SHARED IDIOTYPIC DETERMINANTS ON ANTIBODIES AND T-CELL-DERIVED SUPPRESSOR FACTOR SPECIFIC FOR THE RANDOM TERPOLYMER L-GLUTAMIC ACID\textsuperscript{60}-L-ALANINE\textsuperscript{80}-L-TYROSINE\textsuperscript{10}\textdagger

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T lymphocytes produce a wide variety of effector and regulatory substances. Among these is the suppressor factor (TsF) obtained from suppressor T cells (Ts) stimulated by the synthetic copolymer L-glutamic acid\textsuperscript{60}-L-alanine\textsuperscript{80}-L-tyrosine\textsuperscript{10} (GAT), in mice of Ir nonresponder haplotype (H-2\textsuperscript{p}q's) (1). This laboratory has studied GAT-TsF in detail and found that it (a) is sensitive to pronase, (b) is 40,000–50,000 daltons, (c) bears I-region, and more specifically, I-J determinants, (d) has specific antigen-binding activity, (e) lacks conventional immunoglobulin CH and light-chain determinants, and (f) acts across H-2 and Ig allotype differences, in part by inducing a second population of Ts from virgin T cells (Ts\textsubscript{2}) (1–7).

The presence of an antigen-binding site on a molecule or a tightly bound molecular complex also containing determinants coded for by major histocompatibility complex (MHC) genes raises the question of the nature of this binding site. Is it a new class of highly specific combining region coded for by the MHC itself, or is it in fact an immunoglobulin V region associated in a functional way with MHC products? The recent description by Ju et al. (8, 9) of a guinea pig antiserum detecting a common idiotype (CGAT) possessed by a majority of anti-GAT antibodies in all mouse strains tested, regardless of Ig allotype or Ir gene status, provided a means to explore this issue. The CGAT idiotype is present in the serum of all mice producing anti-GAT antibodies and probably represents a germ line gene product (9). Thus, it might be predicted that if V region gene products were involved in GAT-TsF formation, CGAT determinants would be found on GAT-TsF molecules. The present report describes the results of studies with anti-CGAT immunoadsorbents to test for the presence of CGAT determinants on nonresponder derived GAT-TsF. The data reveal that both DBA/1 (H-2\textsuperscript{b}, Ig-1\textsuperscript{c}) and SJL (H-2\textsuperscript{a}, Ig-1\textsuperscript{b}) GAT-TsF can be specifically adsorbed to

\textsuperscript{*} Supported by National Institutes of Health grant 1P01-AI-14732 and National Science Foundation grant PCM-75-22422.

\textsuperscript{1} Abbreviations used in this paper: oCGAT, anti-CGAT idiotypic antiserum; oI-J\textsuperscript{a}, anti-I-J\textsuperscript{a} alloantiserum; CGAT, cross-reactive idiotype of GAT-specific antibodies; GA, random copolymer of L-glutamic acid\textsuperscript{60}-L-alanine\textsuperscript{80}; GAT, random terpolymer of L-glutamic acid\textsuperscript{60}-L-alanine\textsuperscript{80}-L-tyrosine\textsuperscript{10}; GT, random copolymer of L-glutamic acid\textsuperscript{60}-L-tyrosine\textsuperscript{10}; MBSA, methylated bovine serum albumin; MHC, major histocompatibility complex; NGPS, normal guinea pig serum; PBS, phosphate-buffered saline; PFC, plaque-forming cell(s); SRBC, sheep erythrocytes; Ts\textsubscript{s}, suppressor T lymphocyte; TsF, T lymphocyte-derived suppressor factor(s); Ts\textsubscript{2}, TsF induced suppressor T cell; V region, variable region of immunoglobulin.
and eluted from anti-CGAT-Sepharose columns, while DBA/1 T₆F specific for the
related polymer L-glutamic acid⁴⁰-L-alanine⁴⁰ (GA) is not bound to such anti-idiotype
columns, in concordance with the absence of CGAT idiotype in anti-GA antibodies
(9). Further, it is demonstrated that the active T₆F recovered from the anti-CGAT-
immunoadsorbents still possesses I-J determinants. The limitations and implications
of these findings are discussed with respect to the possible structure of GAT-T₆F and
other antigen specific T-cell products.

