MINIREVIEW

Soluble T Lymphocyte Antigen-Specific Molecules (43436)

ROBERT E. CONE[1]
Department of Pathology, University of Connecticut Health Center, Farmington, Connecticut 06030-3105

The immune response is characterized by the recognition of self versus nonself, specificity, inducibility, and memory. These hallmarks are manifested by the activity of lymphocytes, their differentiated progeny, and some of their soluble products. Specificity of the immune response is ultimately due to cell membrane receptors of T and B lymphocyte clones which bind specifically to antigen. This interaction results in a complex series of events leading to expansion and differentiation of the responding clones, and immunologic memory of the previous exposure to the antigenic stimulus. B lymphocytes extend their specific recognition of antigen by the production of soluble, antigen-specific immunoglobulins with combining sites identical (or very similar) to the heavy and light chain V regions of the B cell membrane immunoglobulin receptor (1) for antigen. In contrast to B lymphocytes, most antigen-specific T lymphocyte activity is mediated by cell membrane-associated receptors which recognize fragments of antigen processed by antigen-presenting cells and associated with class I or II major histocompatibility gene complex (MHC) products (2). The T cell receptor (TCR) for antigen is a heterodimeric molecule consisting of α- and β- or γ- and δ-chains linked by disulfide bonds (2–4), and the organization and sequence of T cell receptor genes demonstrate a significant similarity to immunoglobulin V region genes (3, 4). In addition, murine and human TCR β-chains and immunoglobulin light chains bear cross-reactive epitopes detected by antibodies to synthetic peptides corresponding to the TCR Vβ region (5). However, only low affinity binding of nominal antigen by T cell receptor α-chains has been demonstrated (6). This may be due to conformational changes in the molecule in an aqueous environment and the nature and amount of antigen used. In addition, the affinity of T cell receptors for nominal (non-MHC associated) or MHC-associated antigen may be too low to demonstrate specific binding by conventional methods.

While the "classical" T cell receptor is limited to cell membranes, many T cells secrete immunologically active molecules (lymphokines) after specific interaction with antigen/MHC. These secreted moieties act in a non-specific fashion, even though they are elicited specifically. However, some T cells produce soluble polypeptides that bind nominal antigen with higher affinity than MHC-restricted T cell membrane receptors for antigen (7–17). These molecules have been termed (9,14) antigen-binding molecules (TABM) because they bind nominal antigen with an affinity that permits detection and, in fact, are often purified by specific affinity for antigen (8). TABM occur in T cell membranes (7, 8, 10, 13, 18, 19) and as soluble molecules detected in the culture media of antigen-specific T cells and T cell hybrids (8), T cell hybrid ascites fluid (20, 21), and serum (11, 22–24). Soluble, antigen-specific T cell proteins have been a controversial issue for a number of years (7). However, there is presently substantial information from a number of laboratories demonstrating the structural, serological, and functional properties of these molecules. The structural and functional properties of TABM have been reviewed extensively (7, 8) and, therefore, this review will consider TABM in somewhat more general terms and within the context of the strategy of the immune system to deal with foreign and domestic invaders.

Historical

A description of soluble, antigen-specific T cell products resulted from studies designed to unravel the

[1] To whom requests for reprints should be addressed at Department of Pathology, University of Connecticut Health Center, Farmington, CT 06030.

P.S.E.B.M. 1992, Vol 200: 296–302

0037-9727/92/2003-0296$3.00/0

Table I. Functions of Extracellular (T Cell) Antigen-Specific Molecules

Antigen-specific immunoregulation
a) Suppression (10–12, 15, 16, 27)
b) Induction of suppressor cells (12–13, 16, 28, 32)
c) T cell help (46, 47)
Elicitation of hypersensitivity-like reaction (14, 29–31, 33)

