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(54) **POTENTIATION OF THE IMMUNE RESPONSE**

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(57) **ABSTRACT**

A method for stimulating proliferation of T-cells containing cytoplasmic post-prolyl dipeptidase activity; the method, in one aspect, involves contacting the T-cells with an organic compound at a concentration below 10^{-8}M, wherein the compound is characterized in that: (a) it is capable of crossing the membrane of T-cells to enter the cytoplasm, (b) it binds to the dipeptidase activity at a concentration of below 10^{-8}M, and thus (c) stimulates proliferation of the T-cells at that concentration.

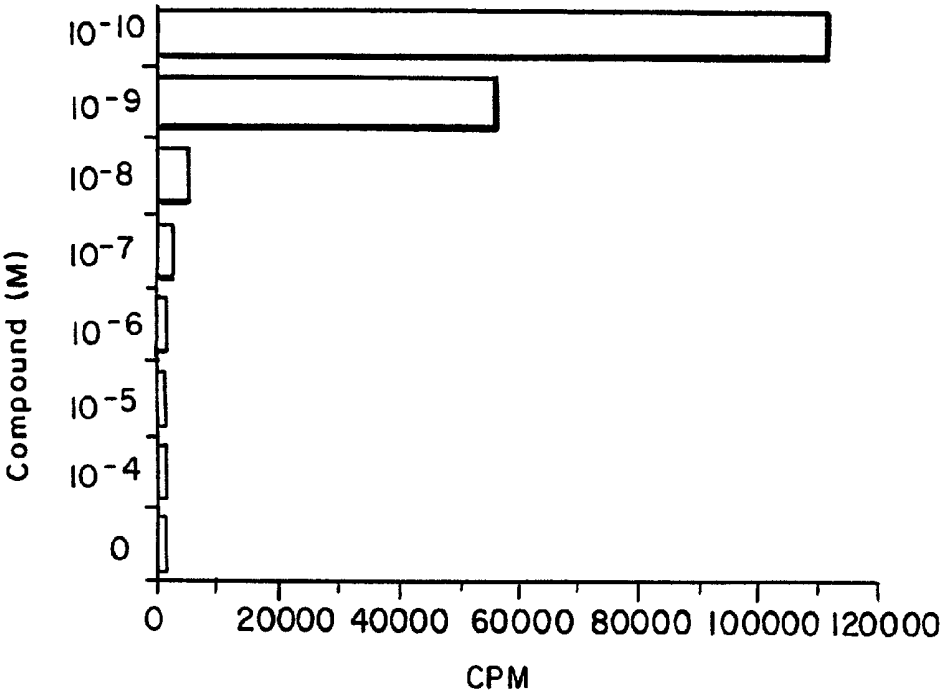

10-10
10-9
10-8
10-7
10-6
10-5
10-4
0
Compound (M)
0
20000
40000
60000
80000
100000
120000
CPM

FIG. 1A

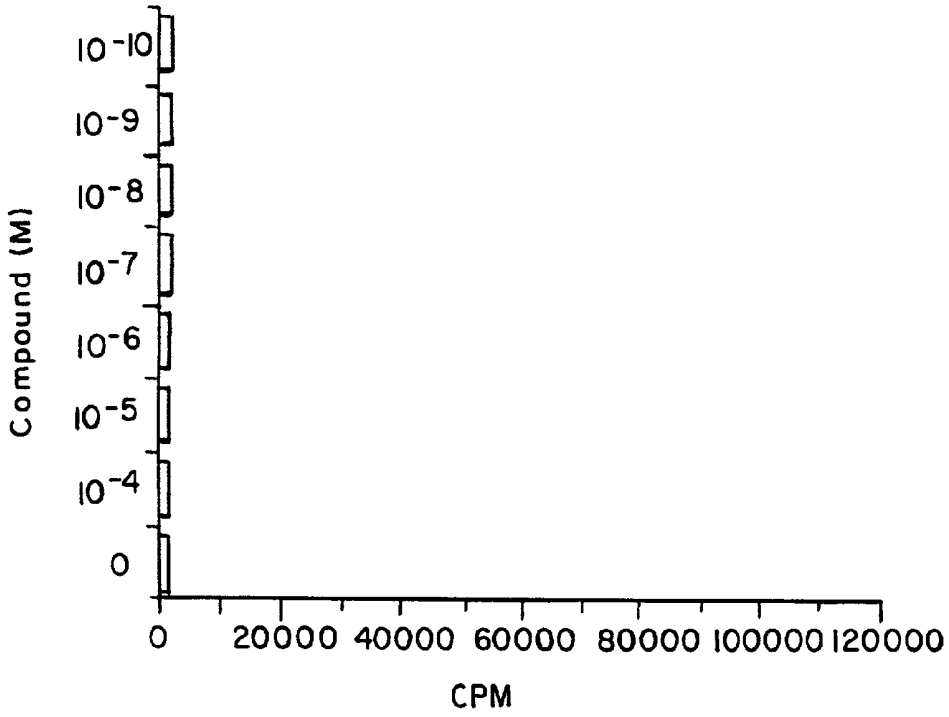

10-10
10-9
10-8
10-7
10-6
10-5
10-4
0
Compound (M)
0
20000
40000
60000
80000
100000
120000
CPM

