hybrid were ascertained by chromosome analysis and isoenzyme characterization. The DNA isolated from each hybrid was digested with *Hind*III restriction enzyme, electrophoresed on agarose, and transferred onto nitrocellulose by the method of Southern (as described in 39).

The T cell receptor gene probe used was 86T5, a 600 nucleotide murine cDNA fragment obtained from a thymocyte cDNA library and containing principally C region sequences (29). 86C3, a 700 nucleotide murine DNA fragment from a library formed from concanavalin A–stimulated spleen cells that contained both C and J regions (S. Hedrick, J. Kavaler, E. Nielson, and M. Davis, unpublished results), and T22.10, a 2.1 kilobase (kb) murine genomic DNA fragment containing only the germline 3′ C ($C_{T'}$) region (33), were also tested and gave equivalent results. The kappa gene probe was a 1.1 kb murine DNA fragment containing the kappa C region. DNA for this probe was the kind gift of R. Wall. After the DNA was nick translated with ^{32}P (as described in 39), the labeled probe was hybridized overnight to Southern blots at 42°C in a hybridization solution containing 50% formamide. The filters were then washed to a stringency of 0.2–

[2] Hedrick, S. M., R. N. Germain, M. J. Bevan, M. Dorf, P. Fink, N. R. J. Gascoigne, M. Green, J. Kapp, Y. Hoffman, F. Melchers, C. Pierce, C. Sorenson, M. Taniguchi, and M. M. Davis. Expression of the T cell receptor chain in lymphocyte subsets. Manuscript in preparation.

[3] Rothbard, J., S. Hedrick, L. Samelson, R. Schwartz, and M. M. Davis. Manuscript in preparation.

0.3× saline sodium citrate (SSC) (1× SSC is 150 mM NaCl, 15 mM sodium citrate) at 55°C and exposed at −70°C with a DuPont Cronex Lightning Plus intensifying screen (DuPont Co., Wilmington, DE).

Results

The autoradiograph showing the results of the hybridization of the T cell receptor gene probe to the DNA from the various somatic cell lines is presented in Fig. 1. Table I shows the chromosome composition of each cell line and the number of discordancies associated with each chromosome (i.e., the number of cell hybrids in which hybridization with the T cell receptor gene probe and a given mouse chromosome did not coincide). The mouse T cell receptor gene probe hybridized with *Hind*III-digested DNA fragments of 3.1 and 9.4 kb. These two bands were present only in cell lines containing an entire mouse chromosome 6 (Fig. 1, *a*, *c*, *m*, and *n*). The DNA in lane *o* came from CeC, a hybrid containing only one mouse chromosome, composed of the distal two-thirds of chromosome 6 translocated onto the X chromosome.[4] The break point in this translocation occurs at the B1/B2 junction or in band B2.[4] The lack of hybridization of the gene for the T cell receptor to this hybrid coupled with hybridization to lines containing a complete chromosome 6 is consistent with the localization of this