Table II. Properties of Soluble Antigen-Specific T Cell Molecules

Reduced
M_r 22,000–31,000 monomer
M_r 50,000–65,000 multimer
M_r 110,000 multimer
Nonreduced
>M_r 250,000 α-globulin
Isoelectric point
a) clonal restricted
b) polyclonal—4.9–7.0
<5% Carbohydrate
Amino acid composition: 40–50% hydrophobic amino acids
Peptides: common, variable

mystery of the T cell receptor for antigen and the demonstration of a soluble, antigen-specific immunobiological activity elicited by T cells. Studies searching for the T cell receptor for antigen were predicated on the notion that such a receptor, soluble or membrane bound, would bind antigen. If an antigen-binding molecule derived from T cells was found, its characteristics would then be defined. This contrasts with the experimental logic used for the B cell receptor for antigen, since soluble, antigen-specific, B cell-derived molecules (immunoglobulins) were a staple of immunology (25). Thus, the B cell receptor had a known candidate. That the T cell receptor for antigen was related to immunoglobulins was a controversial viewpoint which has been resolved more recently with the advent of the description of the sequence and organization of genes for T cell receptors. More than 10 years ago, evidence was presented that some T cells secreted antigen-specific immunoregulatory molecules. Antigen specificity was demonstrated by functional activity and the ability of the molecules to be adsorbed specifically to solid phase antigen. Such molecules have been termed antigen-specific factors. The hallmark of these factors has been their ability to bind nominal antigen, even though their functional activity may be restricted by major histocompatibility glycoproteins (7, 15, 26). This restriction could be due to an enhanced affinity for small amounts of antigen/MHC and/or a restricted association with a non-antigen-specific molecule necessary for biological activity (7, 27, 28).

TABM Functions

A variety of antigens—proteins, erythrocytes, MHC glycoproteins, and haptens (reviewed in Ref. 8)—have been used to elicit TABM, although haptens such as azobenzenearsonate or dinitrophenol are particularly useful because they facilitate affinity purification. Table I shows that a number of immunobiological activities are associated with soluble antigen-specific T cell products. Many TABM affect or effect specific immunoregulation and, in addition to the immunoregulatory activity of T cells, some soluble antigen-specific molecules have been shown to elicit a reaction delayed in time, but similar to immediate hypersensitivity (14, 29–31). Antigen-specific T cell molecules effecting immunoregulatory activity appear to be antigenically distinct from those that elicit a hypersensitivity-like reaction (32), although the molecules are similar structurally. Induction of hypersensitivity may be mediated by the adsorption of antigen-binding molecules to mast cells by a receptor distinct from that for IgE (31). The elicitation of hypersensitivity by some TABM may be very significant clinically since Trentham (14, 33) and colleagues have shown that some TABM specific for collagen induce an arthritic reaction when injected into the joints of naive rats.

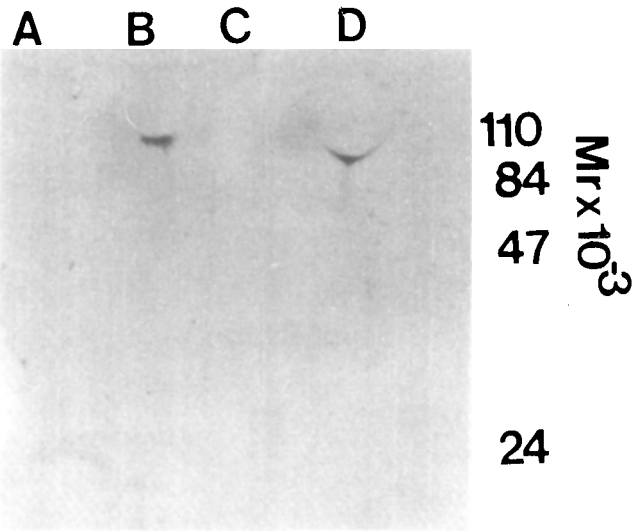

Figure 1. Resolution by sodium dodecyl sulfate-polyacrylamide gel electrophoresis of TABM specific for azobenzenearsonate (21). Azobenzenearsonate-specific TABM were purified from ascites fluid containing an azobenzenearsonate-specific T cell hybrid by a combination of ion exchange chromatography and affinity for azobenzenearsonate. Azobenzenearsonate-specific TABM were mixed with azobenzenearsonate-ovalbumin Sepharose or ovalbumin Sepharose beads and, after 1 hr at 4°C, the beads were washed and eluted with sodium dodecyl sulfate. The eluates and effluents were reduced, alkylated, and resolved in a 10–15% polyacrylamide gradient. (A) Effluent from azobenzenearsonate-sepharose. (B) Effluent from ovalbumin-Sepharose. (C) Eluate from ovalbumin-Sepharose. (D) Eluate from azobenzenearsonate-Sepharose. The gels were stained with silver stain.