FIG. 1B

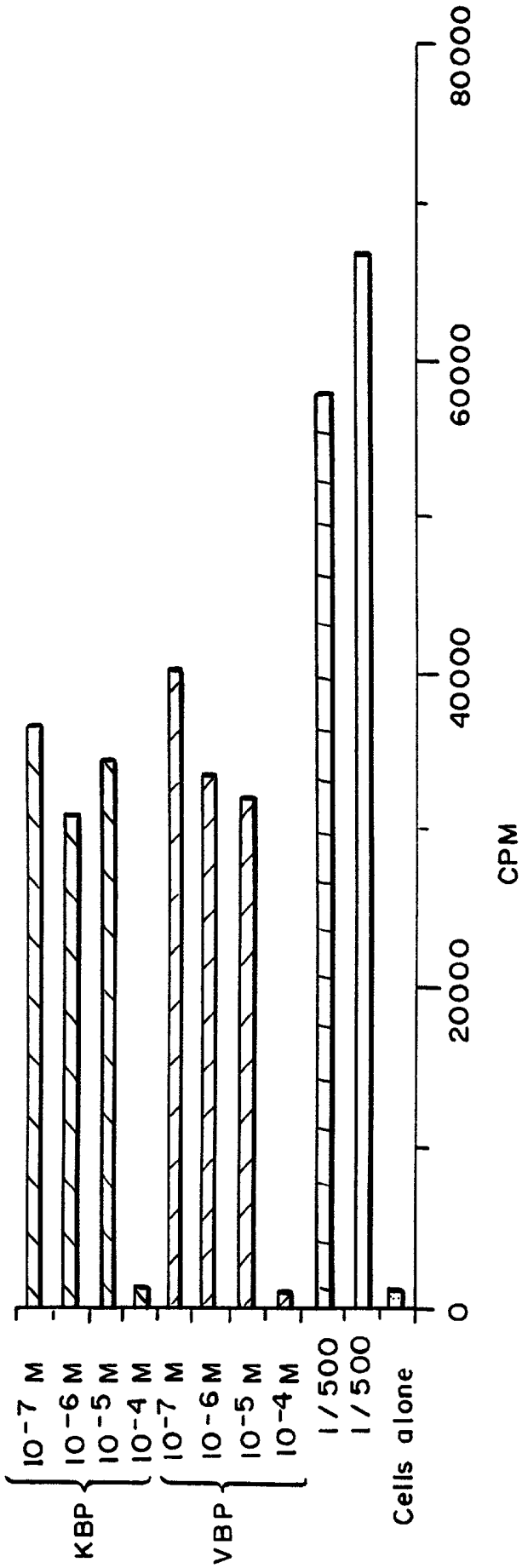

80000
60000
40000
20000
0
CPM
KBP
10-7 M
10-6 M
10-5 M
10-4 M
VBP
10-7 M
10-6 M
10-5 M
10-4 M
1/500
1/500
Cells alone

FIG. 2

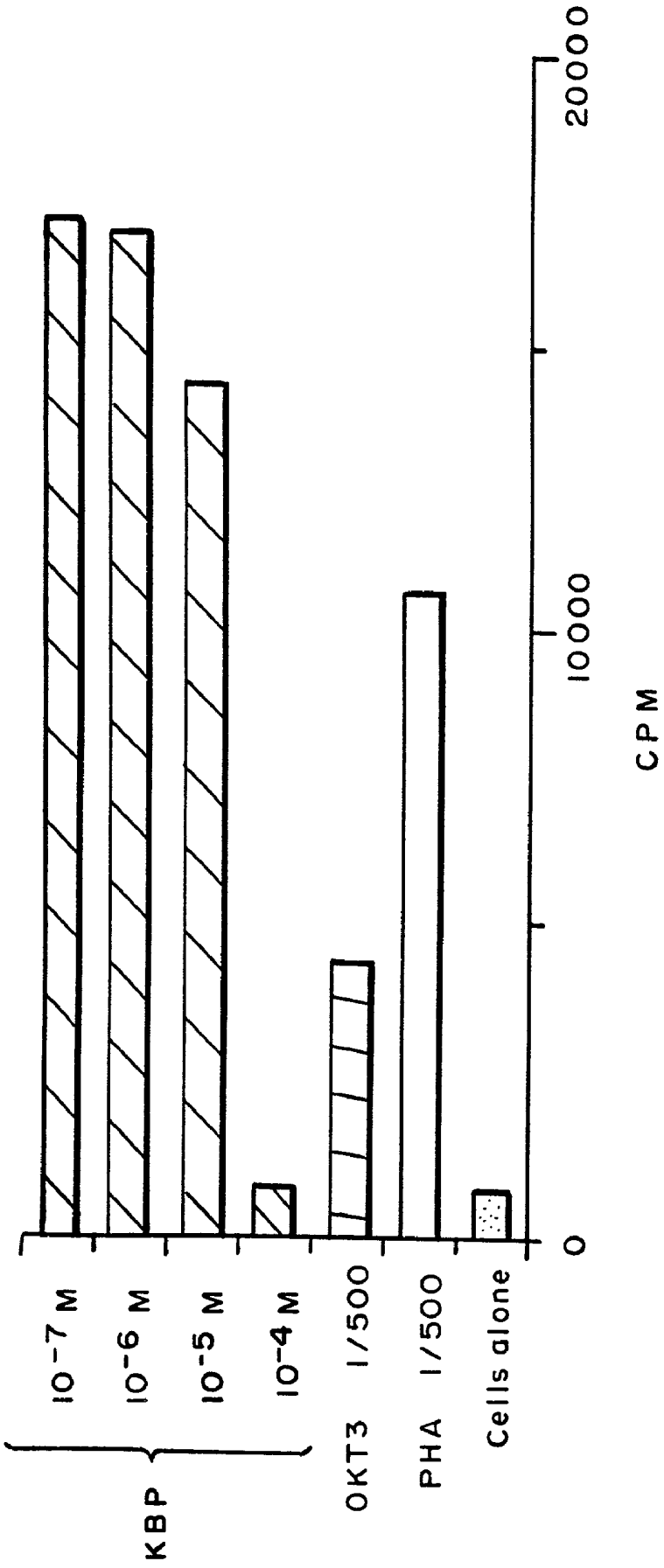

20000
10000
0
CPM
KBP
10^{-7} M
10^{-6} M
10^{-5} M
10^{-4} M
OKT3 1/500
PHA 1/500
Cells alone