Materials and Methods

Mice. SJL (H-2b, Ig-1b) female and DBA/1 (H-2b, Ig-1b) male GAT-nonresponder mice were
purchased from The Jackson Laboratory, Bar Harbor, Maine. BALB/c (H-2d, Ig-1a) GAT-
responder male or female mice were obtained from either Health Research Farms, West Seneca,
N. Y., or Charles River Breeding Laboratories, Wilmington, Mass. All mice were maintained
in our animal facilities on standard laboratory chow and acidified water ad lib, and used at 2-4
mo old.

Antigens. GAT (lot 6, mol wt 32,500) was obtained from Miles Laboratories Inc., Miles
Research Products, Elkhart, Ind. and GA (lot 1, mol wt 36,000) was purchased from New
England Nuclear, Boston, Mass. All antigen solutions, conjugates with methylated bovine
serum albumin (MBSA), GAT-sheep erythrocytes (GAT-SRBC), and Sepharose-4B immuno-
adsorbents were prepared as previously described (4, 10).

Preparation of Specific T₆F. Crude GAT- and GA-T₆F were prepared as extracts of pooled
spleens and thymuses of either DBA/1 or SJL mice immunized i.p. 3-6 d previously with 100
µg GAT or GA in aluminum-magnesium hydroxide gel (Maalox, William H. Rorer, Inc., Ft.
Washington, Pa.) (1). These crude suppressor materials were then partially purified by
adsorption onto and elution from either GAT- or GA-Sepharose columns, respectively (4). This
procedure has been shown to remove a serologically active fragment of GAT from the suppressor
material bearing I region determinants, and was utilized to prevent possible interference by
ligand (GAT) with binding of anti-CGAT antibody directed toward a combining site-associated
idiotypic determinant.

Preparation and Characterization of Anti-CGAT Antiserum and Immunoadsorbents. The purification
of anti-GAT antibodies and production of the anti-idiotypic antiserum have been detailed
elsewhere (8). Briefly, ascites fluid containing anti-GAT antibodies from D1.LP mice was
precipitated with 40% ammonium sulfate. The γ-globulin fraction was passed through a
Sepharose 4B column to which an anti-H-2b antiserum [(B10.A × A)F₁ anti-B10] was coupled
and then passed over a GAT immunoadsorbent. The anti-GAT antibodies were then eluted
with an acid buffer and used to immunize guinea pigs. The resulting guinea pig anti-idiotypic
serum was rendered specific for anti-GAT idiotypic determinants by precipitation, then
adsorption with normal mouse immunoglobulins.

The specific anti-idiotypic serum or control normal guinea serum was then coupled to CNBr-
activated Sepharose 4B (Pharmacia, Uppsala, Sweden). All immunoadsorbents contained
approximately 2 mg of protein per milliliter of packed beads.

Affinity Chromatography of GAT- and GA-T₆F. All manipulations were carried out at 4°C.
Small (0.3-0.5 ml) columns of either anti-CGAT-Sepharose or control normal guinea pig serum
(NGPS)-Sepharose were washed extensively with phosphate-buffered saline (PBS), pH 7.2, then
loaded with 1 ml purified GAT-T₆F or GA-T₆F. The T₆F was run into the gel over a 1-min
period, and allowed to incubate for 60-90 min, then a 2-bed volume PBS wash collected and
termed filtrate. The columns were then washed with at least 10-bed volumes of PBS and the
adsorbed material eluted over a 30-s period with 2-bed volumes of pH 2.5 glycine-HCl buffer.
This collected material was rapidly neutralized with 1 N NaOH and termed eluate. All filtrates
and eluates were stored at -20°C in small aliquots and thawed only once, immediately before
use. In one series of experiments, the eluate of an anti-CGAT immunoadsorbent loaded with
SJL GAT-T₆F was passed over an anti-I-J⁺ [(3R × 9R)F₁ anti-B10.HTT]-Sepharose column and
both the filtrate and eluate assayed for suppressive activity. All factor dilutions are
calculated based on 6 × 10⁹ cells/ml as neat T₆F, and assuming all T₆F applied to a column
to be present in any given filtrate or eluate.
Assay of T\(_F\) Activity. All assays for GAT-T\(_F\) and GA-T\(_F\) activity before and after immunoadsorbent passage were performed in vitro according to previously described techniques (6, 7). In certain experiments, factors and column fractions were tested directly by addition to modified Mishell-Dutton cultures of syngeneic or allogeneic nonresponder spleen cells, by using GAT-MBSA or GA-MBSA as stimulating antigens. In other experiments, factors and column fractions were added to cultures of BALB/c responder spleen cells and incubated for 2 d to permit induction of suppressor cells (T\(_s\)) (7). These precultured cells were then washed and added in graded numbers to fresh cultures of syngeneic BALB/c spleen cells with GAT as antigen. All cultures were harvested and assayed for specific IgG PFC on day 5, by using a modified Jerne plaque assay with GAT-SRBC as indicator cells. Data are expressed as either specific PFC per (7.5 × 10\(^6\) cell) culture or