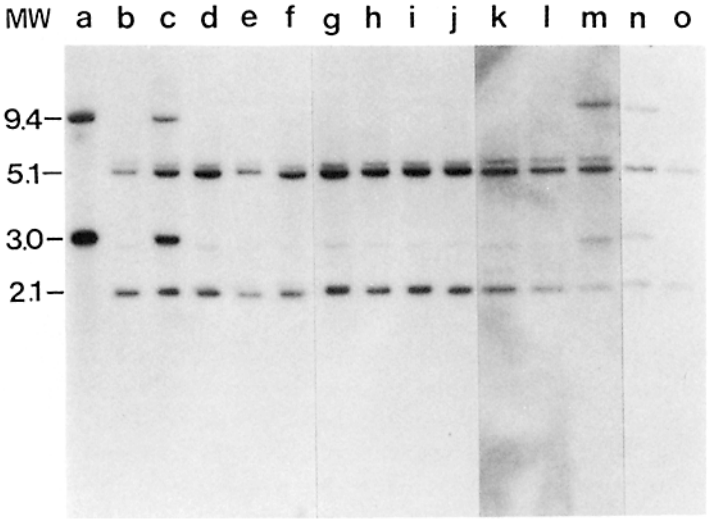

FIGURE 1. Autoradiographs showing hybridization of 86T5 or 86C3 to nitrocellulose filters binding *Hind*III-digested DNA from mouse hamster somatic cell hybrids and their parent cells. High molecular weight DNA (10 μg) from each cell line was digested to completion with *Hind*III restriction endonuclease, subjected to electrophoresis through 0.8–1.0% agarose, and transferred to nitrocellulose filters (39). Hybridization was performed using probes labeled with ^{32}P by nick translation (39). The probes (86T5 for *a–n* and 86C3 for *n–o*) consisted of the 5′ C region of one chain of the T cell receptor (29). 86T5, 86C3, and T22.10 gave equivalent results in *n–o*. The filters were washed to a stringency of at least 0.2× SSC, 55°C, and exposed with an intensifying screen. The DNA in *a* is a mouse parental control (Meth A). That in lane *b* is a hamster parental control (E36). The DNA in lanes *c–o* is taken from the hybrid cell lines listed in Table I. The molecular weights were determined using *Hind*III-digested lambda phage DNA.

[4] Pravtcheva, D., and F. Ruddle. Manuscript in preparation.

TABLE I

Segregation of the T Cell Receptor Gene With Mouse Chromosomes in Mouse-Hamster Hybrids

Chromosomes	BEM1-4 c	4A63 d	4B31Az3 e	2A2-C2 f	MAE-28 g	MAE-32 h	R44.1 i	ECm4e j	TuCE12G14 k	TuCE12G19 l	MFE 2/1/2 m	MFE 2/1/7 n	CeC o	Number discordant (n = 13)
	Hybridization to T cell receptor probe													
	+	−	−	−	−	−	−	−	−	−	+	+	−	
1	+	−	−	+	−	−	−	−	−	−	−	+	−	2
2	+	+	+	+	−	−	−	−	−	+	+	+	−	4
3	+	−	−	+	−	−	−	−	−	−	+	+	−	1
4	−	−	−	−	−	−	−	−	−	−	+	−	−	2
5	+	−	−	−	−	−	−	−	+	+	−	−	−	4
6	+	−	−	−	−	−	−	−	−*	−*	+	+	⅔‡	0
7	−	+	+	+	−	−	−	−	−	−	+	+	−	4
8	+	−	+	+	−	−	−	−	−	−§	+	+	−	2
9	−	−	−	+	−	−	−	−	−	−	+	+	−	2
10	−	−	−	+	−	−	−	−	+	+	+	−	−	5
11	−	−	−	−	−	−	−	−	−	−	−	−	−	3
12	+	+	−	+	+	−	−	−	+	+	+	+	−	5
13	+	+	−	+	−	−	−	−	+	+	+	+	−	4
14	+	−	−	−	−	−	−	+	+	+	+	−	−	4
15	+	+	−	+	−	−	−	+	+	+	+	+	−	5
16	+	+	+	+	−	+	−	−	+	+	−	−	−	8
17	+	+	+	+	−	−	+	−	+	+	+	+	−	6
18	+	+	−	−	−	−	−	−	+	−	+	−	−	3
19	+	+	+	+	−	−	−	−	+	+	+	+	−	5
X	+	−	−	+	+	+	−	−	+	+	+	+	+	6

Hybrid lines were scored as positive for a chromosome if that chromosome was present in ≥20% of the metaphase cells analyzed by trypsin Giemsa staining. The number of discordancies refers to cell lines positive for a given chromosome and negative for hybridization with the probe or negative for a chromosome and positive for hybridization.

* These two cell lines (of common origin) have no cytogenetic evidence of mouse chromosome 6 but are positive for triosephosphate isomerase, a terminal isoenzyme marker.

‡ This cell line contains one mouse chromosome composed of the distal (telomeric) two-thirds of chromosome 6 translocated onto the X chromosome.

§ This cell line contains no cytogenetic evidence of chromosome 8 and is negative for adenine phosphoribosyl transferase, but is positive for glutathione reductase.

chain of the T cell receptor to the proximal one-third of mouse chromosome 6 as indicated in Fig. 2.

The kappa light chain locus is also located on the proximal one-third of chromosome 6 (40). We therefore made a labeled kappa probe to confirm the presence of this region of chromosome 6 in these hybrids. The kappa gene probe hybridized with mouse DNA present in lanes *a*, *c* (data not shown), *m*, *n*, and *o*, as shown in Fig. 3. That the genes are probably not closely linked is indicated by the fact that the kappa gene probe hybridized to DNA from the hybrid containing the X:6 translocation whereas the T cell receptor probe does not. This conclusion is also supported by restriction fragment length polymorphism studies on recombinant inbred mice, which indicate that there is a considerable (>20 cM) distance between this gene and kappa.[5]

Considering the controversy over the mapping of the T cell receptor, it is particularly relevant to note that probes for this chain of the T cell receptor are negative for hybridization with lines containing only chromosomes 12 and X (line MAE-28) and only chromosome 17 (line R44.1). DNA from these hybrid lines was positive for hybridization to IgH and H-2 probes, respectively (data not shown).

