Human Lymphokine Activated Killer (LAK) Cells Suppress Generation of Allospecific Cytotoxic T Cells: Implications for Use of LAK Cells To Prevent Graft-Versus-Host Disease in Allogeneic Bone Marrow Transplantation

By Joseph Uberti, Frank Martilotti, Ta-Hsu Chou, and Joseph Kaplan

We have found that murine lymphokine activated killer (LAK) cells have potent veto and natural suppressor activities in vitro, and prevent graft-versus-host disease (GVHD) in vivo. To determine whether human LAK cells mediate veto and natural suppression we measured their ability to inhibit generation of allospecific cytotoxic T cells (CTL) in mixed lymphocyte culture (MLC). When added to MLCs at low concentrations LAK cells caused veto-type inhibition: stimulator-type LAK cells inhibited generation of CTL but responder or third-party LAK cells did not. At higher concentrations LAK cells caused nonspecific inhibition: all three LAK cell types inhibited generation of CTL. LAK cell veto and natural suppressor activities were largely eliminated by irradiation with 30 Gy and by depletion of CD56+ cells, but increased after depletion of CD3+ cells. LAK cell veto activity is not likely an artifact of cold-target inhibition by the LAK cells themselves or by proliferation of T cells contaminating LAK cell preparations: (1) veto only occurred when LAK cells were added to MLC on days 0 through 2, but not when added on day 5; (2) addition of saturating numbers of labeled targets to fixed numbers of allo-CTL effectors failed to overcome the inhibitory effects of adding stimulator-type LAK cells at the onset of MLC; and (3) CD3-depleted LAK cells showed greater veto activity than threefold greater numbers of control LAK cells. In light of our previous findings in mice, the current results imply that adoptive immunotherapy with LAK cells may be useful in preventing GVHD in human bone marrow transplant recipients.

Preparation of LAK cells. PBMC were cultured for 4 days in T-25 tissue culture flasks at 1 × 10^6 cells/mL in complete medium (RPMI-1640 with 4 mmol/L L-glutamine, 5 mmol/L HEPES, 5 × 10^{-3} mmol/L 2-mercaptoethanol, Pen/Strep, and 10% human AB serum) together with 1,500 U/mL IL-2 (Cetus Corp, Emeryville, CA).

LAK assay. The Daudi cell line used as target cells for the LAK assays was maintained in suspension culture in RPMI-1640 with 10% fetal bovine serum. Two to four million target cells were labeled with 200 μCi of Na2CrO4, 51Cr for 90 minutes at 37°C. After two washes the labeled cells were brought to 5 × 10^6 cells/mL and distributed in 0.1 mL aliquots to 96-well round-bottom microculture plates containing in triplicate 0.1 mL of various dilutions of PBMC effector cells such that the final effector to target (E:T) ratios were 40:1, 20:1, 10:1, and 5:1. Plates were then centrifuged at 40g for 5 minutes and incubated for 4 hours at 37°C. At the end of incubation the plates were centrifuged at 40g for 5 minutes and aliquots of the supernates were collected and counted in a gamma counter. Spontaneous release was determined from the cpm of supernates of target cells incubated alone without added effector cells. Total counts per minute (cpm) incorporated was determined from the cpm of known numbers of labeled target cells. Percent spontaneous release (spontaneous cpm/total cpm) was less than 20% in all instances. Percent specific lysis was calculated by the formula:

\[
\text{% Specific Lysis} = 100 \times \frac{(E - S)}{(T - S)}
\]

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Materials and Methods

Isolation of peripheral blood lymphocytes. Peripheral blood mononuclear cells (PBMC) were obtained by Ficoll-Hypaque (Pharmacia, Piscataway, NJ) separation from heparinized blood of healthy adult donors.

where E is experimental cpm, S is spontaneous cpm, and T is total cpm incorporated. As previously described, an exponential fit equation was applied to this data using a computer program for least squares parameter estimation to calcuate lytic units (LU)/10⁷ effector cells where 1 LU is the number of effector cells required to lyse 20% of 5 x 10⁷ target cells.

Cell marker analysis. LAK cells were stained with a mixture of fluorescein isothiocyanate (FITC)-conjugated anti-CD3 (Beckton-Dickinson San Jose, CA) and phycoerythrin (PE)-conjugated anti-CD56 (NKH-1, Coulter, Hialeah, FL). Control cells were stained with FITC-IgG and PE-IgG to provide an estimate of nonspecific labeling. After correcting for nonspecific staining, the percentage of cells staining positively for one or both markers was determined by flow microfluorometry using a Coulter EPICS C flow cytometer (Coulter, Hialeah, FL) gated on lymphocytes by 90° and forward angle light scatter.

