REDUCED IMMUNOGENICITY AND IMPROVED PHARMACOKINETICS OF HUMANIZED ANTI-Tac IN CYNOMOLGUS MONKEYS

JOHN HAKIMI,[1]* RICHARD CHIZZONITE,' DAVID R. LUKE,' PHILIP C. FAMILLETTI,§
PASCAL BAILON,‖ JO A. KONDAS,* ROBERT S. PILSON,* PING LIN,* DAVID V. WEBER,‖
CHERYL SPENCE,‖ LISA J. MONDINI,* WEN-HUI TSIEN,* JAMES L. LEVIN,¶ VON H. GALLATI,**
LAURENCE KORN,++ THOMAS A. WALDMANN,++ CARY QUEEN,++ AND WILLIAM R. BENJAMIN*

From the Departments of *Immunopharmacology, 'Molecular Genetics, 'Drug Metabolism, §Bioprocess Development, and ‖Protein Biochemistry. Roche Research Center, Hoffmann-La Roche, Inc., Nutley, NJ 07110; ¶TSI Mason Research Institute, Worchester, MA 01608; **Central Research, F. Hoffmann-La Roche Ltd., 4002 Basel, Switzerland; ++Protein Design Labs, Inc., Mountain View, CA 94043; ++Metabolism Branch, National Cancer Institute, National Institute of Health, Bethesda, MD 20892

The anti-Tac mAb has been shown to bind to the p55 chain of the IL-2R, block IL-2 binding and inhibit T cell proliferation. A humanized form of anti-Tac (HAT) has been constructed that retains the binding properties of murine anti-Tac (MAT). These two mAb were evaluated in cynomolgus monkeys to compare relative immunogenicity and pharmacokinetic properties. Monkeys treated with HAT daily for 14 days exhibited anti-HAT antibody titers which were 5- to 10-fold lower than their MAT-treated counterparts and these antibodies developed later than in the MAT-treated monkeys. Two of four monkeys receiving a single injection of MAT developed anti-MAT antibodies, whereas none of four monkeys developed antibodies after a single treatment with HAT. In monkeys injected with either HAT or MAT daily for 14 days, the anti-antibody titers induced were inversely related to the amount of anti-Tac administered. Antibodies that developed against MAT were both anti-isotypic and anti-idiotypic, whereas those developed against HAT appeared to be predominantly anti-idiotypic. The pharmacokinetic properties, that is the half-life and area under the curve values, of HAT were also significantly different from those of MAT. The area under the curve values for HAT in naive monkeys were approximately twofold more than those for MAT, and the mean serum half-life of HAT was 214 h, approximately four- to fivefold more than MAT. These pharmacokinetic values were reduced in monkeys previously sensitized with HAT or MAT suggesting that the presence of anti-antibodies altered these parameters.

The cellular receptor for IL-2 plays an important role in regulation of immune function (1). The IL-2R[2] consists of at least two polypeptide chains that can independently bind IL-2: the p55, IL-2R α chain, or Tac peptide (2, 3), and the more recently discovered p75 or IL-2R β chain (4, 5). Study of the p55 peptide was facilitated by the development of a mAb, MAT, which binds to human p55 (2). The Tac peptide is expressed on the surface of Ag- or mitogen-activated T cells but not on resting T cells. Moreover, treatment of human T cells with MAT strongly inhibits their proliferative response to Ag or to IL-2 by preventing binding of IL-2 to p55 (3, 6).

High levels of p55 are expressed on malignant cells of some lymphoid cancers such as adult T cell leukemia, cutaneous T cell lymphoma and Hodgkin's disease (1). Increased or abnormal IL-2R expression is also associated with many autoimmune conditions including rheumatoid arthritis, SLE, organ transplant rejection, and graft-vs-host disease (1). Hence, the IL-2R is a potentially useful and versatile therapeutic target. Agents that specifically eliminate Tac-expressing malignant cells or activated T cells involved in an autoimmune response could be effective against those disorders without harming normal Tac-negative T cells. These agents would potentially be more selective than other immunosuppressants such as antibodies against the CD3 antigenic epitope (i.e., OKT3). In the case of autoimmune conditions, it might in fact only be necessary to suppress T cell proliferation by IL-2R blockade, without destroying the T cells, to achieve therapeutic benefit.