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\text{as percent control response} = \frac{\text{response in presence of specific } T_F \text{ or } T_s}{\text{response in presence of control } T_F \text{ or cells}} \times 100\%.
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Results

Binding of SJL and DBA/1 GAT-T\(_F\) to Anti-CGAT-Immunoadsorbents. Partially purified GAT-T\(_F\) from either in vivo immunized SJL or DBA/1 nonresponder mice was prepared with a GAT-immunoadsorbent. These purified suppressor factors were then applied to either anti-CGAT or control (NGPS)-immunoadsorbents, and the filtrates and eluates tested for activity directly on nonresponder spleen cells cultured with GAT-MBSA as antigen. Figs. 1 and 2 present the results of several similar experiments. Fig. 1 demonstrates that virtually all the suppressive activity of SJL and DBA/1 GAT-T\(_F\) is removed by passage over anti-CGAT-immunoadsorbents and that the adsorbed T\(_F\) can be fully recovered in the acid eluate of such a column. Further, these experiments reveal that both the original purified GAT-T\(_F\) and the anti-CGAT adsorbed material can suppress not only syngeneic, but also allogeneic nonresponder spleen cells, in agreement with previous data (5). Fig. 2 summarizes a large number of similar experiments assaying immunoadsorbent treated DBA/1 GAT-T\(_F\) preparations on SJL spleen cells in culture. These data are all in agreement with those of Fig. 1. The experiments in Figs. 1 and 2 were performed with several separately prepared batches of purified GAT-T\(_F\), all of which gave identical results. Taken together, these data indicate that the directly suppressive component of nonresponder GAT-T\(_F\) is recognized and bound by immobilized antibody to CGAT determinants.

It is now appreciated that GAT-T\(_F\) acts at least in part by inducing virgin spleen cells (T cells) to become active suppressor cells (T\(_s\)) (6, 7). This induction of T\(_s\) using nonresponder derived GAT-T\(_F\) can occur with syngeneic and allogeneic nonresponder, as well as allogeneic responder, spleen cells. To determine if the T\(_F\) responsible for this inducing activity was also recognized by anti-CGAT antibodies, the same filtrate and eluate materials assayed above in direct culture were used for T\(_s\) generation. BALB/c responder spleen cells were cultured for 2 d with various T\(_F\) preparations and these cultured cells then washed and added in varying numbers to fresh BALB/c cultures stimulated by GAT. Data from one of four experiments of this type, all of which gave similar results, are presented in Fig. 3. Again, as for the direct acting material, the inducing GAT-T\(_F\) was completely removed by the anti-CGAT-immunoadsorbent and could be recovered from the gel by acid elution. Thus, the material(s) in GAT-T\(_F\) responsible for both direct suppression of nonresponder
lymphocytes, and induction of $T_s$ in responder cells are adsorbed by anti-CGAT-immunoadsorbents.

**DBA/1 GA-TsF Fails to Bind to Anti-CGAT-Immunoadsorbents.** We have previously demonstrated that the CGAT idiotype is absent from mouse antibodies induced by the related copolymer GA (9). This finding suggested the possibility that GA-TsF might lack CGAT-determinants and thus serve as an appropriate specificity control for the anti-CGAT column. Therefore, GA specific TsF was prepared from DBA/1 mice, and purified on GA-Sepharose. This material was then passed over control or anti-CGAT-immunoadsorbent columns and tested in culture with DBA/1 spleen cells and GA-MBSA. Table I presents one such experiment. DBA/1 GAT-TsF run in parallel with the GA-TsF was fully adsorbed onto and recovered from the anti-GA-immunoadsorbent, as shown repeatedly above. However, no significant binding of GA-TsF to the anti-CGAT-immunoadsorbent occurred. These data imply that the interaction of GAT-TsF with anti-CGAT antibodies is not due to a nonspecific affinity of this material for $T_s$ bearing I region determinants nor is it likely to be merely a reflection of charge effects resulting from the large glutamic acid content of GAT, because a similar effect would be expected with GA-specific TsF as well.

