



(86) Date de dépôt PCT/PCT Filing Date: 2013/12/06
(87) Date publication PCT/PCT Publication Date: 2014/06/12
(85) Entrée phase nationale/National Entry: 2015/06/05
(86) N° demande PCT/PCT Application No.: US 2013/073658
(87) N° publication PCT/PCT Publication No.: 2014/089480
(30) Priorités/Priorities: 2012/12/06 (US61/734,135);
2013/09/23 (US61/881,266)

(51) Cl.Int./Int.Cl. *C07K 14/155* (2006.01),
A61K 39/21 (2006.01), *A61P 25/00* (2006.01)

(71) Demandeur/Applicant:
PIN PHARMA, INC., US

(72) Inventeurs/Inventors:
GOLDBERG, JOSHUA, US;
BIER, COLIN, US;
HOTZ-BEHOFSTITS, CHRISTOPH, US;
HANSCOM, SOPHIE, US

(74) Agent: SMART & BIGGAR

(54) Titre : TRAITEMENT DES AFFECTIONS INFLAMMATOIRES, AUTO-IMMUNES ET NEURODEGENERATIVES AU
MOYEN DE POLYPEPTIDES IMMUNOSUPPRESSEURS DERIVES DE LA PROTEINE TAT
(54) Title: TREATMENT OF INFLAMMATION, AUTOIMMUNE, AND NEURODEGENERATIVE DISORDERS WITH
IMMUNOSUPPRESSIVE TAT DERIVATIVE POLYPEPTIDES

(57) **Abrégé/Abstract:**

The present specification provides immunosuppressive Tat derivative polypeptides, compositions, and methods of using such polypeptides and compositions to treat an autoimmune disease, an inflammation-associated disease and/or a neurodegenerative disease.



- (51) **International Patent Classification:**
C07K 14/155 (2006.01) *A61P 25/00* (2006.01)
A61K 39/21 (2006.01)

(21) **International Application Number:**
PCT/US2013/073658

(22) **International Filing Date:**
6 December 2013 (06.12.2013)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
61/734,135 6 December 2012 (06.12.2012) US
61/881,266 23 September 2013 (23.09.2013) US

(71) **Applicant:** **PIN PHARMA, INC.** [US/US]; Audubon Technology and Business Center, 3960 Broadway, Suite 206, New York, NY 10032 (US).

(72) **Inventors:** **GOLDBERG, Joshua**; Audubon Technology and Business Center, 3960 Broadway, Suite 206, New York, NY 10032 (US). **BIER, Colin**; Audubon Technology and Business Center, 3960 Broadway, Suite 206, New York, NY 10032 (US). **HOTZ-BEHOFSITS, Christoph**; Audubon Technology and Business Center, 3960 Broadway, Suite 206, New York, NY 10032 (US). **HANSCOM, Sophie**; Audubon Technology and Business Center, 3960 Broadway, Suite 206, New York, NY 10032 (US).
- (74) **Agents:** **CULLMAN, Louis C.** et al.; K&L Gates LLP, 1 Park Plaza, 12th Floor, Irvine, CA 92614 (US).

(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

 - *with international search report (Art. 21(3))*
 - *with sequence listing part of description (Rule 5.2(a))*

- (54) **Title:** TREATMENT OF INFLAMMATION, AUTOIMMUNE, AND NEURODEGENERATIVE DISORDERS WITH IMMUNOSUPPRESSIVE TAT DERIVATIVE POLYPEPTIDES
- (57) **Abstract:** The present specification provides immunosuppressive Tat derivative polypeptides, compositions, and methods of using such polypeptides and compositions to treat an autoimmune disease, an inflammation-associated disease and/or a neurodegenerative disease.

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**Treatment of Inflammation, Autoimmune, and Neurodegenerative Disorders
with Immunosuppressive Tat Derivative Polypeptides**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent applications 61/734,135 filed December 6, 2012 and 61/881,266 filed September 23, 2013, the contents of both of which are incorporated by reference herein in their entirety.

FIELD

[0002] The present application is drawn to immunosuppressive Human Immunodeficiency Virus (HIV) transactivator of transcription (Tat) derivative polypeptides for the treatment of diseases characterized by aberrant immune responses such as neurodegenerative and autoimmune diseases and inflammation-associated diseases.