Anti-IL-2R antibodies have been effective in animal models as well as in early human trials. In vivo administration of anti-IL-2R antibodies greatly prolonged survival of heart allografts in mice and rats (7, 8) and alleviated insulitis in nonobese diabetic mice and lupus nephritis in NZB × NZW mice (9). MAT itself was highly effective in prolonging survival of allografts in cynomolgus monkeys (10) with improved efficacy observed with HAT (11). In phase I clinical trials for kidney transplantation, prophylactic administration of MAT significantly reduced the incidence of rejection episodes, without associated toxicity (12). Another anti-IL-2R antibody was also effective in this setting (13). Treatment with MAT induced temporary partial or complete remission in 7 of 20 patients with adult T cell leukemia (14) (T. A. Waldmann, unpublished observations).

Several major problems limit the effectiveness of a

The mouse antibody is immunogenic in humans and provokes a neutralizing antibody response, and may not be as efficient as a human antibody at recruiting human immune effector functions. In addition, mouse antibodies have a much shorter circulating half-life in humans than do natural human antibodies [15].

Problems associated with the therapeutic use of murine antibodies have been partially addressed by the genetic construction of chimeric antibodies, which combine the V region binding domain of a mouse antibody with human antibody C regions [16]. However, because chimeric antibodies retain the whole mouse V region, they may still be immunogenic. Data on the treatment of human patients with chimeric antibodies are only beginning to accumulate [15, 17].

To further reduce the immunogenicity of murine antibodies, Winter and colleagues [18–21] constructed "humanized" antibodies, in which only the minimum necessary parts of the mouse antibody, the CDR, were combined with human V region frameworks and C regions. Based on this approach, we have recently constructed a humanized anti-Tac antibody [22]. The humanized anti-Tac antibody [HAT] retains several key mouse framework residues, predicted by computer modeling, which are required to maintain high affinity binding for p55. In addition, the humanized antibody mediates antibody-dependent cellular cytotoxicity against T cell leukemia cells [23]. Previously, it was demonstrated in cynomolgus monkeys with cardiac allografts that HAT appeared less immunogenic than MAT [11]. In this study, cynomolgus monkeys were given MAT and HAT to further evaluate the relative immunogenicity and pharmacokinetics of the two mAb. To provide a stringent test of HAT, we applied a dosing schedule of frequent injections that would reveal any immunogenicity.

MATERIALS AND METHODS

Cells. MAT was produced in tissue culture as described previously [2]. HAT was produced from SP2/0 cells transfected with the genes encoding for the H and L chains of the humanized antibody [22, 23]. Cells were optimized for antibody secretion by limiting dilution cloning. Production of HAT was performed in a 3-liter continuous perfusion bioreactor (Bellco Biotechnology, Vineland, NJ) equipped with a glass cylinder matrix as previously described [24, 25]. The cells were grown at 37°C in Iscoves's modified Dulbecco's medium (JRH Biosciences, Lenexam, KS) supplemented with 5% FCS (JRH Biosciences), 100 U/ml penicillin G, 100 µg/ml streptomycin, and 25 mM HEPES buffer, pH 6.9 to 7.0. During the production phase of the fermentation, days 9 to 83, the medium flow rate was maintained at 416 ml/h and the conditioned medium contained approximately 8 mg/liter of HAT.

Proteins. HAT and MAT were purified on separate IL-2R affinity chromatography columns with capacities of 125 and 300 mg, respectively [26]. Briefly, purified recombinant sIL-2R [27] was immobilized on NuGel P-AF Poly-N-hydroxysuccinimide (Separation Industries, Metuchin, NJ). Antibodies eluted and concentrated from the receptor column were further purified on two serially linked Sephacryl S-300 columns (60 × 11.3 cm, Pharmacia Fine Chemicals, Piscataway, NJ) in Dulbecco's PBS (Whittaker Bioproducts, Walkersville, MD). All purification steps were carried out at 4°C, and buffers were prepared with ultra pure water (Hydro, Research Triangle Park, NC). The final products were sterilized through a 0.2 µM Corning filter (Corning Glass Works, Corning, NY) and found to contain less than 10 endotoxin units/mg [28]. Purity was determined by SDS-PAGE under reducing and nonreducing conditions and found to be more than 99%.