Table III. Epitopes of Soluble Antigen-Specific T Cell Molecules

*Ig*H,L	–
TCR VJβ	+
TCR Vβ8	+
TCR Cα	+
TCR Cβ	+
I-J	±

Biochemical Properties of TABM

Although TABM may have functional distinctions, they share many properties (like immunoglobulins). Many sizes have been reported (Table II), ranging from an M_r of 22,500 to 110,000 (reduced) and >250,000 (nonreduced). The range in molecular sizes reported for TABM may be due to these relatively hydrophobic (34, 35) molecules forming stable multimers (8–10, 21, 34–36). Denaturation of TABM in dilute solution by guanidine, low pH, and/or heating at 56°C for 1 hr and reduction generates M_r 22,500 peptide chains that can reassociate to form oligomers with an M_r of 45,000–140,000 after reduction (8, 9, 36). Antigen-specific M_r 140,000 TABM have been produced by translation *in vitro* of immunopurified mRNA (36). However, complementary DNA of 600–900 bases transcribed from the immunopurified mRNA is consistent with mRNA that could code for an M_r 23,000 peptide. The (vexing) variability in TABM quaternary structure can be stabilized when TABM are prepared rapidly at relatively high concentrations (>50 μg/ml) and reduced for <3 min (Fig. 1). Without reduction, TABM generally have an M_r of at least 250,000, which suggests that large multimers are composed of chains linked by interchain disulfide bonds. However, intrachain disulfide bonds may be crucial to a conformation that results in strong, noncovalent interactions between protomers. The extent of multimerization could affect the affinity and avidity of the molecule for antigen. TABM share common structural and antigenic properties, yet, like immunoglobulins, they also exhibit variable properties in isoelectric points, amino acid composition, and peptides (35). These results suggest that like immunoglobulins and TCR, TABM are composed of constant and variable regions. Moreover, polyclonal and monoclonal anti-TABM antibodies recognize TABM with different specificities (11, 13) for antigen, which adds support to the suggestion that TABM have variable and constant regions.

Structurally, TABM are distinct from TCR, and some T cells express both TCR and TABM on the cell membrane (37). However, ontogenetically, TABM appear a few days earlier than TCR (37). In addition, TABM (or antigen-specific immunoregulatory factors) have been shown to bear TCR V region (34) or C region (15, 17, 38) determinants (Table III), and the production of a functional antigen-specific immunregulatory factor bearing TCR Cα determinants is inhibited by anti-sense TCR Vα (39). In addition, the amino acid composition of TABM is significantly similar to TCR α-, β-, or δ-chains (34). Sequence information has been particularly elusive because TABM are difficult to purify in amounts necessary for sequencing. In addition, those TABM purified in quantities sufficient for sequencing have a blocked amino terminus (34). Our attempts to obtain an internal sequence have been frustrated by the hydrophobic properties of the molecule that prevent recovery of peptides for sequencing. Genes for TABM have not been identified with immunoglobulin or TCR probes, which suggests that these molecules are significantly different from immunoglobulins or TCR. It is more likely that the identification of TABM genes will come from TABM probes. Note that the inability of immunoglobulin probes to detect rear-