FIG. 3

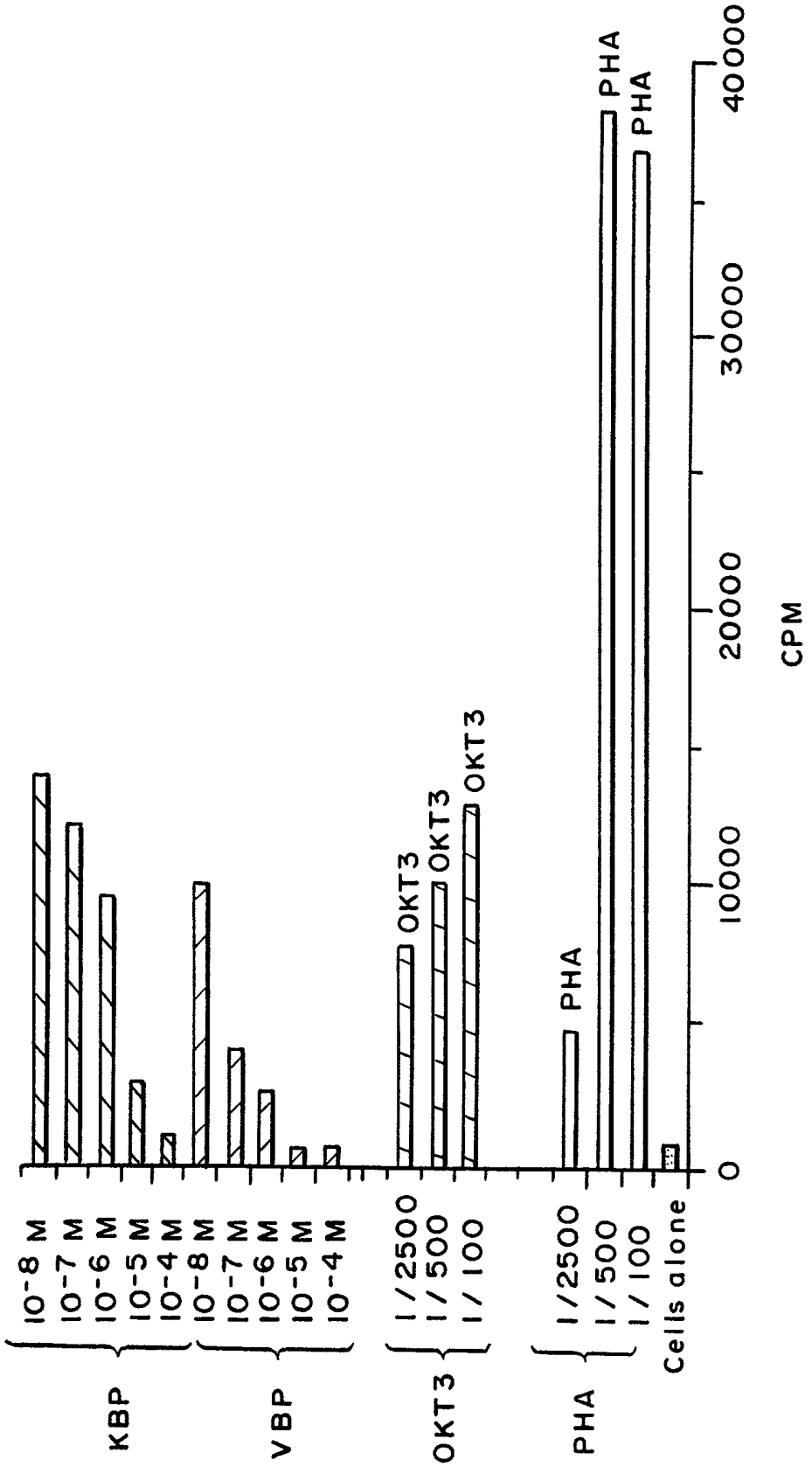

KBP
VBP
OKT3
PHA
10-8 M
10-7 M
10-6 M
10-5 M
10-4 M
10-8 M
10-7 M
10-6 M
10-5 M
10-4 M
1/2500
1/500
1/100
1/2500
1/500
1/100
Cells alone
OKT3
OKT3
OKT3
PHA
PHA
PHA
0
10000
20000
30000
40000
CPM

