Clearance of Phenylalanine Ammonia-lyase from Normal and Tumor-bearing Mice

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SUMMARY

Yeast phenylalanine ammonia-lyase was administered i.p. to normal and tumor-bearing mice, and its clearance from plasma was studied. Single and multiple weekly injections at dosages of 10, 20, 50, and 100 units/kg were administered to C57BL female, C57BL × DBA/2 F male, and A/J female mice. L5178Y murine lymphoblastic leukemia, B16 melanoma, BW10232 adenocarcinoma, and 15091A anaplastic carcinoma were implanted 7 to 11 days prior to enzyme injection in the appropriate host. After a single injection, the average plasma half-lives of phenylalanine ammonia-lyase were 18 to 24 hr in all groups studied. While the other tumors had no effect on the plasma level of phenylalanine ammonia-lyase after a single injection, L5178Y murine lymphoblastic leukemia and 15091A anaplastic carcinoma were implanted 7 to 11 days prior to enzyme injection in the appropriate host. After a single injection, the average plasma half-lives of phenylalanine ammonia-lyase was 18 to 24 hr in all groups studied. While the other tumors had no effect on the plasma level of phenylalanine ammonia-lyase after a single injection, L5178Y murine lymphoblastic leukemia and 15091A anaplastic carcinoma significantly depressed the maximal level of phenylalanine ammonia-lyase attained in the plasma.

After repeated injections of phenylalanine ammonia-lyase, the initial plasma enzyme level was significantly reduced when 20 units/kg were administered, and the clearance of the enzyme from the plasma was greatly accelerated regardless of the amount administered. Furthermore, in tumor-bearing mice, the rate of clearance was significantly more rapid than in the appropriate non-tumor-bearing control.

INTRODUCTION

The nutritional regulation of tumor growth by the use of enzymes that metabolize certain amino acids has been utilized only to a limited extent for the treatment of cancer in mammals. Many enzymes catalyze the essentially irreversible degradation of amino acids, and this quality makes these enzymes potentially useful as agents that can deplete specific amino acids in vivo. Because of the specialization of tissues, biosynthesis of amino acids frequently takes place primarily at a restricted number of organ sites. Certain neoplastic cells may not have the ability to synthesize certain of the nonessential amino acids in adequate quantities. This is the case with certain leukemias in which neoplastic growth is dependent upon plasma concentrations of asparagine (24) and of serine (28).

Asparaginase effectively inhibits several sarcomas and leukemias in mice (5, 23) and some lymphatic leukemias in dogs (25) and humans (16). Asparaginase is the sole enzyme that has been extensively applied to the treatment of human tumors. It has been only partially successful, presumably because: (a) the activity of asparagine synthetase is appreciable or is induced in certain leukemic cells, thus rendering them no longer dependent upon plasma levels of asparagine (32); and (b) microbial asparaginases are foreign proteins, which upon repeated administration are rapidly cleared from the host by the immune system (9, 20, 26, 27).

An alternate approach to nutritional therapy is to utilize an enzyme that depletes an essential amino acid, one which must be supplied exogenously to the host. Phenylalanine ammonia-lyase from the yeast Rhodotorula glutinis catalyzes the deamination of L-phenylalanine to trans-cinnamic acid and L-tyrosine to trans-coumaric acid (17). Recent studies have defined the conditions for maximal induction in yeast and purification of this enzyme on a large scale (12). This enzyme markedly inhibited leukemic growth in vitro (2, 29) and produced cures in approximately 40% of mice with an ascites L5178Y lymphoblastic leukemia (1). These results were correlated with the plasma levels of phenylalanine and tyrosine, which were reduced to 3% of the control values within 7 hr after a single injection of 100 units phenylalanine ammonia-lyase per kg body weight. Since tyrosine is the precursor of catecholamine neurotransmitters, the effects of phenylalanine ammonia-lyase administration on sleep and behavior in trained monkeys have been studied to assess potential deleterious effects on the host (3). A temporary disruption of sleep patterns and inability to perform a complex task were observed, but recovery to normal function occurred rapidly, although plasma phenylalanine and tyrosine remained at levels below 10% of the control.