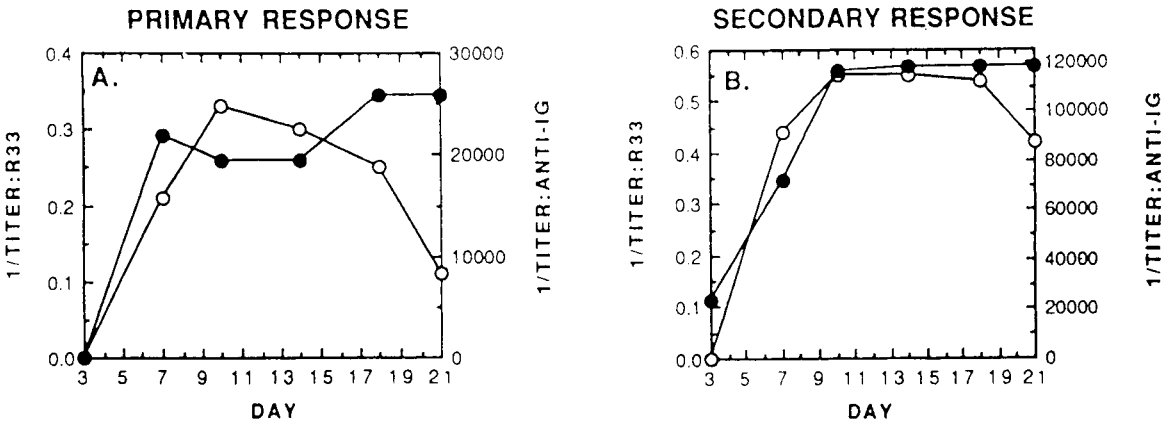

Figure 2. Kinetics of serum TABM and immunoglobulin production during the primary and secondary response (42). BALB/c mice were (A) immunized with bovine serum albumin/poly(A:U) and (B) challenged with bovine serum albumin. Sera were obtained at the indicated times and tested in enzyme-linked immunosorbent assay for binding to bovine serum albumin. TABM titer (O-O) is taken with the amount of serum giving at least 0.2 optical density units with anti-TABM. Immunoglobulin titers (●-●) are taken as the dilution of serum giving 0.2 optical density units with rabbit anti-κ serum in the enzyme-linked immunosorbent assay. Data represent the results of six individual experiments.

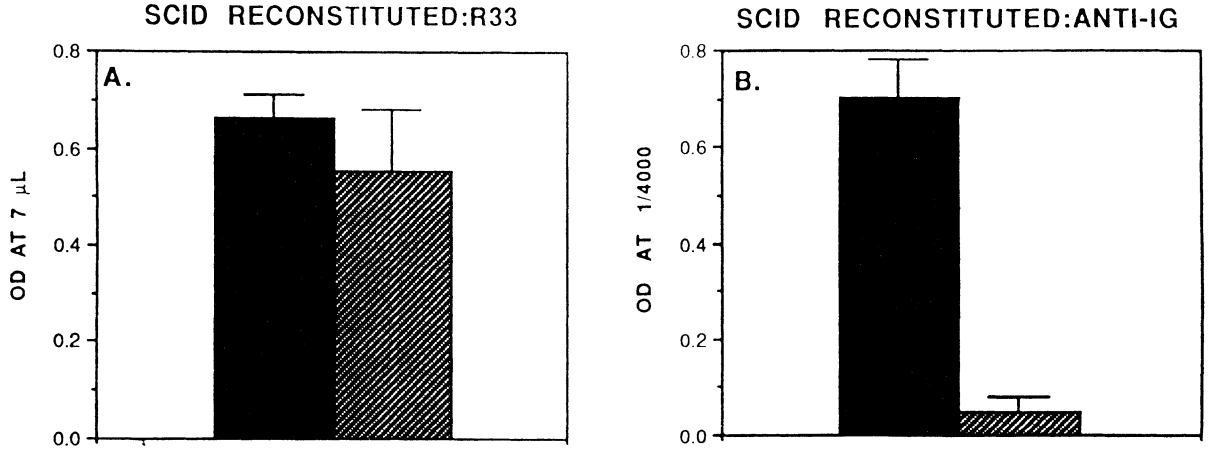

Figure 3. Production of TABM in *scid/scid* mice reconstituted with thymocytes. *Scid/scid* mice were reconstituted with 5×10^7 BALB/c thymocytes and, after 2 weeks, these mice and BALB/c mice were immunized with bovine serum albumin/poly(A:U). After 2 weeks, the mice were challenged with bovine serum albumin and bled 14 days after challenge. The sera were tested for bovine serum albumin-specific TABM (R33) or immunoglobulins (anti-Ig), and the results show the optical density obtained with 100 μl of 1:14 serum (TABM) or 100 μl of 1:4000 serum (Ig). The results are the mean ± SE for six mice per group. (A) TABM response of BALB/c mice (closed), reconstituted *scid/scid* (hatched). (B) Ig response of BALB/c (closed) or reconstituted *scid/scid* (hatched).