FIG. 4

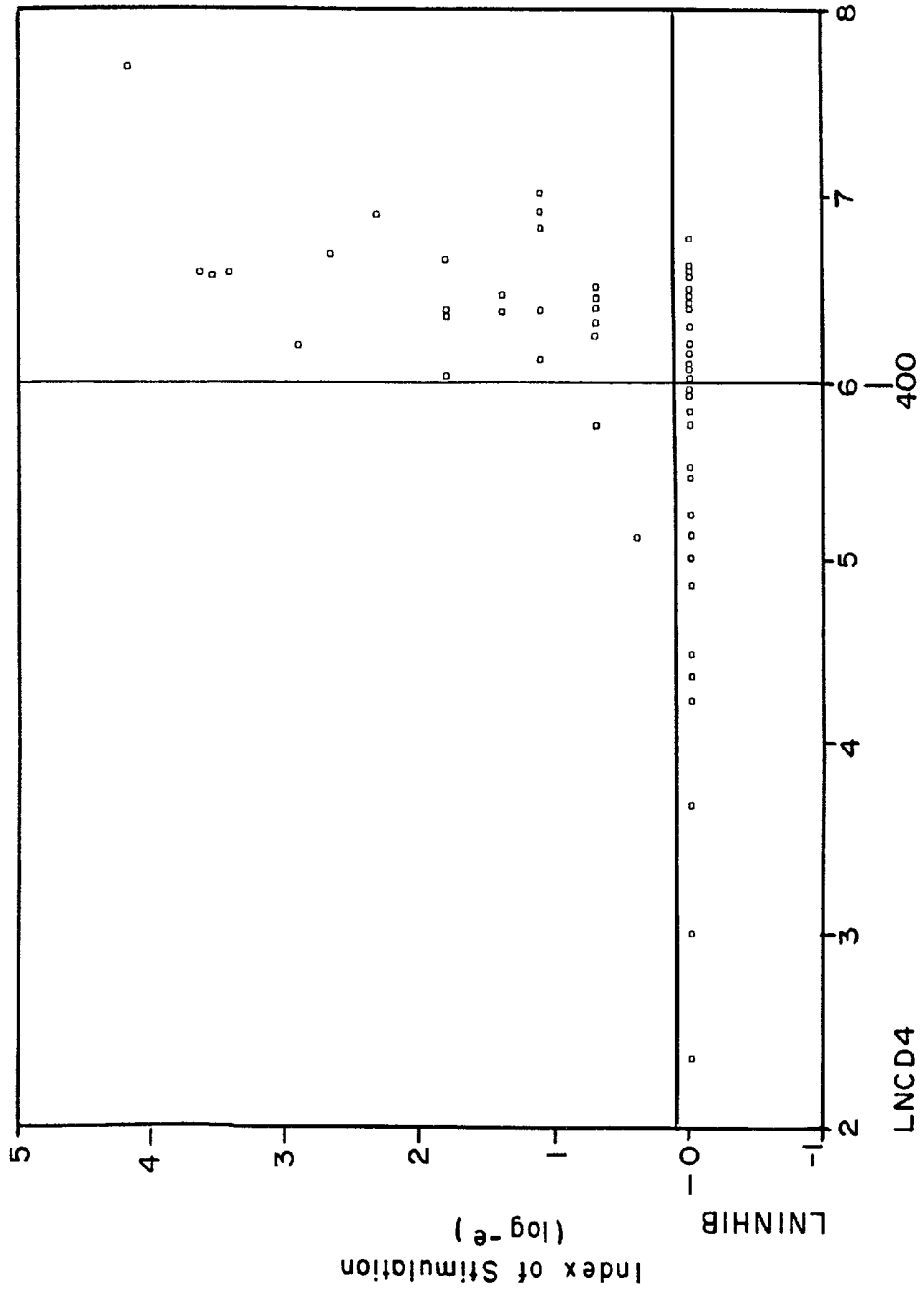

Index of Stimulation
(log -e)
LINNHIB
LNCD4
Absolute CD4 Count
(log -e)
400

FIG. 5

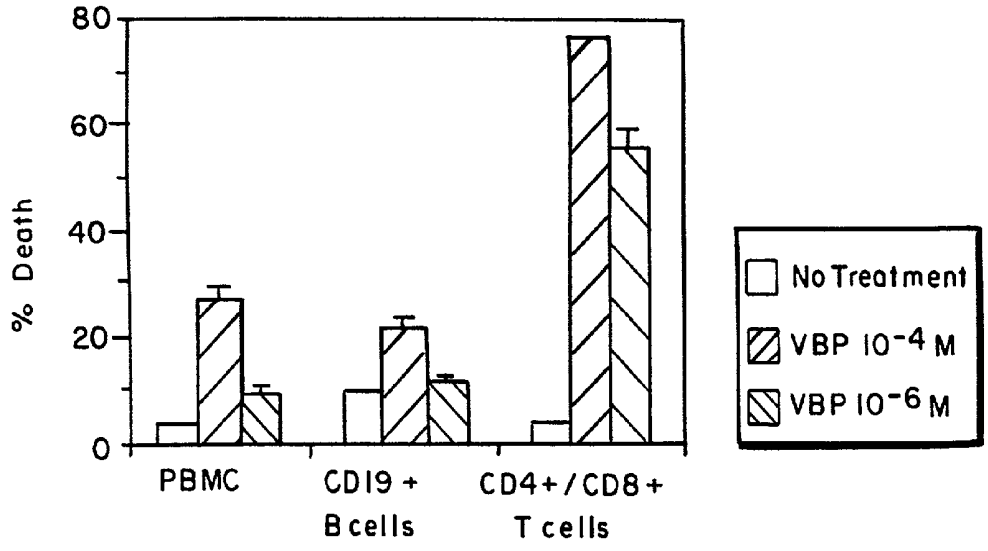

80
60
40
20
0
% Death
PBMC
CD19+
B cells
CD4+/CD8+
T cells
No Treatment
VBP 10-4 M
VBP 10-6 M

FIG.6

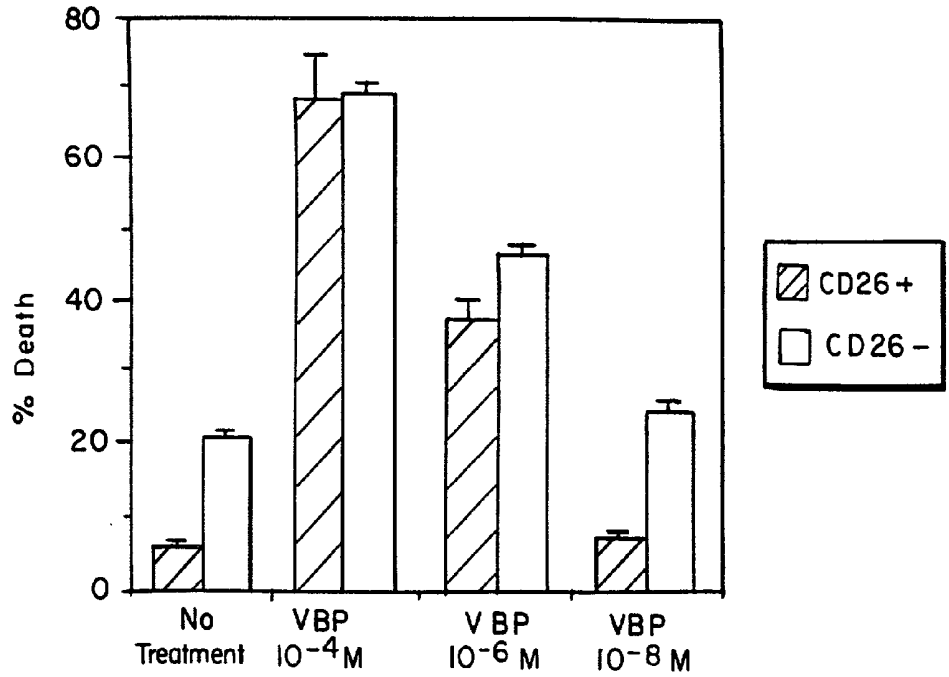

80
60
40
20
0
% Death
No Treatment
VBP 10-4 M
VBP 10-6 M
VBP 10-8 M
CD26+
CD26-

FIG.7

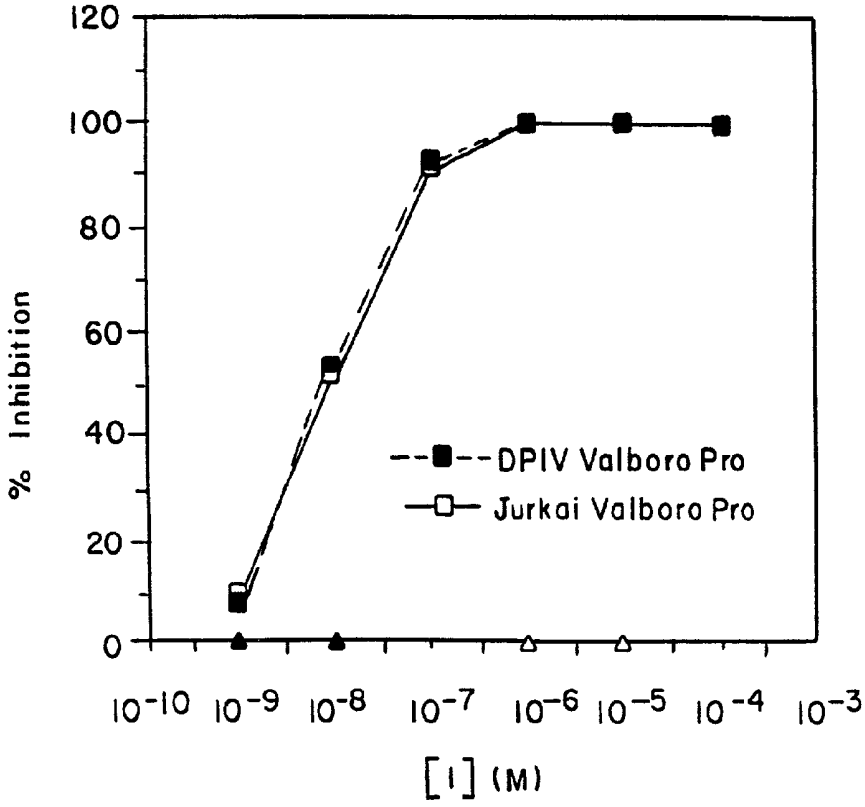

120
100
80
60
40
20
0
% Inhibition
DPIV Valboro Pro
Jurkai Valboro Pro
10-10 10-9 10-8 10-7 10-6 10-5 10-4 10-3
[I] (M)