**Presence of Both CGAT Idiotype Determinants and I-J Determinants on GAT-TsF.** GAT-TsF has been shown to bear I region, more specifically, I-J subregion controlled determinants (2, 3). It was therefore of interest to determine if the anti-idiotype reactive suppressor material studied above also possessed such I-J determinants. To answer this question, the active eluate of an anti-CGAT column loaded with SJL (I-J') GAT-TsF was passed over an anti-I-J' Sepharose immunoadsorbent. Table II details the results obtained with the parent materials and the alloantiserum adsorbed TsF. It is clear that the factor responsible for suppressive activity in the anti-CGAT eluate also possesses I-J' determinants.
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SjL RESPONSE TO 25μg GAT-MBSA (43% = 399 IgG GAT-PFC/Culture)

Filtrate from NGPS-Sepharose

Eluate from NGPS-Sepharose

Filtrate from CGAT-Sepharose

Eluate from CGAT-Sepharose

% OF CONTROL RESPONSE

0 20 40 60 80 100 120 140

Fig. 2. Direct in vitro suppressive activity of DBA/1 GAT-TF before and after passage over anti-CGAT-immunoadsorbents. Purified DBA/1 GAT-TF was adsorbed to and eluted from either control (NGPS) columns or anti-CGAT columns, then added at a final 1/250 dilution to cultures of SJL spleen cells stimulated with 2.5 μg GAT-MBSA. Specific IgG GAT-PFC were assayed 5 d later. Data are expressed as percent control response for several combined experiments.

Discussion

The experiments presented above represent a first approach to the understanding of the nature of the antigen combining site on specific T-cell-derived suppressor factors. The results indicate that GAT-specific TfF can be adsorbed by and eluted from immunoadsorbents prepared from a guinea pig anti-idiotype antiserum recognizing a common (cross-reactive) determinant found on most murine anti-GAT-antibodies. This adsorption appears to be related to the antigen binding specificity of the T,F, because GAT-T,F but not GA-T,F, can be adsorbed by anti-CGAT-immunoadsorbents. Both direct suppressive activity on nonresponder spleen cells, and T,F inducing potential with responder spleen cells are selectively retained by anti-CGAT columns, and the active CGAT+GAT-T,F eluted from such a column still possesses I-J determinants. Further, the data indicate that the great majority of GAT-T,F molecules bind to anti-CGAT-immunoadsorbents, based on the virtually complete removal of suppressive activity on the anti-CGAT immunoabsorbent.

Investigation of the fine antigen specificity of antibodies bearing the CGAT idiotype has revealed that antibodies elicited by GAT and L-glutamic acid-G-L-tyrosine (GT), but not GA, possess CGAT determinants, and that the idiotype from GAT induced antibodies preferentially bound to GT, rather than to GA. These data imply that CGAT determinants are related to an antigen combining site specific for GAT or GT, but not GA, and that not all antibodies reactive with highly anionic polypeptides are bound by anti-CGAT antisera. Similar results were obtained with GAT-T,F versus GA-T,F in this study. The question still remains as to whether or not GT-T,F is CGAT+. The serological data might lead one to predict that GT-T,F would be CGAT+, but the lack of cross-suppression shown by GAT-T,F and GT-T,F in vitro (7) is difficult to reconcile with this hypothesis. Tests of GT-T,F binding to anti-CGAT-immunoadsorbents are under way to resolve this question.