Anti-HAT and anti-MAT standards were prepared by immunizing goats with the respective proteins in CFA. The goat IgG standards were isolated on protein A-Sepharose CL-4b (Pharmacia) and affinity purified on HAT or MAT AffiGel 10 affinity columns (Bio-Rad, Rich-

obtained from Dr. F. Khan, Bioprocess Development, Hoffmann-La Roche Inc., Nutley, NJ.

HRP-labeled IL-2, HAT and MAT were prepared using a modification of a previously described method [29]. A total of 20 mg of HRP, grade 1 (Boehringer-Mannheim, Indianapolis, IN) in 6 ml of distilled water was activated by adding 1.0 ml of 0.1 M NaIO$_4$ for 20 min at room temperature (20–25°C) and subsequently quenched with 1.0 ml of 0.5 M ethylene glycol. The activated HRP was dialyzed against 5 mM sodium acetate buffer, pH 4.5, and brought up to a final volume of 10 ml. Five mg of protein were dialyzed against 0.1 M NaHCO$_3$, pH 8.0, and added to the activated HRP and diluted with 10 ml of 0.5 M sodium carbonate buffer, pH 9.5. After 2 h at room temperature, 3 ml of 0.1 M NaBH$_4$ were added and incubated in the dark for 4 to 6 h at 4°C. The HRP-conjugated proteins were dialyzed against 0.1 M sodium phosphate buffer, pH 6.5, and then diluted with an equal volume of 0.2 M sodium phosphate buffer, 20 mg/ml BSA, 1 mg/ml Thimersol, and 2 mg/ml phenol.

Monkeys and experimental protocol. Eight groups of four 4 to 6 kg cynomolgus monkeys (two males and two females: Mason Research Institute, Worchester, MA) were treated daily on days 1 through 14 (Table I). Groups 1 and 5 received PBS as a vehicle control. Monkeys in groups 2, 3, and 4 received HAT at doses of 0.05, 0.5, or 5.0 mg/kg, respectively, and groups 6, 7, and 8 received MAT at doses of 0.05, 0.5, or 5.0 mg/kg, respectively. On day 42, groups 1 to 4 and groups 5 to 6 received a single 5 mg/kg dose of HAT or MAT, respectively. Test samples were administered via venous catheters surgically placed in the femoral vein attached to a vascular port. Samples were administered as single bolus injections within several seconds. Blood samples were obtained by venipuncture throughout the 55-day study. Monkeys were tranquilized with intramuscular ketamine HCl before administration of test samples and collection of serum samples.

Immunosorbant assays. To measure the serum levels of monkey antibodies against HAT or MAT, Nunc-Immuno MaxiSorp (Nunc, Naperville, IL) wells were coated with 100 ng of either HAT or MAT in 200 µl of PBS overnight (20–24 h) at 4°C. To each well, 100 µl of 1% fatty acid and globulin-free BSA (Sigma Chemical Co., St. Louis, MO) in PBS were added for 1 h at room temperature, followed by washing with PBS containing 0.05% Tween 20. Wells were incubated with 200 µl of goat standards or test samples, plus 50 µl of HRP-HAT or HRP-MAT at a final dilution of 1/4000 overnight at 4°C. Samples were diluted in 25 mM sodium phosphate, 75 mM NaCl, 0.05% Tween 20, 0.01% BSA, 50 µg/ml phenol red, pH 7.4. The initial concentration of the unknowns in the assay was 1/3 with subsequent threefold dilutions. The plates were washed and then developed with 1 mM 2,2'-azinobis (3-ethylbenzthiazoline-sulfonic acid) (Sigma) in 0.1 M citrate buffer, 0.03% H$_2$O$_2$, pH 4.2, for 30 min. The absorbance at 405 nm was determined with a Vmax Kinetic Microplate reader (Molecular Devices, Menlo Park, CA). The color intensity is directly proportional to the antibody concentration in the serum samples. The relative concentrations of anti-HAT and anti-MAT antibodies in the monkey serum samples were calculated from a goat antibody standard curve titrated on each plate. The values expressed are apparent antibody levels, because the detection of antibodies in this assay is dependent on concentration, affinity, and presence of blocking agents such as anti-Tac and sIL-2R. The assay primarily detects free monkey antibodies; however, some antibody from antibody-anti-Tac complexes would be detected if a reequilibrium of the antibody interactions was established in the wells during the overnight incubation.