FIG. 8

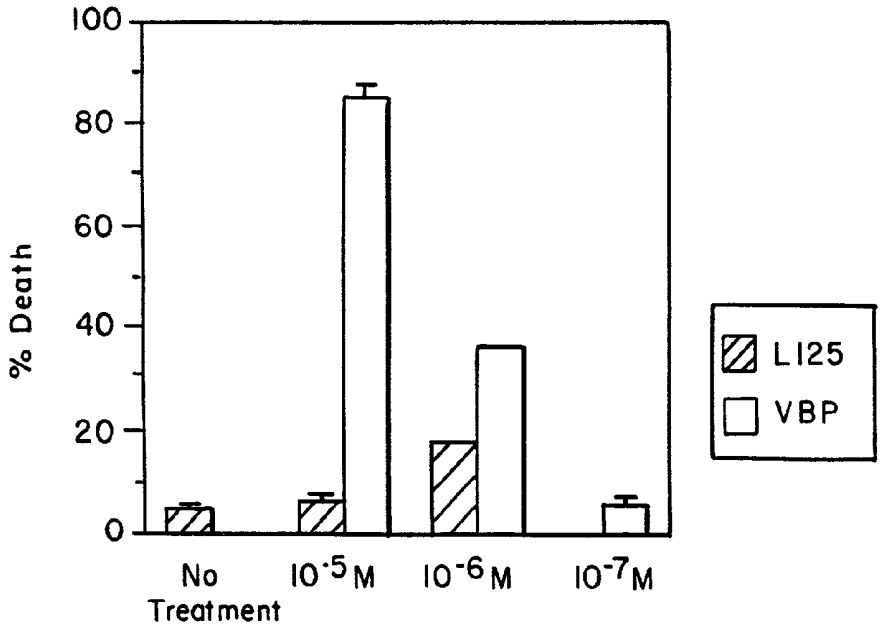

100
80
60
40
20
0
% Death
L125
VBP
No Treatment
10-5M
10-6M
10-7M

FIG. 9

POTENTIATION OF THE IMMUNE RESPONSE

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0001] This invention was made with Government support under NIH grant No. AI36696, and the Government therefore has certain rights in this invention.

BACKGROUND OF THE INVENTION

[0002] This invention relates to treatment of viral infections using organic compounds which interact with T-cell enzymes.

[0003] One of the classic markers of full-blown AIDS resulting from long-term infection with HIV-1 is a severe depletion of $CD4^+$ T-cells, which are a key component of the immune system. Attempts have been made to increase the $CD4^+$counts of AIDS patients, and some of these efforts, notably treatment with protease inhibitors, have met with considerable success. Other approaches, e.g., stimulation of the immune response by vaccination with viral peptides, have been less successfil. The reasons for $CD4^+$ depletion in AIDS, and resistance of $CD4^+$cells to stimulation by some therapies, are not fully understood.

SUMMARY OF THE INVENTION

[0004] We have discovered that the activation state of human T-cells can be affected by compounds which interact with a cytoplasmic post-prolyl dipeptidase activity which has similarities to, but is distinct from, the membrane-bound T-cell serine protease CD26. The compounds useful in the invention are inhibitors of this activity, which is, in naturally-occurring T-cells in healthy individuals, involved in protection of T-cells from apoptosis, or programmed cell death. Thus, in high concentrations, the inhibitors hasten the death of T-cells, by inhibiting the protective enyzme. We have discovered, surprisingly, that at low concentrations the inhibitors exhibit a paradoxical effect: they are potent stimulators of T-cell activity in HIV-infected individuals. The concentrations of inhibitor which induce this T-cell stimulatory response are very low (on the order of 10^{-8}-10^{-12}M), and therefore the inhibitors can be used with minimal side effects, even if, in larger doses, the inhibitors would be toxic.

[0005] Our hypothesis is that the resistance to full activation observed in T-cells of HIV-infected individuals involves a blocking of the cytoplasmic enzymatic activity discussed above. We believe that this blocking of activation, involving this cytoplasmic activity, prevents differentiation of T-cells of HIV-infected individuals into effector cells, eventually leading to T-cell death.

[0006] Thus, the invention features a method for stimulating proliferation of T-cells of a human patient suffering from a disease state characterized by the inability of the patients' T-cells to respond normally to T-cell proliferation-inducing stimuli; the method involves contacting the T-cells with an organic compound at a concentration below 10^{-8}M, wherein the compound is characterized in that it binds to the post-prolyl cleaving dipeptidase activity present in the cytoplasm of human T-cells, e.g., $CD4^+$cells or Jurkat cells.

[0007] Treatment according to the invention can be in vitro or in vivo. In in vivo therapy, the enzyme-interacting compound of the invention is administered such that the blood concentration in the patient (e.g., an HIV-infected patient) is below 10^{-11}. The compounds can also be used in vitro at low concentrations to stimulate proliferation of non-infected, beneficial T-cells, such as $CD4^+$ cells and CTL's. In this embodiment, PBMC are isolated from a patient and incubated with a concentration of lower than 10^{-8}M of the compound, to bring about proliferation of T-cells, which are then reinfused into the patient.

[0008] We believe that administration of low concentrations of the inhibitors of the invention may have an allosteric effect such that the T-cell cytoplasmic enzyme, which is a multimeric (i.e., multiple subunit) enzyme, exhibits an increased affinity of the enzyme for its natural substrate or ligands, allowing the previously blocked T-cell to proceed to full activation, and hence survival, proliferation, and interleukin-2 production. Stimulation of the T-cell immune response in HIV-infected patients according to the invention yields increased numbers of immune effector cells, which can fight both HIV itself, and other opportunistic pathogens.

[0009] Treatment according to the invention has the advantages of specificity and low toxicity, not just because of the low concentrations of inhibitor which can be used, but also because, in T-cells of patients not infected with a virus such as HIV, the inhibitors have no discernable effect. Furthermore, treatment according to the invention advantageously does not necessarily require in vitro manipulation of the T-cells from HIV-infected patients. Furthermore, no immunization is required, and treatment will be effective even where HIV proteins have mutated because the therapy targets a cellular enzyme. The fact that, in T-cells treated according to the invention in vitro, no increase in the level of the HIV protein p24 is observed, probably indicates that the T-cells which are infected with HIV are not stimulated by the low dose inhibitor treatment of the invention.