[5] Epstein, R., M. Cohn, P. Marrack, M. Davis, and S. Hedrick. Manuscript in preparation.

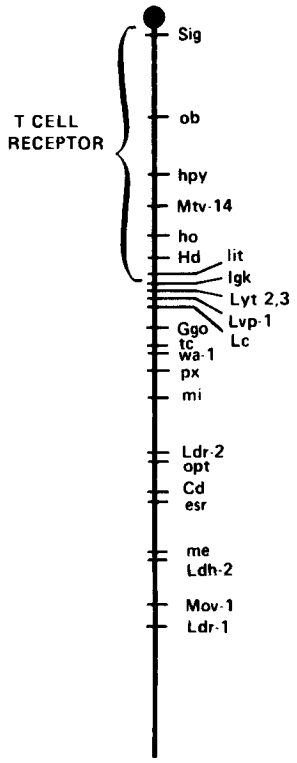

FIGURE 2. Autoradiograph showing hybridization of the kappa C region probe to *Hind*III-digested DNA from mouse-hamster somatic cell hybrids and their parental cell lines. The conditions of the Southern blotting and hybridization were as described in Fig. 1 and in the text.

Discussion

The murine T cell receptor C region gene probe 86T5 cross-hybridizes with several bands of Chinese hamster origin (Fig. 1). This, in combination with the fact that there is a strong cross-hybridization with rabbit and human DNA and an ~80% nucleic acid sequence homology between the corresponding murine and human T cell receptor genes (29, 30), indicates that this gene has been highly conserved in evolution.

The results localizing this gene for the T cell receptor to mouse chromosome 6 conflict with those of Marrack and Kappler (17). In their experiments, Robertsonian fusions between chromosomes 4 and 6 were used to make T cell hybridomas. One of these maintained antigen specificity yet had lost the marker chromosome; another lost both. This apparent contradiction between our data and that of Marrack and Kappler may be due to the inherent differences in sensitivity of the methods used, the frequency of genomic fragmentation and dispersion in the hybridomas, and the difficulty in karyotyping mouse chromosomes.

Gene families appear to arise from the duplication of genes that over time diverge to perform different functions and may disperse in the genome. The striking homologies between B cell and known T cell receptors in amino acid

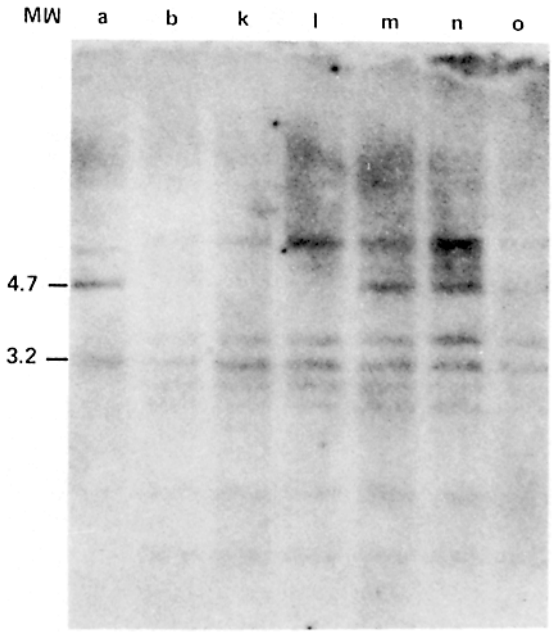

FIGURE 3. Linkage map of mouse chromosome 6 (46) indicating the region which apparently encodes this (β) chain of the T cell receptor.

sequence, function, gene organization, and mechanism of achieving diversity (29, 30, 32, 33) argue that these gene families arose from a common ancestor. The localization of the kappa light chain and the beta chain of the T cell receptor to the same chromosome may indicate that these two members of the Ig family had not yet dispersed in the genome. There may also be some selective value in both genes being in the same chromosomal region, perhaps because such a location may be important for the facilitation of rearrangement, protection of nonrearranging DNA from recombinases, or commitment of lymphoid cells to the T or B lineage. The human beta chain is not located on the same chromosome as any of the Ig genes (T. Mak, personal communication; M. Owen, personal communication). This may indicate that these selective factors are not absolute or, alternately, that location of the kappa light chain and the beta chain of the T cell receptor on the same chromosome of the mouse may be coincidental.