2 Ju, S-T., M. E. Dorf, and B. Benacerraf. 1978. Idiotype analysis of anti-GAT antibodies. III. Determinant specificity and immunoglobulin class distribution of CGAT idiotype. Manuscript submitted for publication.
Although the most likely interpretation of the data presented in this paper is that GAT-T$_s$F shares (a) combining site(s) with anti-GAT antibodies (i.e., possesses at least a part of an immunoglobulin V region), certain limitations of these experiments must be made clear. Although the starting immunogen consisted of (NH$_4$)$_2$SO$_4$ fractionated, GAT affinity column purified antibodies that were also passed over an anti H-2$^b$ immunoabsorbent in an effort to remove I-region coded T-cell products, it is still theoretically possible that the anti-CGAT-serum contains antibodies made directly to GAT-specific T-cell products which copurified with the immunoglobulins and were not removed by the anti-H-2 column. Responder mice are known to be capable of producing GAT-T$_s$F, and Kontiainen et al. have reported preparation of anti-idiotype-like antisera to antigen purified T$_s$F given in trace amounts according to immunization protocols similar to those used to raise anti-CGAT antisera (11). The involvement of such putative anti-T-cell factor antibodies in studies of anti-idiotypic reactivity of T-cell products is also a possibility in the earlier helper factor experiments of Mozes (12), in which no attempt was made to remove I-coded materials from the immunogen. However, if such anti-T-cell product antibodies exist in the anti-CGAT reagent, they are not directed against mouse T$_s$F as a class because GA-T$_s$F is not bound by anti-CGAT columns. Rather, they must resemble immunoglobulin specific anti-CGAT antibodies in that they detect GAT specific products obtained from strains differing at both H-2 and Ig-1 loci. To resolve this issue, we are now cloning B-cell hybridomas secreting CGAT$^+$ antibodies to provide immunoglobulin material free of potential T-cell products. These pure antibodies will then be used to absorb the anti-CGAT antiserum to determine whether or not it is antibody to immunoglobulin which actually binds the T-cell-derived GAT-T$_s$F.

3 Pierres, M., R. N. Germain, and B. Benacerraf. Manuscript in preparation.
4 Pierres, M. Manuscript in preparation.
If, as is likely, it is antibody to idiotypic determinants on anti-GAT antibodies that bind GAT-T,F, then several possible interpretations of the structural relationship between the binding regions of GAT-T,F and antibody may be considered. Because of the high frequency and broad representation of CGAT determinants on anti-GAT antibodies of not only mice, but other species such as the rat (9), it is clear that there has been extensive evolutionary conservation of a major GAT binding site. Therefore, the combining region of the GAT-T,F may have arrived at a configuration similar to immunoglobulin V regions by convergent evolution of independent genetic units, one in the MHC (for T,F) and the other in the Ig germ line V genes. Because of the absence of CGAT- mouse strains, it is not possible to rule out this interpretation on a genetic basis. However, it is not unreasonable to assume that if both GAT-T,F and anti-GAT immunoglobulin possess similar or identical idiotypic specificities, that they are coded for by the same genes, i.e., Ig V region genes. Such a model is consistent with the growing data on the presence of shared idiotypic specificities on B cells or Ig and T cells or T-cell products. These data include the studies of Binz and Wigzell on antibodies and T cells specific for allo-MHC determinants (13), of Black et al. and Hämmerling et al. on streptococcal A carbohydrate specific immune responses of A/J and BALB/c mice (14, 15), Krawinkel et al. on nylon fiber purified mouse B- and T-cell products (16), Cosenza et al. on phosphorylcholine specific helper T cells (17), and the recent data of Pincus et al. on (T, G)-A—L specific antibody and helper T cells (18) as well as the above mentioned work of Mozes on (T, G)-A—L helper factor (12), and the recent detailed studies of Bach et al. on azobenzenearsonate specific T,F.

If one puts aside for the moment alternative explanations for these data, what picture emerges of the relationship between T-cell antigen specific effector molecules

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* Responding spleen cells in modified Mishell-Dutton cultures.
‡ 2.5 μg per culture.
§ See Materials and Methods.
∥ Specific IgG plaque-forming cells (PFC)/(7.5 × 10⁶ cell) culture.
¶ Comparison to no factor added group.
TABLE II

| Cultured cells* | Antigen                     | GAT-T,F§ | PFC/culture$ | Suppression||
|-----------------|-----------------------------|----------|--------------|-------------|
| SJL spleen      | 2.5 µg GAT-MBSA             | —        | 500          | —           |
| SJL spleen      | 2.5 µg GAT-MBSA Filtrate from NGPS-Sepharose | <20      | 100          |             |
| SJL spleen      | 2.5 µg GAT-MBSA Eluate from NGPS-Sepharose | 520      | 0            |             |
| SJL spleen      | 2.5 µg GAT-MBSA Filtrate from aCGAT-Sepharose | 800      | 0            |             |
| SJL spleen      | 2.5 µg GAT-MBSA Eluate from aCGAT-Sepharose | <20      | 100          |             |
| SJL spleen      | 2.5 µg GAT-MBSA Filtrate from α-I-J+ Sepharose loaded with eluate of aCGAT-Sepharose | 400      | 20           |             |
| SJL spleen      | 2.5 µg GAT-MBSA Eluate from α-I-J+ Sepharose loaded with eluate of aCGAT-Sepharose | <20      | 100          |             |