BACKGROUND

[0003] The Human Immunodeficiency Virus (HIV) transactivator of transcription (Tat) mediates at least two independent activities, a receptor-mediated triggering event at the cellular surface and an intracellular trans-activation activity that controls antigen-presenting cell (APC) differentiation. The receptor-mediated triggering event mediated by Tat is specific to APC, committing them for activation and differentiation into highly immunosuppressive antigen presenting cell regulatory macrophages (AReg) or into dendritic cells (DC) that stimulate specific cytotoxic T lymphocytes.

[0004] Antigen-presenting cells, macrophages and dendritic cells are critical in the pathogenesis or response to a variety of diseases, disorders and undesired immune responses. Tat triggers monocytes to differentiate into antigen-presenting macrophages expressing molecules that specifically suppress the immune response to the presented antigen(s). In autoimmune diseases, certain of the body's own endogenous molecules are incorrectly recognized as foreign, resulting in extensive inflammation and tissue damage. In one example, degradation of collagen type II into immunogenic peptides can trigger rheumatoid arthritis (RA) in animals and has been associated with human RA. Considerable research has centered on reducing the immune response to these proteins. The antigen-specific macrophage-induced suppression attributed to Tat can be applied to the reduction of the undesired immune response to foreign and endogenous molecules associated with inflammation and neurodegeneration.

[0005] Attempts to treat inflammation and autoimmune disorders have met with limited success. This is due, in part, to the fact that the etiology of inflammation and autoimmune

disorders is a complex response based in part on the various inflammation-inducing molecules and the multitude of inflammation-mediating and -sensitizing molecules that appear to elicit inflammation via redundant mechanisms. Therefore, compounds, compositions, and methods that can treat inflammation, neurodegenerative disease, or an autoimmune disorder would be highly desirable.

SUMMARY

[0006] The present specification discloses compounds, compositions, and methods for treating an individual suffering from diseases associated with aberrant immune responses, such as neurodegenerative or autoimmune disorders or inflammation-associated diseases. This is accomplished by administering a therapeutically effective amount of an immunosuppressive Tat derivative polypeptide or composition comprising such polypeptides to an individual suffering from the disease. As disclosed herein, the disclosed immunosuppressive Tat derivative polypeptides have demonstrated immunosuppressive activity.

[0007] Disclosed herein are immunosuppressive trans-activator of transcription (Tat) derivative polypeptides comprising an amino acid sequence comprising the following domains in the indicated order; a transcription factor (TF) domain comprising a sequence from an immunosuppressive human immunodeficiency virus (HIV), SIV Tat protein, hairless or an artificial immunosuppressive sequence; a cysteine-rich region from lentiviral Tat or a defensin molecule; and a C-terminal region from a lentiviral Tat protein.

[0008] In another embodiment, the immunosuppressive Tat derivative polypeptide, further comprising an arginine-rich domain from a lentiviral Tat protein. In another embodiment, the TF domain further comprises a repeat sequence comprising (PVDPRLEPWKHPGSQP)_n at the N-terminus, wherein n=2-10. In another embodiment, at least one of the amino acids in the TF domain is modified with a conservative amino acid substitution.

[0009] In another embodiment of the immunosuppressive Tat derivative polypeptide, HIV is HIV-1 or HIV-2. In another embodiment, the lentiviral Tat is from HIV-1, HIV-2, SIV, FIV, BIV, or EIAV.

[0010] In another embodiment of the immunosuppressive Tat derivative polypeptide, the TF domain comprises an amino acid sequence of one of SEQ ID NOs: 36, 39, 44, 48, 50, 54, 59, 60, or 61. In another embodiment, the cysteine-rich domain comprises an amino acid sequence of one of SEQ ID NOs: 37, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 58, 62, 63, 64, or 70. In another embodiment, the C-terminal domain comprises an amino acid sequence of one of SEQ ID NOs: 38, 42, 46, 47, 49, 52, 53, 68, or 71. In yet another

embodiment, both the cysteine-rich region and the C-terminal region are from the same source and the amino acid sequence of the combined cysteine-rich and C-terminal region is one of SEQ ID NOs:47, 49, or 53. In another embodiment, the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity, greater than 90% sequence identity, or greater than 95% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

[0011] Also disclosed herein is a pharmaceutical composition comprising one or more of an immunosuppressive Tat derivative polypeptides and a pharmaceutically acceptable excipient. In another embodiment, the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one or more of SEQ ID NOs:9-11, 13-35, or 69.

[0012] Further disclosed herein is a method of treating a disease characterized by aberrant immune responses, the method comprising: administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptides to a subject in need thereof; and thereby treating the disease by suppressing the immune system.