Phenylalanine ammonia-lyase occurs in higher plants (14, 19, 22), fungi, and yeast (8, 11, 18, 31) but has not been demonstrated in mammals. Consequently, this enzyme is a foreign protein when administered to mammals. For development of this enzyme as an effective therapeutic agent against solid tumors as well as leukemias under conditions where it would be administered over long periods of time, the pharmacokinetic behavior of phenylalanine ammonia-lyase in mammals must be established. Consequently, the purpose of this study is to determine the initial plasma concentration of phenylalanine ammonia-lyase and clearance at different doses from normal and tumor-bearing mice after single and multiple i.p. injections.

MATERIALS AND METHODS

Yeast Culture and Enzyme. R. glutinis (IFO 0559) was either purchased from P-L Biochemicals, Milwaukee, Wis.,...
or cultured in a 14-liter Microferm fermentor (New Brunswick Scientific Co., New Brunswick, N. J.) as previously described (12).

The cells were collected in a continuous flow centrifuge (Cepa-Schnell-Centrifuge, Carl Padberg, Lahr/Baden, Germany) and then either frozen and stored at −5° or immediately disrupted by sonic oscillation (Sonifier cell disruptor, Model 185, Heat Systems-Ultrasonics, Inc., Plainview, N. Y.). Phenylalanine ammonia-lyase was purified by the method of Fritz et al. (12). Briefly, the procedure involved fractional precipitation by ammonium sulfate and sodium citrate followed by chromatography on DEAE-cellulose and Sephadex G-200 columns. All purified enzyme preparations demonstrated a single major band when analyzed on polyacrylamide gels using the Davis standard electrophoretic separation (10), the sodium dodecyl sulfate gel electrophoresis method of Stoklosa and Latz (30), and isoelectric focusing in gels using biolyte ampholytes (4). The enzyme was stabilized by passage through a Millipore filter (0.22 µm) (Millipore Corp., Bedford, Mass.) with positive pressure. The sterilized enzyme was frozen and stored at −60° at a concentration of 20 to 40 mg protein per ml 0.01 M potassium phosphate buffer (pH 7.0). Under these conditions, purified enzyme preparations demonstrated no loss in activity for 6 months.

**Animals.** C57BL × DBA/2 F1 (hereafter called BD2F1) male and C57BL female mice at the age of 5 to 6 weeks were obtained from ARS/Sprague-Dawley Division, The NCI, Madison, Wis. A/J female mice at the age of 5 to 6 weeks were obtained from The Jackson Laboratory, Bar Harbor, Maine. Mice were provided with food and water ad libitum and were held for at least 1 week at the University Animal Care Center before experimentation.

**Tumor Transplantations.** Murine L5178Y lymphoblastic leukemia and 15091A anaplastic carcinoma were maintained in BD2F1 and A/J mice, respectively. B16 melanoma and BW10232 adenocarcinoma were grown in C57BL mice. Tumor brei and ascites fluid were prepared and transplanted as described by Geran et al. (13). The inoculum used for murine L5178Y lymphoblastic leukemia and 15091A anaplastic carcinoma was 105 and 106 cells/animal, respectively. B16 melanoma and BW10232 adenocarcinoma were transplanted with a 13-gauge trochar from a 10-day-old tumor stock. Phenylalanine ammonia-lyase was administered 7 days after inoculation of the tumors, except for 15091A anaplastic carcinoma, for which enzyme treatment began at 11 days.

**Enzyme Assays.** At time intervals after enzyme administration, blood was collected from the tail vein in heparinized tubes. Plasma was prepared by centrifugation (2,000 × g, 5 min, micro-hematocrit centrifuge, Clay-Adams, Parsippany, N. J.) and phenylalanine ammonia-lyase activity in the plasma was determined spectrophotometrically as described previously (12). Enzyme activity was expressed as units/ml plasma. One unit is defined as that amount of protein that catalyzes the conversion of 1 µmole L-phenylalanine to trans-cinnamic acid at 30° per min. The clearance of phenylalanine ammonia-lyase from mouse plasma was obtained by semilogarithmic plots of plasma enzyme activities against time. Initial plasma enzyme activity was defined as the activity obtained by extrapolating the clearance curve to time 0.