* Responding spleen cells in modified Mishell-Dutton cultures.
§ See Materials and Methods.
$ Specific IgG PFC/(7.5 × 10⁶ cell) culture.
|| Comparison to group receiving no T,F.

and immunoglobulin? Rat T-cell products specific for alloantigens, as studied by Binz and Wigzell, possess idiotypes in common with antibodies of the same specificity (13), but both genetic and serologic studies found no evidence of MHC association with these T-cell materials (19). On the other hand, Krammer and Eichmann found the idiotypic pattern of alloreceptors on mouse T lymphocytes can be influenced genetically by both Ig allotype and MHC linked loci, though the presence of either type of gene product in the actual receptor was not demonstrated (20). The present study clearly suggests a physiochemical association of both MHC (I-J) coded products and V region determinants in the GAT-T,F. A minimal model incorporating the bulk of these and other related data would postulate that T cells produce materials with shared Ig V region determinants, presumably reflecting the presence of true Ig V region gene products. These V region products are either (a) part of a single chain also including I region coded material in which the V region portion provides antigen binding specificity and the I region portion provides biologic effector function (e.g., help, suppression, H-2 restricted cell-cell communication) in a manner similar to Ig Fc regions or (b) joined by disulfide or noncovalent bonds to a second chain containing the I region material, forming a tightly bound molecular complex with a similar distribution of functions. This model would provide a single explanation for certain Ir gene effects in terms of both cell interaction and factor activity in that lack of formation or functional expression of the proper I region-V region complex would preclude T-cell activity for the given antigen specificity of the V region and the particular I region effector function involved. Further, this model can accommodate either an altered self concept of T-cell antigen recognition, based on appropriate V region selection and/or mutation, or a dual receptor model involving recognition of a physically linked nominal antigen and H-2 interaction site. Current advances in biochemical analysis of T-cell idiotype positive material will provide evidence for or against this model in the near future. Towards this end, the development of T hybridomas producing large quantities of active specific suppressor factor will provide an important tool, and efforts are underway to derive such hybridomas producing CGAT+ GAT-T,F to be studied in parallel with the monoclonal CGAT+ anti-GAT antibodies now being isolated.
Summary

T-cell derived suppressor factors (T\textsubscript{s}F) specific for the random copolymers L-glutamic acid\textsuperscript{60}-L-alanine\textsuperscript{30}-L-tyrosine\textsuperscript{10} and L-glutamic acid\textsuperscript{60}-L-alanine\textsuperscript{60}, referred to as GAT and GA, respectively, were prepared and partially purified on the appropriate antigen immunoadsorbents. GAT-T\textsubscript{s}F obtained from nonresponder DBA/1 (H-2\textsuperscript{q}) and SJL (H-2\textsuperscript{s}) mice were passed over immunoadsorbents prepared from normal guinea pig serum (NGPS) or guinea pig anti-idiotype antiserum (anti-CGAT) specific for a common cross-reactive idiotype found on most anti-GAT antibodies in all mouse strains tested. Both the directly suppressive activity of the GAT-T\textsubscript{s}F and the ability of GAT-T\textsubscript{s}F to induce new suppressor T cells (T\textsubscript{s}) in vitro were adsorbed to and fully recoverable from the guinea pig anti-CGAT-Sepharose immunoadsorbent, while the T\textsubscript{s}F passed through the control NGPS-Sepharose without appreciable binding. The SJL GAT-T\textsubscript{s}F specifically eluted from anti-CGAT-immunoadsorbents was shown to still possess I-J determinants. These data provide evidence suggesting a sharing of V region structures between B-cell antibody and T-cell suppressor factor specific for an antigen (GAT) under Ir gene control, in agreement with earlier studies on T and B-cell alloreceptors, T-cell helper factors, and T and B-cell receptors for conventional antigens.

The authors wish to thank Mr. William Kwoka for his superb technical assistance and Ms. Teresa Greenberg for her help in preparing this manuscript.

Received for publication 15 November 1978.

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