Serum concentrations of HAT and MAT were determined in an IL-2 immunosorbant receptor assay [27]. Plates were coated with 16 ng of sIL-2R in 200 µl of PBS overnight at 4°C and then blocked with 1% BSA as described above. Wells were washed and incubated with 200 µl of sample overnight at 4°C. Typically, the initial serum in the assay was diluted 1/10 with subsequent 1/2 dilutions. The initial sample concentration varied depending on which treatment group

TABLE I
Immunogenicity study treatment groups

Group	Daily Dose Days 1 to 14	Challenge Dose Day 42	Response
1	Vehicle control	HAT, 5 mg/kg	None
2	HAT, 0.05 mg/kg	HAT, 5 mg/kg	None
3	HAT, 0.5 mg/kg	HAT, 5 mg/kg	None
4	HAT, 5.0 mg/kg	HAT, 5 mg/kg	Anaphylaxis 1/4
5	Vehicle control	MAT, 5 mg/kg	None
6	MAT, 0.05 mg/kg	MAT, 5 mg/kg	Anaphylaxis 4/4
7	MAT, 0.5 mg/kg	None[a]	
8	MAT, 5.0 mg/kg	None[a]	

was studied. Without washing the samples from the wells. 50 μl of HRP-IL-2 was added to a final dilution of 1/2000. After 3 h at room temperature. wells were washed and developed as described above. The color intensity is inversely proportional to the anti-Tac concentration in the samples. HAT and MAT concentrations in the serum were calculated from a standard curve of purified HAT and MAT titrated on each plate. In this assay. only the anti-Tac available to bind to the sIL-2R would be detected. As discussed above for the immunogenicity ELISA. a new equilibrium of the antibody complexes in the serum could occur in the wells during the 24 h incubation.

Pharmacokinetics. The AUC and $t_{1/2}$ values for HAT and MAT were estimated to reflect the total body burden of the antibody within the intravascular pool as well as the serum die-away curve, respectively. Serum concentrations of the antibodies were plotted vs time on a log-linear graph and the AUC values were calculated by trapezoidal rule (30). The apparent elimination $t_{1/2}$ from a single dosing was estimated by linear regression analysis of the terminal portion of the curve from a minimum of four data points.

For multiple dose pharmacokinetics. the maximum serum concentrations and time to reach maximum serum concentrations were obtained visually from the serum concentration-time graphs. The apparent $t_{1/2}$ after multiple dosing was approximated from a minimum of three serum concentration-time points obtained after the final dose.

RESULTS

Study design and clinical observations. A cynomolgus monkey study was designed to evaluate the relative immunogenicity and pharmacokinetic properties of MAT and HAT. A schematic representation of the study design is shown in Figure 1 and details of the treatment groups are described in Table I. During the study. the monkeys remained behaviorally and clinically normal with the following exceptions. On day 42 one female monkey in group 4 exhibited an apparent anaphylactic response posttreatment with 5 mg/kg of HAT. This monkey was treated with epinephrine. dexamethasone. Benadryl. and was hydrated with saline. The monkey gradually improved and by day 44 appeared normal. All four monkeys in group 6 that received 0.05 mg/kg/day MAT initially. also exhibited an apparent anaphylactic response posttreatment with 5 mg/kg MAT. The monkeys responded to epinephrine and fluids. The animals in the MAT treatment groups 7 and 8 were not challenged on day 42. In various ELISA systems. no increase in total monkey IgE was observed, nor was the presence of Ag-specific antianti-Tac IgE detected (data not shown). The cause of this anaphylactic response remains unknown.

Immunogenicity characterization. Monkey antiglobulin levels (i.e., antibodies to HAT and MAT) were evaluated in an Ag-bridging ELISA. which can be used to detect antibodies of various species and isotypes using the same reagents. Affinity-purified goat anti-HAT and goat anti-MAT antibody standards were similarly detected in the range of 100 to 1000 ng/ml in their respective assays (data not shown).