Clearance rate of phenylalanine ammonia-lyase from mouse plasma is expressed as biological half-life, the time required for one-half of the initial enzyme activity to disappear from plasma.

**RESULTS**

The appearance and change of phenylalanine ammonia-lyase in the plasma following i.p. administration to normal BD2F1 mice and mice with L5178Y lymphoblastic leukemia are shown in Chart 1. This enzyme appeared rapidly in the blood within 30 min, reached its maximal plasma activity after 2 to 4 hr, and disappeared exponentially thereafter. Normal and tumor-bearing mice show a similar pattern of enzyme clearance, but the plasma enzyme levels attained are significantly (p < 0.05, the 2-sided Mann-Whitney U test) lower in mice with L5178Y lymphoblastic leukemia. After administration of a dose of 100 units/kg (or 20 units/kg), maximal plasma enzyme concentrations in normal and tumor-bearing mice were 1.14 ± 0.09 and 0.72 ± 0.13 (or 0.236 ± 0.002 and 0.154 ± 0.028) units/ml, respectively. Although the data are not shown, studies on mice implanted with 15091A anaplastic carcinoma revealed that the maximal plasma enzyme activities attained are significantly (0.02 < p < 0.05) lower than in non-tumor-bearing mice but are not affected in mice with B16 melanoma or BW10232 adenocarcinoma.

Following a single i.p. injection of different doses in normal and tumor-bearing mice, plasma phenylalanine ammonia-lyase levels were measured at 2, 8, 24, 48, and 72 hr. Representative enzyme clearance curves are presented in Chart 2 for normal C57BL and in Chart 3 for B16 melanoma-bearing C57BL mice. A monophasic disappearance of...
Phenylalanine ammonia-lyase from the plasma was observed over a dose range of 10 to 100 units/kg. Monophasic distribution curves were also found in normal and tumor-bearing mice: A/J, A/J implanted with 15091A anaplastic carcinoma, C57BL implanted with BW10232 adenocarcinoma, and BD2F1. These results indicate that plasma enzyme activities decrease exponentially at about the same rate and are dose independent. Biphasic distribution curves were noted only in BD2F1 mice inoculated with L5178Y lymphoblastic leukemia at high doses of enzyme (50 and 100 units/kg). In these cases, the change to a slower rate of clearance occurred at approximately 32 hr.

The plasma half-lives of phenylalanine ammonia-lyase are summarized in Table 1. Implantation of tumors does not cause a significant change in the rate of enzyme clearance from the plasma, although the plasma half-lives were relatively low in BD2F1, mice implanted with L5178Y lymphoblastic leukemia. This was confirmed by the 2-sided Mann-Whitney U test when the normal were compared to the corresponding tumor-bearing mice. Since the half-lives of phenylalanine ammonia-lyase are independent of the dose administered, an average plasma half-life was obtained within each strain of mice. Plasma half-lives of phenylalanine ammonia-lyase were 19.0, 18.0, and 22.3 hr in C57BL female, BD2F1, male, and A/J female mice, respectively.

The plasma levels and half-lives of phenylalanine ammonia-lyase after repeated injections were determined (Tables 2 and 3). After multiple doses of 100 units/kg, the initial

<table>
<thead>
<tr>
<th>Mice</th>
<th>10 units/kg</th>
<th>20 units/kg</th>
<th>50 units/kg</th>
<th>100 units/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL</td>
<td>18.0 ± 0.7a</td>
<td>17.3 ± 1.1</td>
<td>18.9 ± 1.1</td>
<td>21.0 ± 0.7</td>
</tr>
<tr>
<td>C57BL-B16*</td>
<td>19.1 ± 1.5</td>
<td>17.7 ± 1.4</td>
<td>18.5 ± 1.0</td>
<td>17.9 ± 0.6</td>
</tr>
<tr>
<td>C57BL-BW10232a</td>
<td>19.8 ± 1.3</td>
<td>20.5 ± 1.2</td>
<td>19.9 ± 2.4</td>
<td>19.3 ± 2.5</td>
</tr>
<tr>
<td>BD2F1</td>
<td>23.2 ± 2.6</td>
<td>18.7 ± 0.1</td>
<td>19.9 ± 0.6</td>
<td>19.2 ± 2.1</td>
</tr>
<tr>
<td>BD2F1-L5178Yc</td>
<td>14.9 ± 1.1</td>
<td>15.5 ± 0.7</td>
<td>15.1 ± 3.7</td>
<td>17.2 ± 0.8</td>
</tr>
<tr>
<td>A/J</td>
<td>22.3 ± 1.4</td>
<td></td>
<td></td>
<td>23.1 ± 1.5</td>
</tr>
<tr>
<td>A/J-15091A</td>
<td>22.4 ± 1.6</td>
<td></td>
<td></td>
<td>21.4 ± 1.4</td>
</tr>
</tbody>
</table>