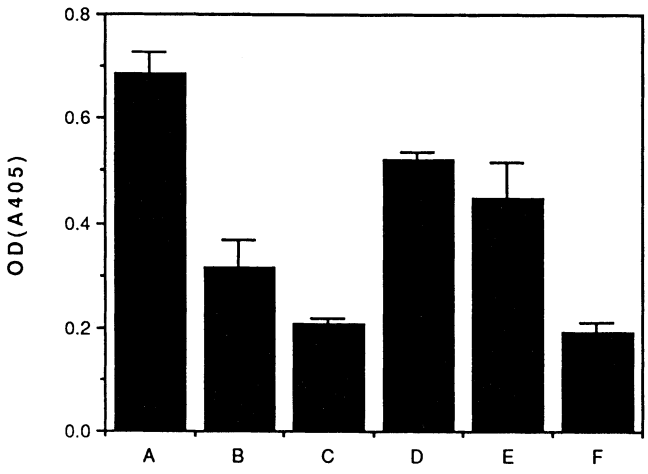

Figure 4. (42) Antigen-specific serum TABM are adsorbed specifically to anti-TCR Cα affinity beads. One milliliter of a 1/10 dilution of serum obtained 14 days after bovine serum albumin-primed mice were challenged with bovine serum albumin was mixed with Sepharose beads conjugated with anti-TCR Cα or normal hamster Ig and incubated 2 hr at 4°C. The beads were centrifuged, washed, then eluted with 0.1 *M* glycine NaCl (pH 2.3). The dialyzed eluate and effluent from anti-Cα-Sepharose or normal hamster Ig or untreated serum was added to bovine serum albumin-coated microtiter trays. Bound TABM were detected with rabbit anti-TABM and alkaline phosphatase-conjugated goat anti-rabbit Ig. Normal rabbit serum (NRS) was used as a control and the NRS optical density (0.150) was subtracted from the optical density obtained with anti-TABM. A, Untreated immune system; B, effluent from anti-TCR Cα-Sepharose; C, normal mouse serum; D, effluent from normal hamster Ig-Sepharose; E, eluate from anti-TCR-Cα Sepharose; F, eluate from normal hamster Ig-Sepharose; OD, optical density.

ranged DNA in T cells was taken as evidence that T cell receptors are not related to immunoglobulins (40). Subsequently, it was suggested that "perhaps the wrong probes are used" (41) to detect rearranged DNA in T cells.

TABM are expressed in the cell membrane by most T cells; however, the antigenic type (isotype?) of membrane TABM differs from that commonly secreted *even by the same cell.* Thus, the membrane "isotype" secreted by some T cells is rare in serum. TABM are present constitutively in serum (11, 22, 23) like immunoglobulins and are similar in size and electrophoretic (α-globulin) mobility to TABM secreted by antigen-specific T cell hybrids or clones (23; R. E. Cone, unpublished observations).

Antigen-Specific Humoral T Cell Response

Because TABM are present in serum in low amounts (<50 μg/ml), it may be that they represent an antigen-specific humoral manifestation of T lymphocyte activity. Doses of antigen that induce an antigen-specific desensitization of mice primed for delayed-type hypersensitivity cause a rise in serum TABM 12 hr after injection. This rise is followed by a rapid fall in serum TABM (22). Some of the TABM are specific for the desensitizing antigen and the induction is antigen specific. Because many of the increased TABM are not specific for the antigen, it may be that desensitization causes the production of some factor that induces secretion of TABM. Preliminary evidence suggests that interleukin 2 may, in fact, induce or increase the secretion of TABM.

The other serum TABM response that we are studying (42) is based solely on the antigen-binding capacity of TABM. Immunization of mice with bovine serum albumin induces a rise in TABM in serum specific for the immunogen (Fig. 2). TABM in serum specific for the immunogen are shown by enzyme-linked immunosorbent assay in which immune serum is added to antigen-coated microtiter trays. TABM (in

Table IV. Properties of Immune System Antigen Recognition Structures

	TABM	Immunoglobulin	MHC-Restricted T cell receptor
T cell specific	+	−	+
Binds nominal antigen	+	+	−
MHC-restricted in specific antigen binding	−	−	+
Heterodimer	−	−	+
Hetero-oligomer	−	+	−
Homo-oligomer	+	−	−
Variable and constant peptides	+	+	+
Rearranged genes	?	+	+
Membrane molecules	+	+	+
Soluble molecule	+	+	−
TCR V region epitope	+	+	+
TCR Cα epitope	+	−	+

the serum) that bind to the antigen are detected with anti-TABM antiserum. This TABM response displays anamnesis and appears to peak somewhat later than immunoglobulins. M_r 110,000 TABM binding the immunogen have been isolated by affinity chromatography and are, therefore, distinct structurally from immunoglobulins. That serum TABM are not immunoglobulins is also shown by the production of TABM but not immunoglobulins in *scid/scid* mice reconstituted with T lymphocytes (Fig. 3). Moreover, serum TABM are bound by monoclonal antibodies to T cell receptor Cα determinants (Fig. 4). Most antigen-specific T cell products reported in serum may be associated with immunoregulatory activity. Reports made in the 1950s of antigen-specific α-globulins in serum which induce a hypersensitivity reaction (43) could be early reports of serum TABM with effector activity (44). Detection and quantitation of serum TABM may provide a new window on T cell activity and an important diagnostic/prognostic tool. We have observed an increase in serum TABM specific for laminin during a mercury-induced autoimmune response (R. E. Cone and P. E. Bigazzi, unpublished observation) and TABM in the cerebral spinal fluid of individuals with multiple sclerosis (M. Dibrino and R. E. Cone, unpublished observations) pointing to a role for TABM in T lymphocyte-associated pathology. The role of these molecules, their genetic origin, and their molecular properties remain to be clarified.