Generation of allospecific cytotoxic lymphocytes. Mixed lymphocyte cultures were performed by culturing 2 million responder PBMC and 2 million 30-Gy irradiated stimulator PBMC in 2 mL complete medium for 6 days in the presence or absence of various numbers of added LAK cells. The cells were then harvested, washed twice, and tested for cytotoxicity against stimulator or responder-type target cells (3-day PHA-stimulated lymphocytes) in a 4-hour chromium release assay identical to that described previously.

Suppression assays. LAK cells were tested for specific and nonspecific suppression of generation of allo-CTL by adding stimulator-type, responder-type, and/or third-party-type LAK cells to MLC and then testing each MLC for allo-CTL against stimulator-type targets. The relative level of allospecific cytotoxicity generated in each MLC culture was calculated as follows:

\[
\text{Relative Cytotoxicity} = \frac{100 \times (\text{LU}/10^7 \text{Added LAK Cells})}{\text{LU}/10^7 \text{Cells Without Added LAK Cells}}
\]

Kinetic analysis. In experiments designed to determine whether competitive or noncompetitive inhibition accounted for any observed suppression of generation of allo-CTL mediated by added responder-type LAK cells, tests for allospecific cytotoxicity were performed using an approach similar to that described by Callewaert et al. Based on the model of enzyme kinetics. According to this approach, use of saturating concentrations of labeled targets should overcome competitive or cold-target inhibition but not noncompetitive inhibition. ABx MLCs were performed as described previously in the absence or presence of stimulator-type "B" LAK cells at a ratio of 1 LAK cell:4 responder cells. At the end of 6 days of culture the MLCs were harvested and tested for allo-CTL using a fixed number of effector cells/well (5 x 10⁴) and increasing concentrations of chromium-51 labeled "B" targets ranging from 2.5 x 10⁴ to 3 x 10⁵/well. In addition, ABx MLC effectors cells were analyzed in this fashion in the absence or presence of a fixed number (5 x 10⁴) of unlabeled B targets to verify that cold target inhibition could in fact be overcome by saturating concentrations of labeled targets. Supernatants were collected and counted after 2 or 4 hours incubation. Velocity (v), the number of target cells lysed per hour, was calculated by the following formula: \( v = \frac{(E - S)(M - S)}{(E - S)(M - S) + (T - S)} \). Experimental (E), spontaneous release (S), and maximal release (M) cpm values were obtained in triplicate assays at each target cell concentration (T) and at each interval of time (t). The percent of inhibition was calculated as 100 x (1 - v experimental/v control ABx).

Complement lysis depletion. LAK cells, 5 x 10⁶ cells in 0.5 mL, were incubated with 25 µg monoclonal anti-CD3 (OKT3; Coulter), 15 µg monoclonal anti-CD5 (OKT5; Ortho Diagnostics, Raritan, NJ), or medium alone for 30 minutes at 37°C. After one wash 0.3 mL of a 1:4 dilution of rabbit complement (Accurate Chemical & Scientific Corp, Westbury, NY) was added and the cells further incubated for 60 minutes at 37°C in 5% CO₂. Cells were then washed three times in medium. By flow cytometric analysis cells remaining after complement lysis with anti-CD5 or anti-CD3 contained less than 5% CD56⁺ or CD3⁺ cells, respectively. Because these experiments were designed to give a quantitative estimate of the relative contribution of antibody-positive cells to the observed LAK effects we did not correct for cell losses after treatment. This approach avoids a potential artifact encountered when one corrects for cell losses by cell reconstitution, ie, artificial enrichment of any antibody-negative cells that might mediate the same effects as antibody-positive cells. Thus, after cell counts, each of the LAK cell suspensions was resuspended to the same volume, and equal volumes were then added to labeled Daudi target cells in tests for LAK activity, and to MLCs in tests of veto and natural suppressor activity.

Statistical analysis. Statistical tests were performed using Statview II software (Abacus Concepts, Berkely, CA). Levels of allospecific cytotoxicity generated by different MLCs were compared by the Mann-Whitney U test. Relative cytotoxicity values were compared by ANOVA using the Scheffe F test. One-sample and two-sample paired t-tests were used to assess the effects of complement lysis-depletion of CD3⁺ and CD56⁺ cells on LAK activity. In all cases significance levels were set at .05.