In a high proportion of B cell neoplasms, particularly (human) Burkitt's lymphoma and murine plasmacytomas, there are specific translocations between regions carrying the cellular oncogene *c-myc* (on mouse chromosome 15) and those carrying the Ig heavy chain genes (mouse chromosome 12) (41). Less frequently, translocations occur between the *c-myc* and those containing the Ig light chain genes (for review, see 42). The most frequent chromosomal aberrations, regardless of the mechanism of carcinogenesis, in murine T cell neoplasms are trisomy 15 and (much less frequently or specifically) trisomy 17 (42, 43). Thus, in contrast to what one might expect from analogy to B cell neoplasms, there does not appear to be a specific, cytogenetically detectable chromosome alteration associated with mouse chromosome 6 in T cell neoplasms. One

observation that may be relevant to this is that the T cell receptor gene examined here is transcribed at a level far less than that for the secreted Ig (0.01–0.2% of the mRNA for this chain of the T cell receptor (44) versus up to 10% for Ig [45]). Thus, the T cell receptor may not have as strong a promoter nor enhancer as Ig and so rearrangements associated with the T cell receptor may not be as important in carcinogenesis as those associated with the heavy chain locus. But, because the beta chain rearrangement of the T cell tumor, BW5147, seems preferentially retained in 30 different hybridomas,[2] it seems possible that some rearrangement associated with this gene and related to carcinogenogenesis may have occurred in at least some cases.

Summary

Southern blot analysis of somatic cell hybrid lines indicates that the beta chain of the T cell receptor for antigen maps to chromosome 6 of the mouse. An experiment testing hybridization of the constant region of this gene to DNA from a hybrid cell line containing a translocation of chromosome 6 supports the localization of this gene to the proximal (centromeric) one-third of chromosome 6, in the same general region as the immunoglobulin kappa chain locus. This may be another indication of the shared evolutionary origins of the genes encoding both T and B cell antigen recognition.

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References

1. Binz, H., H. Wigzell, and H. Bazin. 1976. T-cell idiotypes are linked to immunoglobulin heavy chain genes. *Nature (Lond.).* 264:639.
2. Rajewsky, K., and K. Eichmann. 1977. Antigen receptors of T helper cells. *Contemp. Top. Immunobiol.* 7:69.
3. Lifshitz, R., M. Schwartz, and E. Mozes. 1980. Linkage of murine (T,G)-A--L specific idiotypic determinants to the heavy chain constant region allotypic markers. *Immunogenetics* 11:191.
4. Sherman, L. A. 1982. Genetic linkage of the cytotoxic T lymphocyte repertoire and immunoglobulin heavy chain genes. *J. Exp. Med.* 156:294.
5. Kapp, J. A., B. A. Araneo, and B. L. Clevinger. 1980. Suppression of antibody and T cell proliferation responses to L-Glutamic acid^{60}-L-Alanine^{30}-L-Tyrosine^{10} by a specific monoclonal T cell factors. *J. Exp. Med.* 152:235.
6. Tada, T., K. Hayakawa, K. Okumura, and M. Taniguchi. 1980. Coexistence of variable region of immunoglobulin heavy chain and I region gene products on antigen-specific suppressor T cells and suppressor T cell factor: a minimal model of functional antigen receptor of T cells. *Mol. Immunol.* 17:867.
7. Owen, F. L., R. Riblet, and B. A. Taylor. 1981. The T suppressor cell alloantigen T_{su}^{d} maps near immunoglobulin allotype genes and may be a heavy chain constant-region maker on a T cell receptor. *J. Exp. Med.* 153:801.
8. Owen, F. L., and R. Riblet. 1984. Genes for the mouse T cell alloantigens T_{pre}, T_{thy}, T_{ind}, and T_{su} are closely linked near IgH on chromosome 12. *J. Exp. Med.* 159:313.
9. Kronenberg, M., M. M. Davis, P. W. Early, L. E. Hood, and J. D. Watson. 1980. Helper and killer T cells do not express B cell immunoglobulin joining and constant region gene segments. *J. Exp. Med.* 152:1745.
10. Kurosawa, Y., H. von Boehmer, W. Haas, H. Sakano, A. Trauneker, and S. Tone-

gawa. 1981. Identification of D segments of immunoglobulin heavy-chain genes and their rearrangement in T lymphocytes. *Nature (Lond.).* 290:565.