Perspectives

It is becoming evident that the immune system produces *three* antigen-specific moieties (Table IV) to deal with foreign and domestic invaders. Both soluble and membrane-associated (receptor) immunoglobulins utilize the same V genes to produce immunoglobulin-combining sites for antigen which are joined to membrane-associated or soluble C region genes to produce a functional product. Thus, serum immunoglobulins might be considered the soluble manifestation of the B cell receptor for antigen. T cell receptors for antigen resemble immunoglobulins structurally and utilize the same "rules" as B cells to create combining sites for antigen, although TCR V regions are derived from a distinct family of V region genes. Since TABM share V and C region epitopes with TCR and are significantly similar in amino acid composition, TABM may be the soluble manifestation of the TCR. However, unlike TCR, TABM bind nominal antigen with relatively high affinity and, in fact, appear to precede the appearance of TCR ontogenetically. Does this mean that there is a third "family" of V genes which generate TABM V regions through recombination events? If this was the case, there would be T lymphocytes that express both V gene families. To employ Occam's razor, perhaps TABM V genes are derived from TCR V genes and the antigen-binding capacity of these molecules is due to their multimeric structure, similar to the increased affinity for antigen of immunoglobulin heavy:light chain pairs (45). Perhaps the dimeric association of TCR chains (e.g., α:β) determines the affinity of the intact molecule for MHC/peptide. If this is the case, the association of TABM with TCR β-chains or the polymerization of TCR α-chains might direct the affinity of a TABM for an MHC/antigen fragment or TCR α-chain for nominal antigen. Is the epitope specificity of TABM the same as immunoglobulins? Moreover, can one demonstrate MHC restriction of affinity if TABM are presented with MHC/peptide rather than peptide? Thus, some future studies on TABM require definition of the molecule through sequence of amino acids and/or nucleotides and determination of fine specificity for antigen.

This work was supported in part by a Grant AI22869 from the U.S. Public Health Service and a University of Connecticut Health Center grant. The author gratefully acknowledges Cathy Mitchell for

her help and patience in the preparation of the manuscript and Dr. Elmer L. Becker for his critical review and discussion.