The time-dependent development of antibodies in individual monkeys is shown for MAT in Figure 2 and for
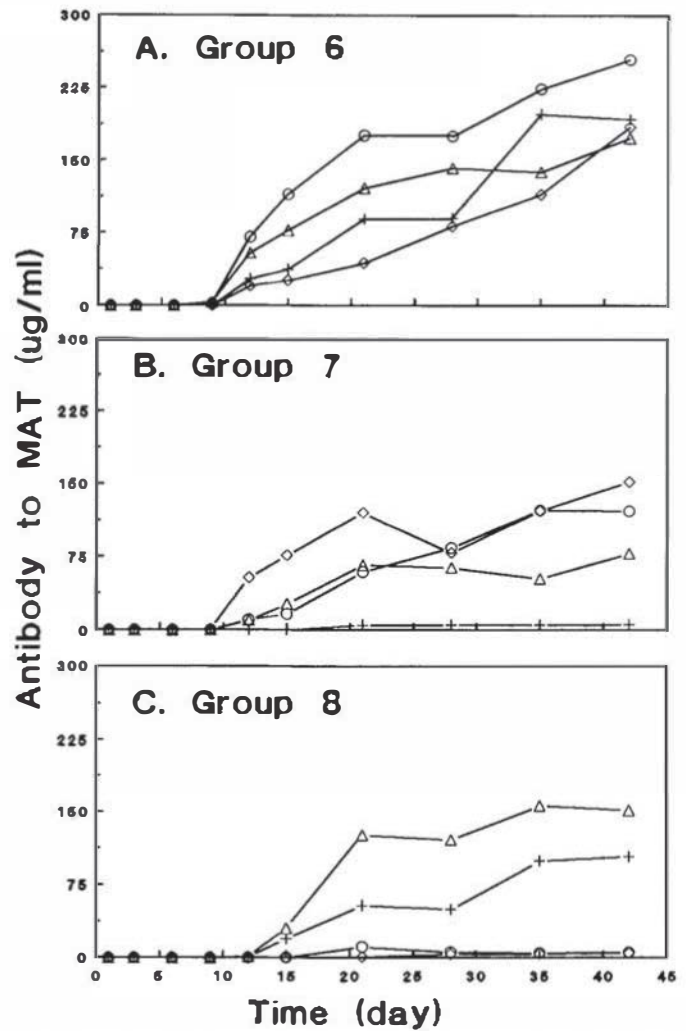
Figure 1. immunogenicity and pharmacokinetic study design for eval-

Figure 2. Time-dependent development of anti-MAT antibodies in individual monkeys administered A. 0.05. B. 0.50. C. 5.0 mg/kg/day MAT for 14 days. Anti-MAT concentrations were determined in an ELISA using an affinity purified goat anti-MAT antibody as a standard.

HAT in Figure 3 (note differences in the ordinate scales). Prebleed sera from all 32 monkeys and sera from day 0 to 42 from control monkeys in groups 1 and 5 showed no activity in the ELISA. In the MAT-treated groups. 9 of 12 monkeys developed antibodies during the initial 14 day treatment period. usually by day 12. In contrast. antiHAT antibodies in all but one of the 12 HAT-treated monkeys were not detected until at least 5 to 10 days after the final dose of HAT was administered. In addition. the HAT-treated monkeys showed dramatically lower serum antiglobulin concentrations than the MAT-treated groups.