a Values are the average ± S.D.
b B16 melanoma or BW10232 adenocarcinoma was implanted 7 days prior to enzyme administration.
c Each mouse was inoculated i.p. with 10⁶ murine L5178Y lymphoblasts 7 days prior to enzyme administration.
d Each mouse was inoculated s.c. with 10⁶ cells of 15091A anaplastic carcinoma 11 days prior to enzyme administration.
plasma enzyme activities were relatively constant, whereas the initial plasma enzyme activities declined steadily after repeated injections of 20 units/kg. In tumor-bearing mice, the rate of decrease in initial plasma enzyme activities after weekly injections was greatly accelerated in comparison to the appropriate normal controls, particularly when 20 units/kg were administered. The decrease was apparent after the 2nd weekly injection in mice bearing B16 melanoma and BW10232 adenocarcinoma. L5178Y lymphoblastic leukemia also induced a precipitous fall in initial plasma enzyme levels following the 2nd injection. After the 6th weekly injection of 20 units/kg, the initial plasma enzyme activities in normal C57BL mice, B16 melanoma-bearing C57BL mice, and normal BD2F1 mice were reduced to 35, 7, and 13%, respectively, of the values obtained after a single injection.

Chart 4 shows that the plasma half-lives of phenylalanine ammonia-lyase in normal C57BL mice declined after each injection. This decrease in plasma half-lives is more dramatic than the fall in the initial plasma enzyme levels. The rate of decrease in plasma half-lives is more rapid during the 2nd and 3rd injections than after subsequent injections. Moreover, this accelerated rate of enzyme clearance from the plasma is essentially identical whether phenylalanine ammonia-lyase is administered at 20 or 100 units/kg.

The effects on plasma half-lives of phenylalanine ammonia-lyase administered weekly in other normal and tumor-bearing mice are summarized in Table 3. The results indicate that the decrease in half-lives starts at the 2nd injection following the 200 units/kg dosage, and this decrease is more rapid after the 2nd injection than after subsequent injections.

### Table 2

Initial plasma phenylalanine ammonia-lyase activity after weekly i.p. injections of different doses to normal and tumor-bearing mice

Yeast phenylalanine ammonia-lyase with a specific activity of 2.03 units/mg protein was administered weekly for 6 weeks to all mice. No significant difference (p < 0.05) was found in all systems except between BD2F1 normal and BD2F1-L5178Y following 100 units/kg at the 1st week.

<table>
<thead>
<tr>
<th>Groups*</th>
<th>1st wk</th>
<th>2nd wk</th>
<th>3rd wk</th>
<th>4th wk</th>
<th>5th wk</th>
<th>6th wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.15 ± 0.04*</td>
<td>1.42 ± 0.07</td>
<td>1.19 ± 0.25</td>
<td>1.21 ± 0.23</td>
<td>0.99 ± 0.19</td>
<td>0.89 ± 0.29</td>
</tr>
<tr>
<td>B</td>
<td>1.26 ± 0.11</td>
<td>1.03 ± 0.02</td>
<td>1.11 ± 0.35</td>
<td>1.23 ± 0.17</td>
<td>1.13 ± 0.20</td>
<td>1.10 ± 0.18</td>
</tr>
<tr>
<td>C</td>
<td>0.94 ± 0.10</td>
<td>1.00 ± 0.06</td>
<td>0.94 ± 0.25</td>
<td>1.02 ± 0.29</td>
<td>0.91 ± 0.31</td>
<td>0.87 ± 0.29</td>
</tr>
<tr>
<td>D</td>
<td>1.20 ± 0.15</td>
<td>1.47 ± 0.31</td>
<td>1.18 ± 0.14</td>
<td>1.12 ± 0.13</td>
<td>1.16 ± 0.31</td>
<td>1.26 ± 0.22</td>
</tr>
<tr>
<td>E</td>
<td>0.86 ± 0.17*</td>
<td>0.07*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Group A, C57BL female normal mice; Group B, C57BL female mice implanted with B16 melanoma 7 days prior to enzyme administration; Group C, C57BL female mice implanted with BW10232 adenocarcinoma 7 days prior to enzyme administration; Group D, BD2F1 male normal mice; Group E, BD2F1 male mice, each inoculated with 10⁶ murine L5178Y lymphoblasts 7 days prior to enzyme administration.