1. Klinman NR, Linton P-J. The clonotype repertoire of B cell subpopulations Adv Immunol **42**:1–94, 1988.
2. Hedrick SM. The specificity of the T cell receptor. Adv Immunol **43**:193–226, 1988.
3. Mak TW, Yanagi Y. Genes encoding the human T cell antigen receptor. Immunol Rev **81**:221–234, 1984.
4. Davis MM, Chien Y-H, Gascoigne NRJ, Hedrick SM. A murine T cell receptor gene complex: Isolation structure and rearrangement. Immunol Rev **81**:235–258, 1984.
5. Shluter SF, Marchalonis JJ. Antibodies to synthetic joining segment peptide of the T cell receptor beta chain. Serological cross-reaction between products of T cell receptor genes antigen binding T cell receptors and immunoglobulins. Proc Natl Acad Sci USA **83**:1872–1876, 1986.
6. Siliciano RF, Hemesath TJ, Pratt JC, Dintzis JC, Acuto O, Shin HS, Reinherz E. Direct evidence for the existence of nominal antigen binding sites on T cell surface. Ti α-β heterodimers of MHC-restricted T cell clones. Cell **47**:161–171, 1986.
7. Cone RE, Zheng H, Chue B, Beaman K, Ferguson T, Green DR. T cell-derived antigen binding molecule (T-ABM). Molecular and functional properties. Int Rev Immunol **3**:205–228, 1988.
8. Cone RE. Non-MHC restricted T cell antigen binding proteins. Methods in Enzymolology **150**:666–681, 1987.
9. Cone RE, Beaman KD. Antigen binding molecules of T cells: Charge heterogeneity and structural lability. Mol Immunol **22**:399–406, 1985.
10. Healy CT, Kapp JA, Webb DR. Purification and biochemical analysis of antigen-specific suppressor factors obtained from supernatant membrane or cytosol of a T cell hybridoma. J Immunol **131**:2843–2847, 1983.
11. Ferguson TA, Iverson GM. Isolation and characterization of an antigen-specific suppressor inducer molecule from serum of hyperimmune mice using a monoclonal antibody. J Immunol **137**:3896–3902, 1986.
12. Fresno M, McVay-Boudreau I, Nobel G, Cantor H. Antigen specific T cell clones II. Purification and biological characterization of an antigen-specific suppressive protein synthesized by cloned T cells. J Exp Med **173**:1250–1274, 1981.
13. Cone RE, Rosenstein RW, Janeway CA, Iverson G, Murray JH, Cantor H, Fresno M, Mattingly JA, Cramer M, Krawinkel U, Wigzell H, Binz H, Frischnecht H, Ptak W, Gershon RK. Affinity purified antigen specific products produced by T cells share epitopes recognized by heterologous antisera raised against several different antigen specific products from T cells. Cell Immunol **82**:232–245, 1985.
14. Trentham DE. An arithritogenic lymphokine in the rat. J Exp Med **162**:1532–1545, 1985.
15. Fairchild RL, Kubo RT, Moorhead IW (1990) DNP specific Class I MHC-restricted suppressor molecules bear determinants of the T cell receptor α and β chains. J Immunol **141**:3342–3348, 1988.
16. Steele JK, Chu NR, Chan AR, North J, Levy DG. Isolation of an antigen-specific T suppressor factor that suppresses the *in vivo* response of DBA/2 mice to ferredoxin. J Immunol **19**:469–477.
17. Steele JK, Kawaskaki H, Kuchroo VK, Minami M, Levy JG, Dorf ME. A monoclonal antibody raised to tumor-specific T cell derived suppressor factors also recognizes T suppressor inducer factors of the 4-hydroxy-3-nitrophenyl acetyl hapten suppressor network. J Immunol **139**:2629–2634, 1987.
18. Cone RE, Beaman KD, Ruddle NH. Isolation of antigen binding molecules from the membrane of an antigen specific T cell hybrid. Cell Immunol **99**:247–263, 1986.
19. O'Connor S, Eardley DD, Gershon RK, Cone RE. Isolation and partial characterization of antigen binding molecules produced *in vitro* by "educated" T cells. Mol Immunol **17**:913–921, 1980.
20. Beaman KD, Cone RE. Production and purification of monoclonal T lymphocyte antigen binding molecules (TABM). Biochem Biophys Res Commun **125**:475–479, 1984.
21. Cone RE, Weischedel A-K, Urbanski M, Kristie J. Specific antigen binding by proteins secreted by an antigen-specific T cell hybrid. Mol Immunol (in press).
22. Cone RE, Gerardi D, Davidoff J, Petty D, Cohen S. Quantitation of T cell antigen binding molecules (TABM) in the sera of non-immunized, immunized and desensitized Mice. J Immunol **138**:234–239, 1987.
23. DiBrino M, Ravindran B, Cone RE. T cell-derived proteins from normal human sera and their relationship to T cell antigen binding molecules. Clin Immunol Immunopathol **59**:271–287, 1991.
24. Passenen TJ, Moller G. ELISA assay for the detection of a dextran binding product secreted by a T cell hybrid Th1. Scand J Immunol **25**:349–357, 1987.
25. Cone RE, Beaman KD. T cell antigen binding proteins and their cell membrane analogues. In: Marchalonis JJ, Ed. Antigen-Specific T Cell Receptors and Factors. Boca Raton, FL: CRC Press, pp67–86, 1987.
26. Lowy A, Flood P, Tominasa A, Daubauska JT, Gershon RK, Green MI. Analysis of hapten-specific T suppressor factors. Genetic restriction of T suppressor activity analyzed with synthetic hybrid suppressor molecules. J Immunol **132**:640–643, 1984.
27. Taniguchi M, Tokuhisa R, Itoh T, Kanno M. Functional roles of two polypeptide chains that compose an antigen-specific suppressor T cell factor. J Exp Med **159**:1096–1103, 1984.
28. Chue B, Ferguson TA, Beaman KD, Rosenmann SJ, Cone RE, Flood P, Green DR. An approach to the unification of suppressor T cell circuits. A simplified assay for the induction of suppression by T cell-derived antigen-binding molecules (T-ABM). Cell Immunol **118**:30–36, 1989.
29. Ptak W, Askenase PW, Rosenstein RW, Gershon RK. Transfer of an antigen-specific immediate hypersensitivity-like reaction with an antigen binding factor produced by T cells. Proc Natl Acad Sci USA **79**:1969–1976, 1982.
30. Askenase PW, Rosenstein RW, Ptak W. T cells produce an antigen binding factor with *in vivo* activity analogous to IgE antibody. J Exp Med **157**:862–869, 1983.
31. Kops SK, Van Loveren H, Rosenstein RW, Ptak W, Askenase PW. Mast cell activation and vascular alterations in immediate hypersensitivity-like reactions induced by a T cell-derived antigen binding factor. Lab Invest **50**:421–433, 1984.
32. Cone RE, Rellahan B, Wong R, Clark RB. Membrane associated and secreted non-MHC-restricted T cell antigen binding molecules are antigenically distinct. Cell Immunol **137**:529–538, 1991.
33. Trentham DE. Collagen arthritis in rats. Arthritogenic lymphokines and other aspects. Int Rev Immunol **4**:25–33, 1988.
34. Hubbard RA, Speidel M, Marchalonis JJ, Cone RE. A monoclonal antigen-binding T cell immunoprotein: Antigenic relatedness to T cell receptor β chain Fr IV and J peptide segments: physicochemical distinctiveness from classical immunoglobulins and T cell receptor heterodimers. Mol Immunol **26**:447–455, 1989.
35. Cone R, Takeda A, Beaman KD, Ferguson T, Iverson GM. Phenotypic similarity between T cell antigen binding molecules. Exp Clin Immunogenet **3**:208–216, 1986.
36. Beaman KD, Ruddle NH, Bothwell ALM, Cone RE. Messenger RNA for an antigen-specific binding molecules from an antigen-specific T cell hybrid. Proc Natl Acad Sci USA **81**:1524–1528, 1984.
37. Rellahan BL, Cone RE. Ontogeny and Expression of non-MHC restricted T cell antigen binding molecules by thymocytes and peripheral T cell subsets. Cell Immunol **130**:176–185, 1990.