RESULTS

Human LAK cells exhibit both veto and natural suppressor activities. To determine whether human LAK cells, like murine LAK cells, exhibit veto and/or natural suppressor activity, several different approaches were taken. In the first approach, increasing doses of LAK cells from donor "B" were added on day 0 to ABx MLCs containing responder cells from subject "A," and irradiated fresh stimulator cells from LAK donor "B" and an unrelated subject "C." MLCs were harvested on day 6 and tested for specific cytotoxicity against stimulator-type PHA blasts. The results of a single experiment are shown in Fig 1. (Similar results were obtained in three additional experiments.) They show that LAK cells are highly efficient inhibitors of generation of allo-CTL directed against their own MHC antigens, and at lower efficiency also inhibit generation of allo-CTL directed against unrelated MHC antigens. At the LAK cell:MLC responder cell ratio of 1:8 added "B" LAK cells significantly inhibited by 67% the generation of allo-CTL by "A" responder cells directed against homologous "B" targets (P = .02), but failed to significantly inhibit the generation of allo-CTL by "A" responder cells against unrelated third-party "C" targets (P = .11). At higher LAK cell:MLC responder cell ratios of 1:2, and 1:1, added "B" LAK cells caused significant inhibition of the reaction against both homologous "B" targets and allogeneic "C" targets (P = .04). However, even at this higher concentration, added "B" LAK cells inhibited the reaction against homologous B targets significantly more than they inhibited the reaction against third-party C targets (P = .02).

These results implied that LAK cell veto-type "self-specific" inhibition is more efficient than LAK cell nonspe-
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Fig 1. Dose-response comparison of the ability of human LAK cells to inhibit generation of allospecific CTL against (1) homologous target cells and (2) target cells from an unrelated donor. Increasing numbers of LAK cells from donor “B” were added on day 0 to an A(Bx + Cx) MLC containing responder cells from subject “A” and irradiated fresh stimulator cells from LAK donor “B” and unrelated subject “C.” Cultures were harvested on day 6 and tested for specific cytotoxicity against stimulator-type PHA blasts. Control MLC without added LAK cells generated 21.2 and 10.6 LU/10^7 cells against B and C targets, respectively. ( ), Anti-B; ( ), Anti-C.

Fig 2. Crisscross comparison of ability of LAK cells to specifically and nonspecifically inhibit generation of allo-CTL. Identical numbers of LAK cells from donors “B” or “C” were added on day 0 to an A(Bx + Cx) MLC containing responder cells from subject “A” and irradiated fresh stimulator cells from LAK donors “B” and “C.” The ratio of added LAK cells to “A” responder cells was 1:2. Cultures were harvested on day 6 and tested for specific cytotoxicity against stimulator-type PHA blasts. Control MLC without added LAK cells generated 13.4 and 11.8 LU/10^7 cells against B and C targets, respectively. LAK cells added to A(Bx + Cx) MLC: ( ), B LAK cells; ( ), C LAK cells.

Table 1 provides a summary of the results of eight experiments comparing the effects of responder-type, stimulator-type, or third-party-type LAK cells on MLC generation of anti-B CTL, although, as shown previously, responder-type A LAK cells were less inhibitory than stimulator-type B LAK cells. These results confirm that in addition to their veto-type inhibitory activity LAK cells also exhibit natural suppressor-type nonspecific inhibitory activity.

In the experiments shown above in Figs 1 and 2, subjects B and C, although unrelated, may have shared one or more HLA antigens. Therefore, some of the observed inhibition by B LAK cells of MLC-induced anti-C allo-CTL could have been due to veto-type inhibition rather than nonspecific inhibition. To provide an unequivocal measure of nonspecific inhibition we tested the ability of LAK cells generated from the responder “A” or the stimulator “B” to inhibit generation of anti-B allo-CTL (P = .02) but not generation of anti-C allo-CTL, whereas the opposite was true of “C” LAK cells.