[0010] The invention also permits immunization of HIV-infected patients with, e.g., HIV peptides. Under normal circumstances, such patients cannot be vaccinated because of the defect in the T-cell stimulation pathway. Use of inhibitors in low doses as adjuvants can render T-cells responsive to vaccination with HIV antigens, in particular peptides.

[0011] Treatment of HIV-infected patients with low doses of inhibitors according to the invention can also enhance the activity of other AIDS drugs, in particular protease inhibitors. We have found that treatment according to the invention generally fails to bring about an increase in $CD4^+$ count in patients whose $CD4^+$ count is already very low, i.e., below about 400. In such patients, the $CD4^+$ count can be increased to above this level using known protease inhibitors, and the newly generated $CD4^+$T-cells resulting from such treatment are particularly susceptible to the stimulatory effects of treatment according to the invention, leading to an optimal combination AIDS therapy. Preferably, the drugs are administered orally.

[0012] The low dose administration of inhibitors of the invention can also be used to produce an adjuvant effect in HIV-negative individuals, who are to be immunized with peptides or other viral antigens; this mode of vaccination can be used for prophylaxis for HIV, as well as any other viral pathogen. Ordinarily, meaningful cytolytic T-lymphocyte ("CTL") responses, both in vitro and in vivo, have been difficult to achieve with peptide immunization. The inven-

tion should make it possible to produce significant CTL responses to viral peptides, e.g., peptides from influenza, HIV, human papilloma virus, and herpes peptides. This adjuvant effect can also be used to stimulate CTL responses to peptide antigens from other pathogens as well, e.g., pathogenic bacteria such as toxigenic *E. coli*, and protozoan pathogens such as the pathogens which are the causative agents of malaria and amoebic dysentery. The compounds, when used as adjuvants, are preferably administered orally.

[0013] The invention provides a new and highly advantageous method of potentiating the immune response in both HIV infected and uninfected patients, in methods employing extremely low concentrations of inhibitors which, at these concentrations, exhibit a paradoxical effect (i.e., they act as stimulatory rather than inhibitory molecules, as they would at higher concentrations). The very low concentrations employed according to the invention allows treatment with minimal side reactions and toxicity. The specificity of the treatment of the invention also avoids such adverse effects, which are seen, for example, in treatment with immune stimulatory compounds such as interleukin-2.

[0014] Other features and advantages of the invention will be apparent from the following detailed description thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **FIG. 1** is a pair of graphs showing the lymphocyte stimulatory effect of treatment of the invention on peripheral blood mononuclear cells (PBMC) from HIV-infected and uninfected patients.

[0016] **FIG. 2** is a graph illustrating the T-cell stimulatory effects of two inhibitory compounds used according to the invention.

[0017] **FIGS. 3, 4**, and **9** are graphs showing stimulatory effects of treatment according to the invention in lymphocytes of HIV-infected patients, compared to treatment using two control compounds.

[0018] **FIG. 5** is a graph illustrating a stimulatory effect of an inhibitor according to the invention on PBMC in vitro, showing the correlation with $CD4^+$counts. The data are plotted as the natural 10g of the stimulation index (vertical dimension) versus the natural log of the $CD4^+$count of the patient (horizontal dimension).

[0019] **FIG. 6** is a histogram demonstrating that an inhibitor according to the invention induces dose-dependent apoptosis in resting T-cells (these dosages are higher than the extremely low doses used according to the invention).

[0020] **FIG. 7** is a histogram demonstrating that an inhibitor according to the invention induces, at higher doses than in the invention, dose-dependent apoptosis in both $CD26^+$ and $CD26^+$populations of PBMC.

[0021] **FIG. 8** is a graph showing that an inhibitor of CD26 inhibited the cytoplasmic enzyme as well.

DETAILED DESCRIPTION

[0022] Therapeutic Compounds

[0023] Any organic compound can be used according to the invention which exhibits the following properties: (1) it is capable of crossing the membrane of human T-cells to reach the cytoplasm, where the compound can (2) intereact with the cytoplasmic dipeptidase present in the T-cells, in order to (3) stimulate activation/proliferation of T-cells (and most preferably $CD4^+$ cells or CTL's) at concentrations below 10^{-8}M.

[0024] A simple screening method is described below for the identification of compounds which are candidate therapeutic compounds according to the invention.

[0025] Substrate and Enzyme Preparation

[0026] The first step is to provide a cytoplasmic enzyme preparation. The preparation need not be a pure enzyme sample; a crude cytoplasmic extract is sufficient to screen compounds for the desired activity. The extract can be prepared from any human T-cell line which is negative for CD26; an example of such a suitable cell line is the commercially available Jurkat cell line.

[0027] A suitable enzyme-containing cell extract can be prepared as follows. First, Jurkat cells (10^6-10^{11} cells) are grown and a cell pellet is obtained by centrifugation. The cell pellet is stored in frozen condition.

[0028] For use in the assay, the frozen pellet is thawed by the addition of ice cold lysis buffer, in the amount of approximately 1 ml per 10^8 cells. The liquified material is homogenized with ten strokes of a Dounce homogenizer, and then clarified by centrifugation at 1500 g. The supernatant is removed (and saved), and the 1500 g. pellet is resuspended in lysis buffer and homogenized with ten strokes of a Dounce homogenizer. Clarification is again carried out by centrifugation at 1500 g, 4° C.

[0029] The 1500 g supernatants are then combined, and EDTA is added to 5mM. The resultant liquid is centrifuged at 75,000 g at 4° C. for twenty minutes, and the supernatant is then removed and centrifuged at 175,000 g. at 4° C., for 60 minutes. The resultant supernatant, containing the cytosolic extract, is the DPPV activity-containing preparation used in the assay, described below, for candidate therapeutic compounds of the invention.

[0030] The assay is based on our observation that the T-cell cytoplasmic enzyme of interest is a post-prolyl cleaving serine protease. We therefore chose as a reporter substrate a compound which contains proline in the penultimate position; any of a number of substrates meeting this requirement can be used. In the assay described herein. we employed a fluorescent cleavage assay using the substrate AlaProAFC. Alternatively, a calorimetric assay can be carried out using as a substrate Gly-Pro-pNA. The choice of terminal amino acid is not critical, provided that the substrate contain a free terminal amino group.

[0031] In the assay we carried out, we employed a fluorescence spectrometer for excitation at 400 nm and emission at 505 nm. The spectrometer was calibrated for fluoresence intensity of 0.000=10 mM HEPES, pH 7.4; and fluoresence intensity of 1.000=10 Mm HEPES, 1 μM AFC.