38. Bisonette R, Zheng H, Kubo RT, Singh B, Green DR. A helper cell hybridoma produces an antigen-specific regulatory activity. J Immunol **146**:2898–2907, 1991.
39. Zheng H, Sahai BM, Boyer P, Kilgannon P, Fotedar A, Green DR. Specific inhibition of cell-surface T cell receptor expression by anti sense oligonucleotides and its effect on induction of an antigen specific regulatory T cell factor. Proc Natl Acad Sci USA **86**:3758–3763, 1989.
40. Jensenius T, Williams AF. The T lymphocyte antigen receptor paradigm lost. Nature **300**:583–584, 1982.
41. Cone RE. On the expression of immunoglobulin genes by T cells. Scand J Immunol **18**:86–88, 1983.
42. Urbanski M, Cone RE. Appearance of T lymphocyte-derived proteins specific for the immunizing antigen in serum during a humoral immune response. J Immunol **148**:2840–2844, 1992.
43. Cole LA, Favour C. Correlation between plasma protein fractions and the passive transfer of delayed and immediate cutaneous reactivity to tuberculin PPD and tuberculopoly/saccharides. J Exp Med **101**:391–420, 1955.
44. Van Loveren H, Ratzlaff RE, Kato K, Meade R, Ferguson T, Iverson JM, Janeway CA, Askenase P. Immune serum from mice contact sensitized with picrylchloride contains an antigen specific T cell factor that transfers immediate cutaneous reactivity. Eur J Immunol **16**:1203–1211, 1986.
45. Smith-Gill SJ, Hamel PA, Klein MH, Rudikoff S, Dorrington KJ. Contributions of the V_k4 light chain to antibody specificity for lysozyme and β (1,6) D-galactan. Mol Immunol **23**:919–926, 1986.
46. Guy R, Urich ST, Foo-Philips Hathlock KS, Apella E, Hodes T. Antigenic helper function of cell free T cell products bearing TCR Vβ determinants. Science **244**:1477–1478, 1989.
47. Krowka TF, Shiozawa C, Diener E, Paetkau U, Pilarski LM. Induction of cytotoxic lymphocyte responses by antigen-specific helper factors. J Immunol **133**:2018–2024, 1984.