In the experiments shown above in Figs 1 and 2, subjects B and C, although unrelated, may have shared one or more HLA antigens. Therefore, some of the observed inhibition by B LAK cells of MLC-induced anti-C allo-CTL could have been due to veto-type inhibition rather than nonspecific inhibition. To provide an unequivocal measure of nonspecific inhibition we tested the ability of LAK cells generated from the responder “A” or the stimulator “B” to inhibit generation of anti-B allo-CTL. As shown in Fig 3, at the LAK cell:MLC responder cell ratio of 1:2 only stimulator-type B LAK cells inhibited generation of cytotoxicity for B-target cells. However, at the LAK cell:MLC responder cell ratio of 1:1 both stimulator-type B LAK cells and responder-type A LAK cells inhibited generation of anti-B CTL, although, as shown previously, responder-type A LAK cells were less inhibitory than stimulator-type B LAK cells. These results confirm that in addition to their veto-type inhibitory activity LAK cells also exhibit natural suppressor-type nonspecific inhibitory activity.

Table 1 provides a summary of the results of eight experiments comparing the effects of responder-type, stimulator-type, or third-party-type LAK cells on MLC genera-
tion of allo-CTL. On average, all three types of LAK cells significantly inhibited generation of allo-CTL when added at 1 LAK cell:2 MLC responder cells. However, addition to MLC of stimulator-type LAK cells was significantly more inhibitory than addition of similar numbers of either responder-type or third-party LAK cells (P = .008).

**Veto-type LAK cell inhibition affects an early event in MLC-generation of allo-CTL.** As shown in Fig 4, although stimulator-type LAK cells specifically inhibited generation of allo-CTL against homologous targets when added to MLC on day 0 or day 2 (P = .03), they did not inhibit when added on day 5, 1 day before harvesting and testing the MLC for allo-cytotoxicity. These results indicate that LAK cell veto-type inhibition affects an early event in the MLC-induced generation of allo-CTL. They also provide evidence against the possibility that cold-target inhibition accounts for the observed veto-type inhibition by stimulator-type LAK cells added on days 0 through 2 to MLC.

**Radiation sensitivity of LAK suppressor activity.** As shown in Fig 5, the ability of both stimulator-type and responder-type LAK cells to inhibit MLC-generated CTL was eliminated by exposure to 30-Gy irradiation, a dose that failed to affect LAK cytolytic activity against Daudi target cells (data not shown).

<table>
<thead>
<tr>
<th>LAK Cells Added To MLC</th>
<th>Relative Cytotoxicity (mean ± SD)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulator type</td>
<td>14 ± 16</td>
<td>.0001</td>
</tr>
<tr>
<td>Responder type</td>
<td>56 ± 26</td>
<td>.0091</td>
</tr>
<tr>
<td>Third-party type</td>
<td>46 ± 26</td>
<td>.0263</td>
</tr>
</tbody>
</table>

*One sample t-test comparing relative cytotoxicity with added LAK cells to 100% control value.

**II-2–stimulated PBMC that mediate veto and natural suppression express the CD3+CD56+ LAK cell phenotype.** Results of flow cytometric analysis of cell surface markers showed, as expected, that most of the cells in 4-day LAK cell cultures expressed the CD3+CD56+ T-cell phenotype (range = 60% to 75%), a smaller population expressed the CD3+CD56+ NK cell phenotype (range = 10% to 25%), and a very small population expressed the CD3+CD56+ phenotype of “non–MHC-restricted cytotoxic T cells” (range = 0% to 5%). The results of analysis of a representative LAK cell preparation are shown in Fig 6.

To determine the phenotype of the cells responsible for the veto and natural suppressor activities of human LAK cell cultures we tested them for LAK cytotoxicity and suppressor activity after complement-lysis depletion of either CD3+ or CD56+ cells. To avoid artificial enrichment of antibody-nonreactive cells, no correction was made for cell losses after antibody treatments. The results of a representative experiment testing the effect of depleting LAK cell suspensions of CD56+ cells are shown in Fig 7. In keeping with the findings reported previously that 10% to 25% of cells in a 4-day LAK cell culture are CD56+, LAK cell suspensions “A” and “B” treated with anti-CD56+C contained 18% and 13% fewer cells, respectively, than identical LAK cell suspensions treated with C alone. As expected from the fact that LAK activity is mediated by CD56+ cells,2 the CD56-depleted LAK cell suspensions “A” and “B” exhibited 74% and 91% less LAK activity, respectively (P = .02), than control LAK cells (Fig 7A). The effect of antibody-depletion on the veto and natural suppressor activities of these cells is shown in Fig 7B. Control “A” and “B” LAK cells treated with C alone both inhibited ABx MLC-induced anti-B allo-CTL, but “B” LAK cells, as expected, inhibited more efficiently than “A” LAK cells. In parallel with the reduction in their LAK
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activity, the nonspecific and specific inhibitory activities of "A" and "B" LAK cells were reduced by 100% and 80%, respectively, after depletion of CD56⁺ cells.