[0032] To carry out the assay, between 10 and 100 μl of enzyme extract, above, is diluted to 1 ml with 10 mM HEPES, pH 7.4, containing 10 mM Ala-Pro-AFC. At least one extract/substrate sample is run without test compound, to provide a standard for comparison with the test sample.

[0033] In the test samples, multiple samples are run containing varying concentrations, down to 10^{-8} M, of the test

compound. The sample (with or without test compound) is placed in a cuvette, and inserted into a fluoresent spectrometer. Enzymatic activity is measured as the accumulation of fluoresence intensity (i.e., substrate cleavage product) over time (1 min.). A compound is identified as an inhibitor if the accumulative fluoresence is decreased as a result of the presence of the inhibiting compound.

[0034] Once a compound has been identified as an enzymatic inhibitor, as described above, further assays are carried out to determine whether the compound is capable of moving across the T-cell membrane into the cytoplasm; this is an assay which can be carried out using well-known techniques.

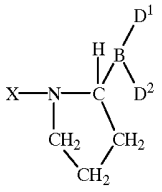
[0035] If desired, additional in vitro assays can be carried out using candidate compounds of the invention, prior to their use in vivo. One such assay employs the candidate compound at a very low concentration, in a test designed to determine whether at low concentrations the compound can stimulate the proliferation of PBMC from HIV infected patients in vitro. As is shown in the data of **FIG. 4**, stimulation can be measured by, e.g., incorporation of a labelled nucleotide.

[0036] The compounds can also be tested at higher doses to determine whether they exhibit the opposite effect of proliferation, as above, i.e., dose-dependent apoptosis caused by enzyme inhibition, as in the experiments of **FIG. 6**.

[0037] Candidate Compounds

[0038] As is discussed above, compounds which are potentially capable of apoptosis induction at high doses and proliferation induction at low doses are those which, at normal or high doses, inhibit cytoplasmic T-cell dipeptidase, and can cross the T-cell membrane into the T-cell cytoplasm, where the enzyme interaction occurs. The compounds thus should be organic compounds which have a free amino group at the amino terminus; a proline or proline analog at the penultimate position; and an enzyme binding site which mimics the post-prolyl cleavage site of cytoplasmic dipeptidase.

[0039] A number of known classes of compounds can be screened and used according to the invention. Once such class are CD26 (i.e., DPPIV) inhibitors, including those described in Bachovchin et al. U.S. Pat. No. 4,935,493, hereby incorporated by reference. In the '493 patent, there are described compounds having the structure:



[0040] where each D1 and D2, independently, is a hydroxyl group or a group which is capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH; and X comprises an amino acid or a peptide which mimics the site of the substrate recognized by a post-prolyl cleaving enzyme.

[0041] The compounds in the '493 patent are inhibitors of CD26, and are also candidate inhibitors of the invention. As is discussed above, because of the low concentrations of compounds used according to the invention, it is acceptable to use, in the invention, a compound which interacts not only with the cytoplasmic enzyme, but also CD26.

[0042] The class of compounds described in the '493 patent are also discussed and exemplified in Takacs et al. U.S. patent application Ser. No. 07/923,337, corresponding to PCT Application No. WO 94/03055, hereby incorporated by reference. In this application, one of the families of molecules in the '493 patent is described as the "Xaa-boroPro molecules," exemplified by Ala-boroPro, Pro-boroPro, and Gly-boroPro. These Xaa-boroPro molecules are all candidate compounds for use in the methods of the present invention. Two of these compounds are used in some of the examples described below; those compounds are Lys-boroPro ("KPB"), and Val-boroPro ("VBP").

EXAMPLE 1

[0043] Peripheral blood mononuclear cells (PBMC) were obtained by standard methods from HIV-infected individuals, and from uninfected individuals. Varying dosages of KBP or VBP were contacted with the PBMC in vitro, and stimulation of proliferation was measured by incorporation of ^{3}H thymidine (cpm). The results of these experiments are shown in **FIG. 1**: very low doses of the Val-boroPro and Lys-boroPro stimulated proliferation of PBMC from HIV-infected patients, but not PBMC from uninfected patients.

[0044] As shown in **FIG. 1**, at no concentration of the boroPro enzyme inhibitor did it affect the PBMC from uninfected individuals. The inhibitor, at moderate concentrations, also did not cause proliferation of PBMC from HIV-infected individuals. but it did cause marked proliferation at very low concentrations (10^{-9} and 10^{-10}). These results are consistent with our hypothesis, discussed above, that, at low concentrations, these enzyme inhibitors exhibit a paradoxical effect: rather than inhibiting the apoptosis-controlling cytoplasmic T-cell enzyme, they interact with that enzyme in a manner which blocks inactivation and causes proliferation of T-cells.

[0045] Concordant results are shown in **FIG. 2, a** histogram showing that low doses of Lys-boroPro and Val-boroPro cause proliferation of PBMC of HIV-infected patients, while higher doses (10^{-4}M) do not have this effect.

[0046] The same results are shown in **FIGS. 3, 4, 9**, and **10** which also present data for two control compounds OKT3, and PHA, both of which are non-specific mitogens.

[0047] Referring to **FIG. 5**, data are presented in a form which shows that low concentrations of the inhibitors of the invention have little effect on the PBIMC of HIV-infected patients whose CD4 counts are lower than about 400 (the clinical indication for AIDS). In the graph of **FIG. 5**, the natural log of the stimulation index (the vertical axis) is plotted against the natural log of the CD4 count of the patients; as shown, above a count of 400 there is particularly significant stimulation of proliferation.

[0048] **FIG. 6** is a graph demonstrating that purified T-cells are highly sensitive to cytoplasmic T-cell dipeptidase inhibitors in moderate concentrations. CD19$^-$B cells and CD4$^-$/CD8$^-$ T-cells were isolated to high purity and incu-

bated overnight in Val-boroPro. The amount of cell death was determined by 7AAD flow cytometry analysis. Data represent % of cell death from duplicate samples. These data are consistent with our hypothesis that the inhibitors, in moderate concentration, inhibit a cytoplasmic enzyme which ordinarily protects against apoptosis.

[0049] **FIG. 7** presents data demonstrating that $CD26^+$ and $CD26^-$ PBMC are equally susceptible to T-cell cytoplasmic enzyme inhibitor-induced death, where the inhibitor is administered in moderate concentrations. CD26+ and $CD26^-$ populations were incubated overnight in the presence or absence of various concentrations of Val-boroPro. The amount of cell death was determined by 7AAD flow cytometry analysis. Data represent mean % of death from duplicate samples. These data indicate that apoptosis-inhibiting T-cell cytoplasmic enzyme is present in both $CD26^+$ and $CD26^-$ T-cells.