The antibody titer developed to HAT as well as MAT was in general inversely related to the protein dose administered. In group 4 which was treated with 5 mg/kg/day HAT. only one monkey had detectable antibodies by day 42. This was the only HAT-treated monkey that exhibited an anaphylactic response upon challenge with HAT on day 42 (Table I). even though monkeys from other groups had apparently higher serum antibody levels on day 42. All monkeys in group 6 that received 0.05 mg/kg/day MAT exhibited an anaphylactic response upon rechallenge on day 42. Monkeys in groups 7 and 8
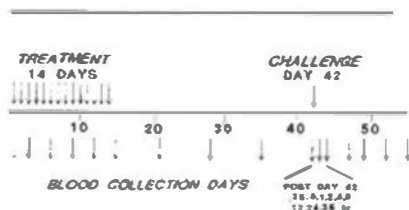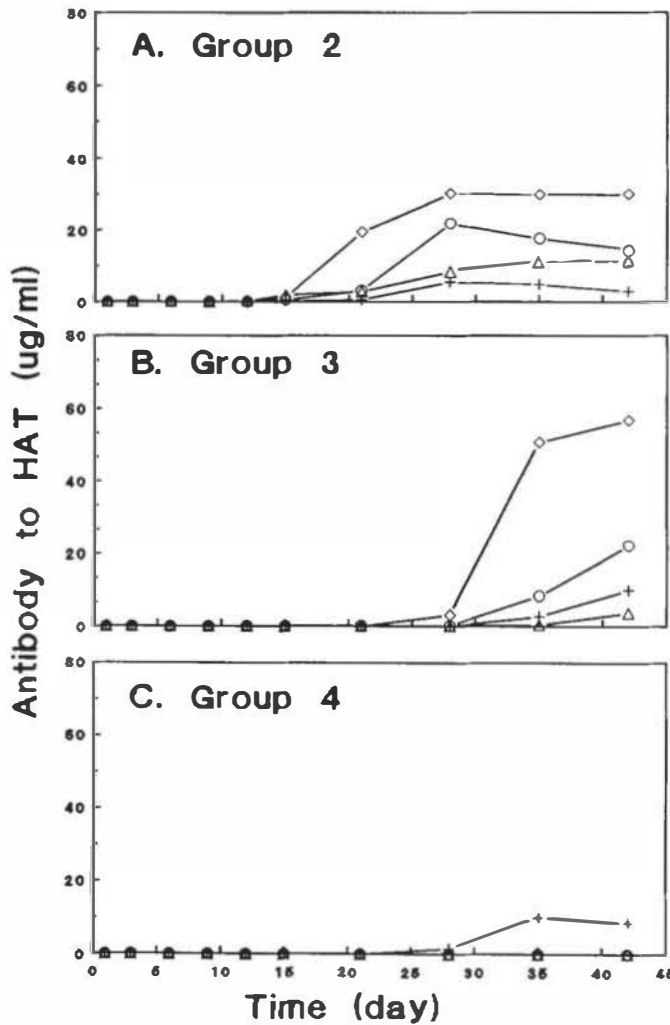
Figure 4. Primary and secondary immune responses to HAT and MAT. Anti-HAT (O) and anti-MAT (Δ) antibody concentrations from individual monkeys on day 42 before high-dose challenge and on day 55. Data in *A* represents the anti-MAT response on day 55 in two naive monkeys from group 5. No anti-HAT antibodies developed in any monkeys from group 1. Before challenge animals received multiple doses of *B.* 0.05, *C.* 0.50, *D.* 5.0 mg/kg/day of anti-Tac antibody for 14 days. Monkeys dosed with MAT in *C* and *D* were not rechallenged with MAT on day 42 (data not shown).

Figure 3. Time-dependent development of anti-HAT antibodies in individual monkeys administered *A.* 0.05, *B.* 0.50, *C.* 5.0 mg/kg/day HAT for 14 days. Anti-HAT concentrations were determined in an ELISA using an affinity purified goat anti-HAT antibody as a standard.

Figure 5. Characterization of anti-HAT and anti-MAT responses in monkeys on day 35. *A* shows the anti-MAT from a monkey in group 6 and *B* shows the anti-HAT response from a monkey in group 2. A fixed amount of antiserum was incubated in the presence of various concentrations of HAT (◊), MAT (Δ), sIL-2R (O), human IgG (∇), or mouse IgG (☐). These data are representative of the data obtained from all of the monkeys with antiglobulin antibodies on day 35.

with MAT developed an anaphylactic response at a dose 100-fold lower than the individual high dose HAT-treated monkey.

A comparison of day 42 (prechallenge) and day 55 serum antiglobulin levels from all challenged monkeys in groups 1 to 6 is shown in Figure 4. A primary immune response to the single treatment with MAT was observed in two naive monkeys in group 5, although the same treatment with HAT to group 1 monkeys resulted in no antibodies (Fig. 4A). A secondary immune response was observed in all animals previously treated with antibody. No secondary response was observed in groups 7 and 8, because they were not challenged. The greatest secondary responses were observed in the monkeys receiving either 0.05 mg/kg MAT or HAT (Fig. 4B).