11. Nakanishi, K., K. Sugimura, Y. Yaoita, K. Maeda, S. I. Kashiwamura, T. Honjo, and T. Kishimoto. 1982. A T15-idiotype-positive T suppressor hybridoma does not use the T15 VH gene segment. *Proc. Natl. Acad. Sci. USA.* 79:6984.
12. Kraig, E., M. Kronenberg, J. A. Kapp, C. W. Pierce, A. F. Abruzzini, C. M. Sorensen, L. E. Samelson, R. H. Schwartz, and L. E. Hood. 1983. T and B cells that recognize the same antigen do not transcribe similar heavy chain variable region gene segments. *J. Exp. Med.* 158:192.
13. Kronenberg, M., E. Kraig, G. Siu, J. A. Kapp, J. Kappler, P. Marrack, C. W. Pierce, and L. Hood. 1983. Three T cell hybridomas do not contain detectable heavy chain variable gene transcripts. *J. Exp. Med.* 158:210.
14. Steinmetz, M., K. Minard, S. Horvath, J. McNicholas, J. Srelinger, C. Wake, E. Long, B. Mach, and L. Hood. 1980. A molecular map of the immune response region from the major histocompatibility complex of the mouse. *Nature (Lond.).* 300:35.
15. Kronenberg, M., M. Steinmetz, J. Kobori, E. Kraig, J. A. Kapp, C. W. Pierce, C. M. Sorensen, G. Suzuki, T. Tada, and L. Hood. 1983. RNA transcripts for the I-J polypeptides are apparently not encoded between the I-A and I-E subregions of the murine major histocompatibility complex. *Proc. Natl. Acad. Sci. USA.* 80:5704.
16. Kobori, J. A., A. Winoto, J. McNicholas, and L. Hood. 1984. Molecular characterization of the recombinant region of six murine major histocompatibility complex (MHC) I-region recombinants. *J. Mol. Cell. Immunol.* 1:125.
17. Marrack, P., and J. Kappler. 1983 Use of somatic cell genetics to study chromosomes contributing to antigen plus *I* recognition by T cell hybridomas. *J. Exp. Med.* 157:404.
18. Swan, D., P. D'Eustachio, L. Leinwand, J. Seidman, D. Keithley, and F. H. Ruddle. 1979. Chromosomal assignment of the mouse κ light chain genes. *Proc. Natl. Acad. Sci. USA.* 76:2735.
19. Hengartner, H., T. Meo, and E. Muller. 1978. Assignment of genes for immunoglobulin κ and heavy chains to chromosomes 6 and 12 in mouse. *Proc. Natl. Acad. Sci. USA.* 75:4494.
20. D'Eustachio, P., A. L. M. Bothwell, T. K. Takaro, D. Baltimore, and F. H. Ruddle. 1981. Chromosomal location of structural genes encoding murine immunoglobulin λ light chains. *J. Exp. Med.* 153:793.
21. Klein, J. 1975. Biology of the Mouse Histocompatibility-2 Complex: Principles of Immunogenetics Applied to a Single System. Springer-Verlag, New York.
22. Lonai, P., G. Reclavi, E. Arman, and D. Givol. 1983. Retention and loss of immunoglobulin heavy chain alleles in helper T cell hybridoma clones. *EMBO (Eur. Mol. Biol. Organ.) J.* 2:781.
23. D'Eustachio, P., D. Pravtcheva, K. Marcu, and F. H. Ruddle. 1980. Chromosomal location of the structural gene cluster encoding murine immunoglobulin heavy chains. *J. Exp. Med.* 151:1545.
24. Allison, J. P., R. W. McIntyre, and D. Block. 1982. Tumor-specific antigen of murine T lymphoma cells defined with monoclonal antibody. *J. Immunol.* 129:2293.
25. Haskins, K., R. Kubo, J. White, M. Pigeon, J. Kappler, and P. Marrack. 1983. The major histocompatibility complex-restricted antigen receptor on T cells. I. Isolation with a monoclonal antibody. *J. Exp. Med.* 157:1149.
26. Samelson, L. E., and R. H. Schwartz. 1983. The use of antisera and monoclonal antibodies to identify the antigen-specific T cell receptor from pigeon cytochrome-*c*-specific T cell hybrids. *Immunol. Rev.* 76:59.
27. Meuer, S. C., K. A. Fitzgerald, R. E. Hussey, J. C. Hodgdon, S. F. Schlossman, and

E. L. Reinherz. 1983. Clonotypic structures involved in antigen-specific human T cell function: relationship to the T3 molecular complex. *J. Exp. Med.* 157:705.