In contrast to the effects of removing CD56⁺ cells from LAK cell suspensions, depletion of CD3⁺ cells resulted in a greater loss in cell number, only a minimal loss of LAK activity, and an enhancement of both specific and nonspecific inhibitory activity when added to MLCs. In the experiment shown in Fig 8, following treatment with anti-CD3 + C "B" LAK cells showed a 64% reduction in cell yield compared to the control "B" LAK cell suspension treated with C alone. However, they showed only an insignificant loss of LAK activity (P = .09) compared to control LAK cells treated with C alone (Fig 8A). Moreover, when tested for suppressor activity (Fig 8B), the CD3-depleted LAK cells showed a somewhat enhanced veto-type inhibition of generation of allo-CTL by "B" responders against "B" targets, and markedly increased nonspecific inhibition of generation of allo-CTL by "B" responders against "A" targets. We have observed (unpublished data, 1991) that anti-CD3 by itself can inhibit MLC-induced generation of allo-CTL at a concentration of 1 ng/mL but not at a concentration 100 pg/mL. Therefore, it is important to note that any possible contribution of anti-CD3 to inhibition of generation of allo-CTL, care was taken in this experiment to wash the LAK cells sufficiently to reduce any anti-CD3 carried over with the treated LAK cells into the MLC to less than 2 pg/mL.

LAK cells cause noncompetitive rather than competitive inhibition of allo-cytotoxicity generated in MLC. To further determine whether cold-target inhibition accounts for LAK cell-mediated veto-type inhibition we applied a previously described model for analysis of cell-mediated cytotoxicity that is based on the classical analysis of enzyme kinetics. In this model timed cytotoxicity assays are performed using fixed concentrations of effector cells and varying concentrations of labeled target cells. This analysis requires that a maximal rate of cytotoxicity, Vmax, is achieved by using increasing numbers of labeled target cells that eventually saturate the relatively small number of cytotoxic lymphocytes. By analogy to classical studies of enzyme inhibitors, this approach yields information regarding the mechanism of LAK cell inhibition of allo-cytotoxicity. Thus, in simple terms, if addition of LAK cells to MLC causes cold-target
targets that was similar to that achieved in their absence. This shows that cold-target inhibition can in fact be overcome by saturating levels of homologous labeled targets. By contrast, effector cells derived from the MLCs to which “B” LAK cells were added at culture initiation exhibited impaired velocities of cytotoxicity even when twice the saturating number of labeled targets were added. As shown another way in Fig 9B, the fixed number of unlabeled targets inhibited the velocity of cytotoxicity by roughly 60% at the lowest number of labeled homologous targets, but as the labeled target cells increased to the saturating numbers equal to 1.5 times the number of unlabeled target cells, this inhibitory effect was completely overcome. By contrast, the inhibition of cytotoxicity medi-
ated by addition of LAK cells at onset of MLC was not overcome even when the numbers of labeled targets were equivalent to 48 times the numbers of added LAK cells.

**DISCUSSION**

The findings presented here indicate that human LAK cells, like murine LAK cells, exhibit both veto and natural suppressor activities. The presence in MLCs of low concentrations of LAK cells selectively inhibited the generation of allo-CTL against homologous targets but did not inhibit generation of allo-CTL against unrelated allogeneic targets. This specific inhibition of reactivity against “self” but not “non-self” antigens is characteristic of veto. Higher concentrations of LAK cells in MLCs caused nonspecific inhibition of generation of allo-CTL against allogeneic targets from donors unrelated to the LAK cell donor, albeit not to the same extent as the inhibition observed for the generation of allo-CTL against targets homologous to the LAK cells. This nonspecific inhibition of alloreactivity is characteristic of natural suppression.

