

every 8 hours or every 4 hours. In another embodiment, the interval is every 3 hours or every 6 hours.

**[0018]** In a preferred embodiment, a first dose of rapamycin of 0.7 mg/kg is administered by IN, followed by daily dose of 1.6 mg/kg by IP until 96 hours. Preferably, the first dose of rapamycin is administered in less than 24 hours following exposure to a toxin. More preferably, the first dose of rapamycin is administered in less than 23 hours, less than 22 hours, less than 21 hours, less than 20 hours, less than 19 hours, less than 18 hours, less than 17 hour, less than 16 hours, less than 15 hours, less than 14 hours, less than 13 hours, less than 12 hours, less than 11 hours, less than 10 hours, less than 9 hours, less than 8 hours, less than 7 hours, less than 6 hours, less than 5 hours, less than 4 hours, less than 3 hours, less than 2 hours, or less than 1 hour.

**[0019]** In some embodiments, rapamycin is administered to a subject via gastrointestinal administration, (such as oral, gavage and rectal administrations) or via parenteral administration (such as intravenous, intramuscular, intranasal, intraperitoneal, and subcutaneous administrations).

**[0020]** Preferably, one or more doses of rapamycin are administered intranasally and additional one or more doses of rapamycin are administered intraperitoneally. More preferably, all doses of rapamycin are administered intranasally.

**[0021]** In a related aspect, the invention relates to use of rapamycin or a pharmaceutical composition comprising rapamycin for the treatment of toxic shock, particularly toxic shock induced by *Staphylococcal* enterotoxin A (SEA), *Staphylococcal* enterotoxin B (SEB), toxic shock syndrome toxin 1 (TSST-1), *streptococcal* pyrogenic exotoxin A (SPEA), or *streptococcal* pyrogenic exotoxin C (SPEC).

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0022]** FIG. 1 demonstrates inhibition of TNF $\alpha$ , IL-1 $\beta$ , IL-6 (FIG. 1A), IL-2, IFN $\gamma$  (FIG. 1B), and MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$  (FIG. 1C) production by human PBMC stimulated with SEB alone or in the presence of various concentrations of rapamycin. Values represent the means $\pm$ SD of duplicate samples from three experiments.

**[0023]** FIG. 2 demonstrates inhibition of T-cell proliferation in PBMC stimulated with SEB alone or in the presence of various concentrations of rapamycin. Values are the means $\pm$ SD of triplicate cultures and represent three experiments.

**[0024]** FIG. 3 demonstrates inhibition of T-cell proliferation in PBMC stimulated with SEA, TSST-1, SPEA, SPEC alone or in the presence of 1  $\mu$ g/mL of rapamycin. Values are the means $\pm$ SD of quadruplicate cultures and represent two experiments.

**[0025]** FIG. 4 demonstrates rapamycin attenuation of the hypothermic response of C3H/HeJ mice treated with SEB. Body temperatures of mice exposed to BSA, SEB, SEB+rapamycin (0.7 mg/kg intranasal) at different time points after SEB exposure are shown. Rapamycin (1.6 mg/kg) was administered i.p. to all mice at 24, 48, 72, and 96 h. Mice received delayed treatment of rapamycin until 24 h also received i.p. doses of rapamycin (1.6 mg/kg) at 30, 48, 72, 96 h following i.n. rapamycin (0.7 mg/kg) at 24 h. Points represent the mean temperature $\pm$ standard deviation (SD) for each group (n=10).

**[0026]** FIG. 5 demonstrates rapamycin prevention of weight loss in murine SEB-mediated shock model. Percentage mean weight data of mice exposed to SEB, SEB+rapamycin (0.7 mg/kg intranasal) at different time points after

SEB are shown. Rapamycin (1.6 mg/kg) was administered i.p. to all mice at 24, 48, 72, and 96 h. Mice receiving delayed treatment of rapamycin until 24 h also received i.p. doses of rapamycin (1.6 mg/kg) at 30, 48, 72, 96 h following i.n. rapamycin (0.7 mg/kg) at 24 h. Points represent the % mean weight change for each group (n=10).