The specificity (i.e., anti-Id or anti-isotype) of the anti-HAT and anti-MAT responses was determined in a competitive ELISA assay (Fig. 5). Inhibition of antibody binding in the ELISA by HAT, MAT, as well as sIL-2R indicates the presence of anti-CDR or anti-idiotypic antibodies, because these proteins specifically compete for or block recognition of the CDR regions of anti-Tac. Competition by irrelevant human and mouse IgG proteins
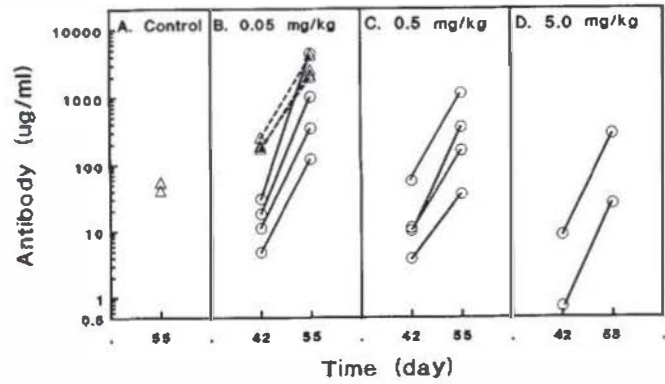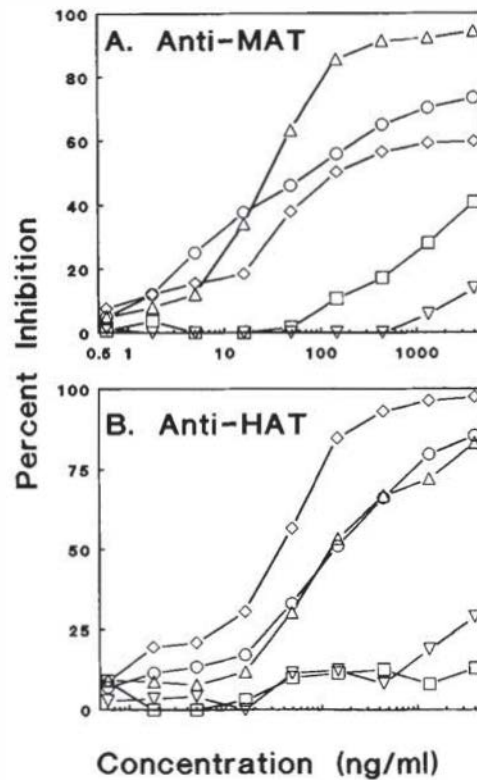
goat anti-HAT and anti-MAT antibodies were partially inhibited by all of the competitors (data not shown), indicating that HAT and MAT administered to goats induced both an anti-idiotypic and anti-isotypic response.

Serum from all MAT-treated monkeys was completely inhibited with excess MAT, demonstrating that the ELISA assay is specific for MAT (Fig. 5A). HAT and sIL-2R were the next most effective inhibitors followed by mouse IgG. Thus, the monkey response to MAT was a

similar to the goat anti-MAT and anti-HAT responses. Complete inhibition of monkey anti-HAT antibodies was achieved with HAT, again demonstrating assay specificity (Fig. 5B). Human and mouse IgG had little effect indicating that the anti-HAT response in monkeys is not an anti-isotypic response. MAT and sIL-2R were almost as effective as HAT in inhibiting anti-HAT binding. Thus, the monkey anti-HAT antibodies are directed toward determinants shared by MAT and HAT, and blocked by sIL-2R, i.e., toward the CDR regions. This supports our conclusion that the anti-HAT response is anti-idiotypic in monkeys.

Pharmacokinetic characterization. The pharmacokinetic characteristics of HAT and MAT were determined in a competitive immunosorbant receptor assay. In this assay, both proteins inhibited IL-2 binding within twofold of each other. The detection limit was in the range of 125 to 500 ng/ml. Serum concentrations of HAT and MAT were measurable only in monkeys receiving doses of 0.5 and 5 mg/kg/day of antibody (Figs. 6 and 7, respectively, note the differences of the ordinate scales). In general, HAT concentrations were increased over the dosing period, suggesting that equilibrium was not achieved with receptor sites or the extravascular space. The mean maximum concentrations after dosing with 0.5 and 5 mg/kg/day of HAT for 14 days were 57 ± 20 (mean $\pm$ SD) and 726 ± 115 μg/ml, respectively. In contrast, maximum concentrations of 0.5 and 5.0 mg/kg/day of MAT were 26 ± 9 and 311 ± 57 μg/ml, respectively, but occurring at approximately 7 to 9 days after the initiation of therapy. The mean time course of decline or $t_{1/2}$ values of HAT from the serum after 14 days of dosing were highly
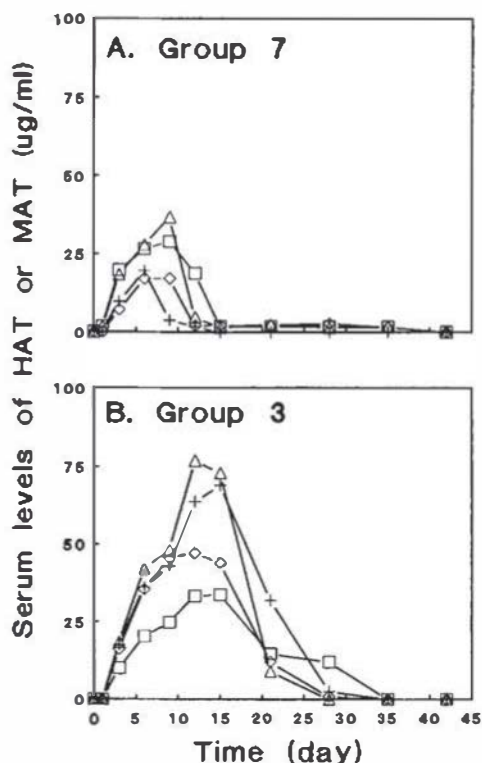