Values are the average ± S.D.

Table 3

Plasma half-life of phenylalanine ammonia-lyase after weekly i.p. injections of different doses to normal and tumor-bearing mice

Yeast phenylalanine ammonia-lyase with a specific activity of 2.03 units/mg protein was administered weekly for 6 weeks to all mice.

<table>
<thead>
<tr>
<th>Groups*</th>
<th>1st wk</th>
<th>2nd wk</th>
<th>3rd wk</th>
<th>4th wk</th>
<th>5th wk</th>
<th>6th wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>23.8 ± 2.9*</td>
<td>16.1 ± 4.6</td>
<td>6.1 ± 3.4</td>
<td>4.7 ± 1.4</td>
<td>1.3 ± 0.7</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>B</td>
<td>21.9 ± 2.1</td>
<td>16.1 ± 4.2</td>
<td>4.1 ± 1.0</td>
<td>2.8 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>C</td>
<td>26.7 ± 3.3</td>
<td>18.1 ± 2.4</td>
<td>11.7 ± 2.6</td>
<td>4.7 ± 4.0</td>
<td>1.1*</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>23.7 ± 3.3</td>
<td>12.5 ± 3.4</td>
<td>2.7 ± 0.3</td>
<td>1.8 ± 0.9</td>
<td>1.4 ± 0.4</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>E</td>
<td>20.3 ± 1.7</td>
<td>8.5*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Groups are defined in Table 2.

Values are the average ± S.D.

Average of 2 mice.

plasma enzyme activities were relatively constant, whereas the initial plasma enzyme activities declined steadily after repeated injections of 20 units/kg. In tumor-bearing mice, the rate of decrease in initial plasma enzyme activities after weekly injections was greatly accelerated in comparison to the appropriate normal controls, particularly when 20 units/kg were administered. The decrease was apparent after the 2nd weekly injection in mice bearing B16 melanoma and BW10232 adenocarcinoma. L5178Y lymphoblastic leukemia also induced a precipitous fall in initial plasma enzyme levels following the 2nd injection. After the 6th weekly injection of 20 units/kg, the initial plasma enzyme activities in normal C57BL mice, B16 melanoma-bearing C57BL mice, and normal BD2F1 mice were reduced to 35, 7, and 13%, respectively, of the values obtained after a single injection.
and continues to decrease further following each additional injection. Although there are variations in the plasma half-lives between normal and tumor-bearing mice after the first injection, the 2-sided Mann-Whitney U test indicates no significant difference. Although all normal and tumor-bearing mice had approximately the same initial half-lives (after a single injection), the plasma half-lives decreased at a faster rate in tumor-bearing mice than in normal controls after multiple injections. Plasma half-lives following the sixth weekly injections were between 1.1 and 1.5 hr in B16 melanoma-bearing mice.

DISCUSSION

The results of this study demonstrate that yeast phenylalanine ammonia-lyase injected i.p. appears rapidly and persists for a considerable time in the plasma of mice. The normal plasma half-lives of phenylalanine ammonia-lyase, i.e., the enzyme clearance rate of a single injection, range from 18 to 24 hr. These values were consistently observed in 3 strains of mice and in the appropriate host with 4 different types of tumors. This relatively longer plasma half-life as compared to that of Escherichia coli L-asparaginase, which is only 2.5 to 7.3 hr (33), may be advantageous for therapeutic application. Broome (6) reported that yeast L-asparaginase had no antineoplastic activity because it was almost completely cleared from the blood in less than 1 hr. Boyse et al. (5) also reported that L-asparaginase EC-I was chemotherapy-inactive due to its extremely fast clearance from the plasma of mice.