[0013] Further disclosed herein is a method of increasing the expression of Fas ligand (FasL) on antigen presenting cell regulatory macrophages (AREgs), the method comprising: administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptides to a subject; and thereby increasing the expression of FasL on the AREgs.

[0014] Further disclosed herein is a method of reducing inflammation, the method comprising: administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptides to a subject in need thereof; and thereby increasing reducing inflammation in the subject.

[0015] In one embodiment of the methods disclosed herein, the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

[0016] In another embodiment of the methods, the treatment increases the expression of Fas ligand on antigen presenting cell regulatory macrophages (AREgs). In yet another embodiment, the AREgs are CD14+ macrophages.

[0017] In another embodiment of the methods, the disease is an autoimmune, neurodegenerative or inflammation-associated disorder. In one embodiment, the autoimmune disorder is an acute disseminated encephalomyelitis (ADEM), an Addison's disease, an allergy, allergic rhinitis, an Alzheimer's disease, an anti-phospholipid antibody syndrome (APS), an arthritis, an asthma, an autoimmune deficiency syndrome, an

autoimmune hemolytic anemia, an autoimmune hepatitis, an autoimmune inner ear disease, a bullous pemphigoid, a celiac disease, a Chagas disease, a chronic obstructive pulmonary disease (COPD), a diabetes mellitus type 1 (IDDM), an eczema, an endometriosis, a gastrointestinal disorder, a Goodpasture's syndrome, a Graves' disease, a Guillain-Barré syndrome (GBS), a Hashimoto's thyroiditis, a hidradenitis suppurativa, an idiopathic thrombocytopenic purpura, an inflammatory bowel disease, an inflammatory dermatologic disease, an interstitial cystitis, a lupus, a morphea, a multiple sclerosis (MS), a myasthenia gravis, a myopathy, a narcolepsy, a neuromyotonia, a pemphigus vulgaris, a pernicious anaemia, a primary biliary cirrhosis, a psoriasis, a recurrent disseminated encephalomyelitis, a rheumatic fever, a schizophrenia, a scleroderma, a Sjögren's syndrome, a skin disorder, a tenosynovitis, a uveitis, a vasculitis, or a vitiligo. In another embodiment, the disease associated with inflammation is an acne, an acid reflux/heartburn, an allergy, an allergic rhinitis, an Alzheimer's disease, an appendicitis, an arteritis, an arthritis, an asthma, an atherosclerosis, an autoimmune disorder, a balanitis, a blepharitis, a bronchiolitis, a bronchitis, a bursitis, a cancer, a carditis, a celiac disease, a cellulitis, a cervicitis, a cholangitis, a cholecystitis, a chorioamnionitis, a chronic obstructive pulmonary disease (COPD), a cirrhosis, a colitis, a conjunctivitis, a cystitis, a common cold, a dacryoadenitis, a dementia, a dermatitis, a dermatomyositis, an eczema, an emphysema, an encephalitis, an endocarditis, an endometritis, an enteritis, an enterocolitis, an epicondylitis, an epididymitis, a fasciitis, a fibrositis, a gastritis, a gastroenteritis, a gingivitis, a glomerulonephritis, a glossitis, a heart disease, a hepatitis, a hidradenitis suppurativa, a high blood pressure, an ileitis, an insulin resistance, an interstitial cystitis, an iritis, an ischemic heart disease, a keratitis, a keratoconjunctivitis, a laryngitis, a lupus, a mastitis, a mastoiditis, a meningitis, a metabolic syndrome (syndrome X), a migraine, a multiple sclerosis, a myelitis, a myocarditis, a myopathy, a myositis, a nephritis, a neuropathy, an obesity, an omphalitis, an oophoritis, an orchitis, an osteochondritis, an osteopenia, an osteoporosis, an osteitis, an otitis, a pancreatitis, a Parkinson's disease, a parotitis, a pelvic inflammatory disease, a pericarditis, a peritonitis, a pharyngitis, a phlebitis, a pleuritis, a pneumonitis, a proctitis, a prostatitis, a psoriasis, a pulpitis, a pyelonephritis, a pyelephlebitis, a rheumatic fever, a rhinitis, a salpingitis, a sialadenitis, a sinusitis, a spastic colon, a stomatitis, a synovitis, a tendonitis, a tendinosis, a tenosynovitis, a thrombophlebitis, a tonsillitis, a trigonitis, a tumor, an urethritis, an uveitis, a vaginitis, a vasculitis, or a vulvitis. In yet another embodiment, the neurodegenerative disease is Alexander disease, Alper's disease, Alzheimer's disease, amyloidoses, amyotrophic lateral sclerosis, anxiety, ataxia telangiectasia, attention deficit disorders, Canavan disease, central nervous system injuries, Charcot Marie Tooth disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, encephalitis (e.g., bacterial, parasitic, fungal, or viral), Friedreich's ataxia frontotemporal