Veto-type inhibition mediated by human LAK cells is not an artifact of cold-target inhibition mediated by added LAK cells themselves, or by T cells contaminating stimulator-type LAK cells that might proliferate in response to the alloantigen stimulation by the responder lymphocytes in the MLC preparations. Rather, it appears to be an active process mediated by proliferating LAK cells that inhibit a relatively early event in the generation of allospecific CTL. This conclusion derives from the following lines of evidence: (1) Specific veto-type inhibition occurred when stimulator-type LAK cells were added to MLC on days 0 through 2 of culture but not when added on day 5, one day before testing the MLC for cytotoxicity against stimulator-type target cells. If the stimulator-type LAK cells themselves cause cold-target inhibition one would expect such cold-target inhibition to occur when LAK cells are added at day 5 as well as when added at days 0 through 2. (2) Kinetic analysis showed that LAK cells added at onset of MLC noncompetitively rather than competitively inhibited allocytotoxicity generated in the MLC. Addition of saturating numbers of labeled targets to fixed numbers of MLC effectors overcame inhibition by unlabeled homologous targets added at the time of the cytotoxicity assay but failed to overcome the inhibition mediated by LAK cells added at onset of the MLC. (3) Anti-CD3 + C treated LAK cells caused even more veto-type inhibition than a threefold greater number of control LAK cells treated with C alone. By considerations of cell dose alone this latter finding provides strong evidence against cold target inhibition in general. In addition, it specifically eliminates the possibility of cold-target inhibition mediated by any T cells in the LAK cell preparation that might proliferate in response to the MLC “responder” cells.

Although the majority of cells present in 4-day cultures of IL-2-stimulated peripheral blood lymphocytes are CD3⁺ CD56⁻ T cells, as shown here and elsewhere, the LAK cytolytic activity of such cultures is mediated by a minor fraction of cells that express the CD3⁺ CD56⁻ NK marker phenotype. This same NK-type LAK cell appears to mediate both the veto and natural suppressor activities of IL-2-stimulated human lymphocytes. Both of these LAK cell suppressor activities were nearly completely eliminated after complement lysis depletion of cells expressing CD56. By contrast, as described previously, both activities increased after complement lysis depletion of cells expressing CD3. In addition to showing that human suppressor LAK cells are CD3⁺, these latter findings suggest that LAK cell veto and natural suppressor activities may be downregulated by CD3⁺ T cells and/or upregulated by lymphokines rapidly released by anti-CD3-activated CD3⁺ T cells. Both of these possibilities are currently under investigation.

Cloned murine LAK cells can mediate both veto and natural suppression, suggesting that a single LAK cell is capable of both suppressor activities. Whether the same is true of human LAK cells remains to be determined. If a single LAK cell does in fact mediate both activities the different dose requirements for expression by LAK cells of each suppressor activity could be due to differences in the mechanisms involved in veto and natural suppression. Veto requires cell-cell contact whereas natural suppression involves release of soluble suppressor factors. Thus, on a cell-for-cell basis veto is probably a more efficient mechanism for inhibition of alloreactivity because the target cells for veto-type inhibition specifically bind to the suppressor cells, which then directly inactivate them. By contrast, the targets of natural suppression are inactivated by suppressor cell-derived factors released at a distance.

We and others have shown that murine LAK cells not only inhibit alloreactions in vitro but also inhibit bone marrow graft rejection and lethal GVHD in vivo in class I and class II MHC mismatched transplants. Therefore, the present demonstration that human LAK cells show the same ability to inhibit in vitro alloreactions as murine LAK cells strongly suggests that LAK cell adoptive immunotherapy might be useful in preventing marrow graft rejection and GVHD in human bone marrow transplant recipients. Approaches similar to those that have been used to generate large numbers of human LAK cells ex vivo for use in adoptive immunotherapy trials in patients with cancer could readily be used to generate the large number of LAK cells likely to be needed for adoptive immunotherapy in BMT recipients.

LAK cell adoptive immunotherapy would provide a number of potential advantages over donor marrow T-cell depletion as an approach to the prevention of GVHD in recipients of allogeneic marrow. Although BMT with T-cell-depleted allogeneic marrow has resulted in a decreased incidence of GVHD it has also been associated with an increased incidence of graft rejection, and an increased rate of leukemic relapse as a result of impairment of a graft-versus-leukemia (GVL) effect. By contrast, animal studies indicate that adoptively transferred LAK cells enhance both short-term and long-term engraftment of allogeneic marrow. Although the effect of LAK cell adoptive immunotherapy on GVL remains to be determined, the fact that LAK cells are able to kill both autologous and allogeneic leukemic blasts implies that adoptively transferred LAK cells might themselves provide a direct antitumor effect.
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Human lymphokine activated killer (LAK) cells suppress generation of allospecific cytotoxic T cells: implications for use of LAK cells to prevent graft-versus-host disease in allogeneic bone marrow transplantation

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