Figure 6. Serum concentration profile of A, MAT or B, HAT in individual monkeys receiving 0.50 mg/kg/day of antibodies for 14 days. Anti-MAT and anti-HAT concentrations were determined in a competitive IL-
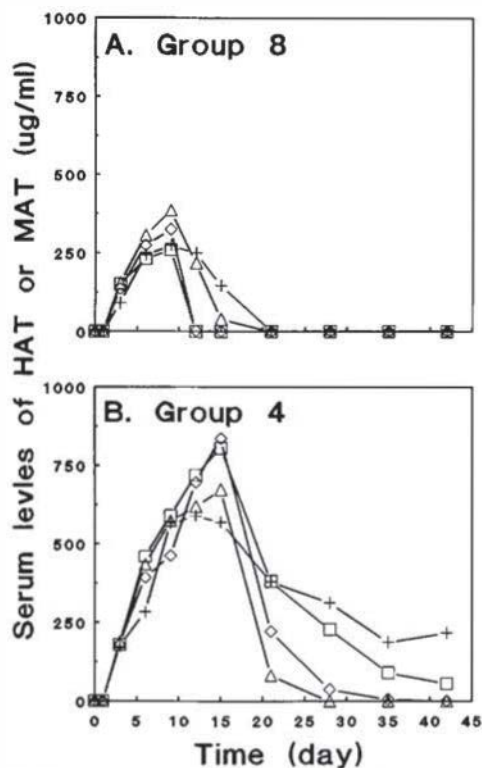

Figure 7. Serum concentration profile of A, MAT or B, HAT in individual monkeys receiving 5.0 mg/kg/day of antibodies for 14 days. See Figure 6 for additional details.

variable, ranging from approximately 47 to 432 h, and independent of dose. The $t_{1/2}$ of MAT was not calculated due to the rapid decline of serum concentrations even during the 14-day dosing regimen.

In control naive animals, the serum concentration-time profiles of HAT were significantly different from the profiles with MAT (Table II). The individual AUC and $t_{1/2}$ values after a single i.v. dose of 5 mg/kg of HAT or MAT to control monkeys in groups 1 and 5, respectively, on day 42 are shown in Table II. The mean AUC was approximately twofold more in the HAT-treated control monkeys when compared to the MAT-treated control counterparts, $26,657 \pm 6237$ vs $11,442 \pm 3563$ μg·h/ml, respectively. A four- to fivefold difference was observed in the mean $t_{1/2}$ values between HAT and MAT (213.6 ± 58.8 and 47.8 ± 9.04 h, respectively) (Fig. 8).

The pharmacokinetic profiles in the multiple-dosed groups were significantly altered. Only four MAT-treated monkeys were rechallenged on day 42 due to the observed anaphylactic response. Three of the monkeys had no detectable serum MAT levels, whereas in the fourth monkey, levels were detectable but not within the quantitation limits of our assay governed by the standard curve (data not shown). Clearly, the elimination of MAT from group 6 animals that were treated with 0.05 mg/kg/day MAT was significantly enhanced compared to group 5 animals that had not received MAT previously. Kinetic parameters of all but two of the HAT-treated monkeys in groups 2 to 4 were estimated (Table II). The AUC values in groups 2 and 3 were lower than those in naive animals (group 1). In animals treated with 5 mg/kg/day (group 4), the $t_{1/2}$ and AUC values were higher than the values obtained for group 2 and 3 monkeys. One monkey in

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