28. Hedrick, S. M., D. I. Cohen, E. A. Nielson, and M. M. Davis. 1984. Isolation of cDNA clones encoding T cell-specific membrane-associated proteins. *Nature (Lond.).* 308:149.
29. Hedrick, S. M., E. A. Nielson, J. Kavaler, D. I. Cohen, and M. M. Davis. 1984. Sequence relationships between putative T-cell receptor polypeptides and immunoglobulins. *Nature (Lond.).* 308:153.
30. Yanagi, Y., Y. Yoshikai, K. Leggett, S. P. Clark, I. Aleksander, and T. W. Mak. 1984. A human T cell-specific cDNA clone encodes a protein having extensive homology to immunoglobulin chains. *Nature (Lond.).* 308:145.
31. Acuto, O., M. Fabbi, J. Smart, C. B. Poole, J. Protentis, H. D. Royer, S. F. Schlossman, and E. L. Reinherz. 1984. Purification and NH_2-terminal amino acid sequencing of the β subunit of a human T-cell antigen receptor. *Proc. Natl. Acad. Sci. USA.* 81: 3851.
32. Chien, Y., N. R. J. Gascoigne, J. Kavaler, N. E. Lee, and M. M. Davis. 1984. Somatic recombination in a murine T cell receptor gene. *Nature (Lond.).* 309: 322.
33. Gascoigne, N. R. J., Y. Chien, D. M. Becker, J. Kavaler, and M. M. Davis. Genomic organization and sequence of T cell receptor β chain constant and joining region genes. *Nature (Lond.).* 310: in press.
34. Tonegawa, S. 1983. Somatic generation of antibody diversity. *Nature (Lond.).* 302:575.
35. D'Eustachio, P., and F. H. Ruddle. 1983. Somatic cell genetics and gene families. *Science (Wash. DC).* 220:919.
36. Pravtcheva, D. D., A. B. DeLeo, F. H. Ruddle, and L. J. Old. 1981. Chromosome assignment of the tumor-specific antigen of a 3-methylcholanthrene-induced mouse sarcoma. *J. Exp. Med.* 154:964.
37. Goff, S. P., P. D'Eustachio, F. H. Ruddle, and D. Baltimore. 1982. Chromosomal assignment of the endogenous proto-oncogene C-*abl*. *Science (Wash. DC).* 218:1317.
38. Ruddle, N. H., B. S. Conta, L. Leinwand, C. A. Kozak, F. Ruddle, P. Besmer, and D. Baltimore. 1978. Assignment of the receptor for ecotropic murine leukemia virus to mouse chromosome 5. *J. Exp. Med.* 148:451.
39. Maniatis, T., E. F. Fritsch, and J. Sambrook. *In* Molecular Cloning. 1982. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.
40. Gibson, D. M., S. J. Maclean, and M. Cherry. 1983. Recombination between kappa chain genetic markers and the *Lyt-3* locus. *Immunogenetics.* 18:111.
41. Shen-ong, G. L. C., E. J. Keath, S. P. Piccoli, and M. D. Cole. 1982. Novel *myc* oncogene RNA from abortive immunoglobulin-gene recombination in mouse plasmacytomas. *Cell.* 31:443.
42. Klein, G. 1981. The role of gene dosage and genetic transposition in carcinogenesis. *Nature (Lond.).* 294:313.
43. Wiener, F., S. Ohno, J. Spira, N. Haran-Ghera, and G. Klein. 1978. Chromosome changes (trisomy #15 and 17) associated with tumor progression in leukemias induced by radiation leukemia virus. *J. Natl. Cancer Inst.* 61:227.
44. Davis, M., Y. Chien, N. R. J. Gascoigne, and S. Hedrick, *Immunol. Rev.* In press.
45. Schibler, U., K. B. Marcu, and R. P. Perry. 1978. The synthesis and processing of the messenger RNAs specifying heavy and light chain immunoglobulins in MPC-11 cells. *Cell.* 15:1495.
46. 1983. *Mouse News Lett.* 69:7.