[0050] **FIG. 8** presents data showing the effects of an inhibitor useful in the invention, Val-boroPro. The experiments were carried out using two preparations: purified DPPIV (i.e., CD26), and Jurkat T-cell cytoplasmic extract, described above (Jurkat cells contain the cytoplasmic T-cell enzyme, but do not bear CD26 on their surfaces). These preparations were incubated with varying concentrations of Val-boroPro, and enzymatic activity was determined by measuring the accumulation of the fluorescent cleavage product 7-amino-4-trifluoromethylcoumarin (AFC) released from the substrate Ala-ProAFC upon enzymatic cleavage. Val-boroPro inhibited both the enzyme DPPIV and the cytoplasmic T-cell enzyme in the Jurkat preparation.

[0051] Other embodiments are within the following claims.

What is claimed is:

1. A method for stimulating proliferation of T-cells of a human patient suffering from a disease state characterized by the inability of said patient's T-cells to respond normally to T-cell proliferation-inducing stimuli; said method comprising contacting said T-cells, in vitro or in vivo, with an organic compound at an in vitro concentration below 10^{-8}M, or an in vivo blood concentration below 10^{-8}M, wherein said compound is characterized in that it bind to the post-prolyl cleaving dipeptidase activity present in the cytoplasm of Jurkat cells.

2. The method of claim 1, wherein said disease state is caused by HIV infection.

3. The method of claim 1, wherein said compound is further characterized in that, at a concentration of 10^{-4}M, it inhibits the cytoplasmic post-prolyl cleaving dipeptidase activity found in Jurkat T-cells.

4. The method of claim 3, wherein said compound is further characterized in that, at a concentration of 10^{-8}M, it binds to the cytoplasmic post-prolyl cleaving dipeptidase activity of $CD4^+$ T-cells of HIV-infected patients, to stimulate proliferation of said cells.

5. The method of claim 1, wherein said patient is infected with HIV, and said compound is administered to said patient to bring about a blood concentration of said compound below 10^{-10}M.

6. The method of claim 5, wherein said compound is further characterized in that it is capable of crossing the membrane of human $CD4^+$ T-cells to enter the cytoplasm.

7. A method for stimulating proliferation of T-cells which contain cytoplasmic post-prolyl cleaving dipeptidase activity and which are further characterized by the inability to respond normally to T-cell proliferation-inducing stimuli, said method comprising contacting said T-cells with an organic compound at a concentration below 10^{-8}M, wherein said compound is characterized in that:

(a) it is capable of crossing the membrane of said T-cells to enter the cytoplasm,

(b) it binds to said dipeptidase activity at a concentration below 10^{-8}M, and thus

(c) stimulates proliferation of said T-cells at said concentration.

8. The method of claim 7, wherein said T-cells are $CD4^+$ cells.

9. The method of claim 8, wherein said compound enhances the ability of said $CD4^+$ T-cells to proliferation in response to antigenic stimulation.

10. The method of claim 1, wherein said compound is a serine protease inhibitor.

11. The method of claim 1, wherein said compound is administered to an HIV-infected patient.

12. The method of claim 10, wherein said serine protease inhibitor has a cleavage site or a binding site which mimics a post-proline serine protease cleavage site.

13. A method for testing a compound for enzyme inhibitory activity, said method comprising the steps of

(a) providing a post-prolyl cleaving dipeptidase activity-containing cytoplasmic extract from T-cells which lack CD26 on their surfaces,

(b) contacting said extract with a serine protease reporter substrate of said dipeptidase activity, and with said compound, and

(c) determining whether said compound inhibits cleavage of said reporter substrate.

14. A method of treating a patient infected with HIV, said method comprising administering to said patient an organic compound characterized in that:

(a) it inhibits T-cell cytoplasmic post-prolyl cleaving dipeptidase activity at a concentration above 10^{-3}M,

(b) it interacts with said dipeptidase activity at a concentration below 10^{-8}M, enhancing the ability of said activity to inhibit apoptosis of T-cells of said patient, and

(c) it is capable of crossing the membrane of T-cells of said patient to enter the cytoplasm,

wherein said compound is administered to said patient so that its concentration in the blood of said patient does not exceed 10^{-8}M.

15. The method of claim 14, wherein the $CD4^+$ cound of said patient is higher than 400.

16. The method of claim 14, wherein said compound is administered in conjunction with a therapeutic agent which increases the $CD4^+$ count of HIV-infected patients.

17. A method of treating a viral infection in a patient, said method comprising administering to said patient a viral antigen, together with an adjuvant-acting amount of a compound characterized in that:

(a) it inhibits T-cell cytoplasmic post-prolyl dipeptidase activity at a concentration about 10^{-5}M,

(b) it interacts with said dipeptidase activity at a concentration below 10^{-8}M, enhancing the ability of said activity to inhibit apoptosis of T-cells of said patient, and

(c) it is capable of crossing the membrane of T-cells of said patient to enter the T-cell of cytoplasm,

wherein said compound is administered so that its concentration in the blood of said patient does not exceed 10^{-8}M.

18. The method of claim 11, wherein said virus is HIV.

19. The method of claim 17, wherein said compound is administered orally.

* * * * *

专利名称(译)	增强免疫反应		
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摘要(译)

一种刺激含有细胞质后脯氨酰二肽酶活性的T细胞增殖的方法;在一个方面，该方法涉及使T细胞与浓度低于10-8M的有机化合物接触，其中该化合物的特征在于：（a）它能够穿过T细胞膜进入细胞质，（b）它以低于10-8M的浓度与二肽酶活性结合，因此（c）刺激该浓度下T细胞的增殖。

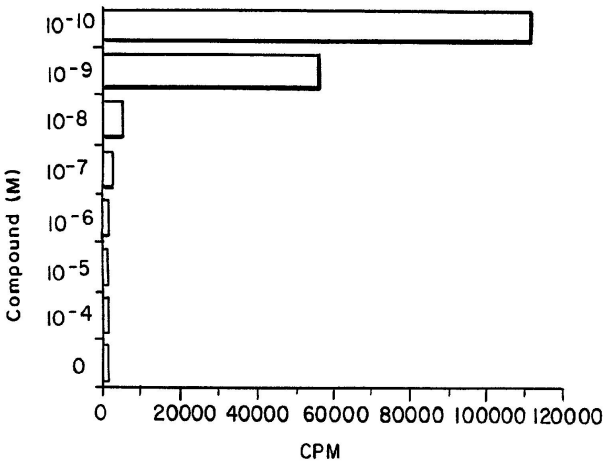

FIG. IA