The presence of some types of tumor cells affected the maximal enzyme activities attained in the plasma. While BW10232 adenocarcinoma and B16 melanoma have no effect on lowering the maximal plasma enzyme level, L5178Y lymphoblastic leukemia and 15091A anaplastic carcinoma significantly depressed the level of phenylalanine ammonia-lyase attained in plasma. The reason for these differences is not known. However, since incubation of phenylalanine ammonia-lyase in vitro with plasma from tumor-bearing mice has no effect on enzymic activity, the tumors in vivo may reduce the rate of passage of enzyme molecules from the peritoneal cavity into the bloodstream.

Implantation of tumor cells does not significantly alter the rate of phenylalanine ammonia-lyase clearance from the plasma after a single injection, although lower levels of plasma enzyme were observed in mice with some types of tumors, as discussed above. That tumor cells per se do not contribute to a change in half-life of the injected enzyme was also observed by Broome (7), who showed that the marked delay in the clearance of E. coli L-asparaginase from the blood of mice implanted with 6C3HED lymphoma cells was actually due to the "lactic acid dehydrogenase virus" carried by tumor cells.

In contrast to the clearance curves found after a single injection, all mice and, in particular, tumor-bearing mice show a faster rate of decrease in the plasma half-life and, in some models, the initial plasma level of phenylalanine ammonia-lyase after repeated injections of this enzyme. Presumably, the presence of tumor cells acts as an adjuvant to enhance the immune response of the host. In previous studies, Fritz et al. (12) found that, upon repeated injections of phenylalanine ammonia-lyase every other day, tumor-bearing mice demonstrated lower levels of enzyme circulating 24 hr later than did the non-tumor-bearing controls. These results (12) are supported by the determination of decreased half-lives of phenylalanine ammonia-lyase under similar conditions (Table 3). The plasma half-life of phenylalanine ammonia-lyase appears to vary with the purity of the enzyme administered. The presence of impurities in enzyme preparations induces a faster rate of enzyme clearance from the plasma. Interestingly, Maral (21) reported that the average survival time in tumor-bearing mice treated with less purified batches of L-asparaginase was shorter than that in mice treated with highly purified batches.

Yeast phenylalanine ammonia-lyase is a macromolecule with a molecular weight of 330,000 (15). Since this enzyme has not been found in mammals, it is potentially antigenic. Phenylalanine ammonia-lyase antiserum has been prepared from rabbits, and the antibody obtained precipitated phenylalanine ammonia-lyase (12). Thus, the accelerated rate of clearance of this enzyme following repeated injections in mice might be due to the formation of antibodies. Although the Ouchterlony double-diffusion technique was negative, the presence of antibody in mice was demonstrated by the passive hemagglutination assay (12).

After repeated injections of E. coli L-asparaginase, this enzyme was rapidly cleared in humans (9, 26), dogs and rabbits (27), and mice (20). For example, the detection of anti-L-asparaginase was reported by Putter (27), who found that repeated injections of L-asparaginase at a dose of 300 IU/kg into dogs and rabbits at intervals of 7 to 8 days greatly accelerated its elimination from the plasma.

This study demonstrates that yeast phenylalanine ammonia-lyase has a plasma half-life of 18 to 24 hr in mice.
However, repeated injections induce an immune response that results in an accelerated rate of removal of the enzyme. In studies not presented here, mammary tumors and melanomas were suppressed by phenylalanine ammonia-lyase treatment, but an increase in their rate of growth occurred concomitant with the onset of the rapid clearance of enzyme. Therefore, the formation of antibodies is a critical problem to the therapeutic effectiveness of phenylalanine ammonia-lyase. Current studies are directed toward suppression of the immune response of the host with either total-body irradiation or immunosuppressive agents and toward chemical modification of phenylalanine ammonia-lyase to render it nonimmunogenic.

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