**[0027]** FIG. 6 demonstrates survival analysis of mice treated with (i) SEB, (ii) SEB+dexamethasone starting at 5 h (D5) post SEB exposure, (iii) SEB+rapamycin starting at 2 h (R2) post SEB, (iv) SEB+rapamycin starting at 3 h (R3) post SEB, (v) SEB+rapamycin starting at 4 h (R4) post SEB, (vii) SEB+rapamycin starting at 5 h (R5) post SEB. Time to death is in h after SEB exposure. For comparison, dexamethasone treatment (1.2 mg/kg) administered i.n. at 5 h after SEB, followed by dexamethasone (5 mg/kg) i.p. at 24, 48, 72 and 96 h after SEB was shown (D5).

**[0028]** FIG. 7 shows peak serum levels of MCP-1, IL-6 and IL-2 in mice (n=5) treated with SEB alone or SEB+rapamycin (0.7 mg/kg intranasal at 2 h). Values represent the mean $\pm$ SD of duplicate samples. The “\*” indicates P<0.05 when compared with mice treated with SEB.

**[0029]** FIG. 8 demonstrates rapamycin attenuation of the hypothermic response of C3H/HeJ mice treated with SEB using a shorter time course and a lower dose schedule. Body temperatures of mice exposed to SEB, SEB+rapamycin (0.4 mg/kg intranasal) at 5 h after SEB exposure are shown. Rapamycin group also received rapamycin (0.8 mg/kg) i.p. at 24, and 48 h (ds2). Points represent the mean temperature $\pm$ standard deviation (SD) for each group (n=10).

**[0030]** FIG. 9 demonstrates rapamycin prevention of weight loss in murine SEB-mediated shock model using a shorter time course and a lower dose schedule. Percentage mean weight data of mice exposed to SEB, SEB+rapamycin (0.4 mg/kg intranasal) at 5 h after SEB exposure are shown. Rapamycin group also received rapamycin (0.8 mg/kg) i.p. at 24, and 48 h (ds2). Points represent the % mean weight change for each group (n=10).

**[0031]** FIG. 10 demonstrates rapamycin attenuation of the hypothermic response of C3H/HeJ mice treated with SEB using a lower dose and treatment schedule. Body temperatures of mice exposed to SEB, SEB+rapamycin (0.08 mg/kg intranasal) at 24 h after SEB exposure are shown. Rapamycin group also received rapamycin (0.3 mg/kg) i.p. at 30, 48, 72, and 96 h (ds3). Points represent the mean temperature $\pm$ standard deviation (SD) for each group (n=10).

**[0032]** FIG. 11 demonstrates rapamycin prevention of weight loss in murine SEB-mediated shock model using a lower dose and treatment schedule. Percentage mean weight data of mice exposed to SEB, SEB+rapamycin (0.08 mg/kg intranasal) at 24 h after SEB exposure are shown. Rapamycin group also received rapamycin (0.3 mg/kg) i.p. at 30, 48, 72, and 96 h (ds3). Points represent the % mean weight change for each group (n=10).

**[0033]** FIG. 12 demonstrates rapamycin attenuation of the hypothermic response of C3H/HeJ mice treated with SEB using intranasal doses of rapamycin. Body temperatures of mice exposed to SEB, SEB+rapamycin (0.16 mg/kg intranasal) using 3 different treatment schedules after SEB exposure are shown. Rapamycin (0.16 mg/kg) was administered intranasally to mice at (i) 5, 24, 48, 72, and 96 h; (ii) 5, 24, 48, and 72 h; (iii) 17, 23, 41, 65, and 89 h. Points represent the mean temperature $\pm$ standard deviation (SD) for each group (n=10).

**[0034]** FIG. 13 demonstrates rapamycin prevention of weight loss in murine SEB-mediated shock model using