dementia, hereditary spastic paraparesis, Guillain-Barre syndrome (and its variants acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher syndrome), HIV/AIDS dementia complex, Huntington's disease, ischemic damage to the nervous system, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, meningitis (e.g., bacterial, parasitic, fungal, or viral) multiple sclerosis, multiple system atrophy, neural trauma, e.g., percussive brain damage, spinal cord injury and traumatic damage to the nervous system, a neuropathy such as e.g., chemotherapy-induced neuropathy, diabetes-associated neuropathy, and peripheral neuropathy, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, prion disorders, progressive supranuclear palsy, Refsum's disease, Sandhoff disease, schizophrenia, Schilder's disease, spinocerebellar atrophies, Steele-Richardson-Olszewski disease, stroke, tabes dorsalis, or vascular dementia.

[0018] In yet another embodiment of the methods, the administration further causes the reduction of at least one symptom associated with the autoimmune disease, neurodegenerative disease, or disease associated with inflammation and therein the symptom is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, infertility or reduced sex drive (low libido), blood sugar changes, and depending on the type of autoimmune disease, an increase in the size of an organ or tissue, or the destruction of an organ or tissue.

[0019] In another embodiment of the methods, the subject is not immunocompromised. In another embodiment, the immune system of the subject is not compromised as a result of the administration. In yet another embodiment, as a result of the administration, secretion of cytokines by ARegs is decreased.

[0020] In another embodiment of the methods, the immunosuppressive Tat derivative polypeptide is administered in a plurality of doses. In another embodiment, the immunosuppressive Tat derivative polypeptide is administered daily, weekly, biweekly, monthly, or bimonthly. In yet another embodiment, the administering step comprises a repetitive administration cycle wherein each cycle comprises administering a plurality of doses of the immunosuppressive Tat derivative polypeptide in a defined time period followed by a rest period and wherein the cycle is repeated a plurality of times.

[0021] Also disclosed herein is the use of one or more immunosuppressive Tat derivative polypeptides in the manufacture of a medicament for treatment of a disease characterized by aberrant immune responses in a subject in need thereof; wherein the one

or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, and wherein administration of the immunosuppressive Tat derivative polypeptide treats the disease by suppressing the immune system in the subject.

[0022] Further disclosed herein is the use of one or more immunosuppressive Tat derivative polypeptides in the manufacture of a medicament for increasing the expression of Fas ligand (FasL) on antigen presenting cell regulatory macrophages (AREgs) in a subject wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, wherein administration of the immunosuppressive Tat derivative polypeptides increases the expression of FasL on the AREgs.

[0023] Further disclosed herein is the use of one or more immunosuppressive Tat derivative peptides in the manufacture of a medicament for reducing inflammation in a subject, wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, and wherein administration of the immunosuppressive Tat derivative polypeptides reduces inflammation in the subject.

[0024] In another embodiment of the use, the treatment increases the expression of Fas ligand on antigen presenting cell regulatory macrophages (AREgs). In another embodiment, the AREgs are CD14+ macrophages. In another embodiment, secretion of cytokines by AREgs is decreased. In yet another embodiment, the subject is not immunocompromised. In yet another embodiment, the immune system of the subject is not compromised as a result of the administration.

[0025] In yet another embodiment of the use, the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

[0026] In another embodiment of the use, the disease is an autoimmune, neurodegenerative or inflammation-associated disorder. In another embodiment, the autoimmune disorder is an acute disseminated encephalomyelitis (ADEM), an Addison's disease, an allergy, allergic rhinitis, an Alzheimer's disease, an anti-phospholipid antibody syndrome (APS), an arthritis, an asthma, an autoimmune deficiency syndrome, an autoimmune hemolytic anemia, an autoimmune hepatitis, an autoimmune inner ear disease, a bullous pemphigoid, a celiac disease, a Chagas disease, a chronic obstructive pulmonary disease (COPD), a diabetes mellitus type 1 (IDDM), an eczema, an endometriosis, a gastrointestinal disorder, a Goodpasture's syndrome, a Graves' disease, a Guillain-Barré

syndrome (GBS), a Hashimoto's thyroiditis, a hidradenitis suppurativa, an idiopathic thrombocytopenic purpura, an inflammatory bowel disease, an inflammatory dermatologic disease, an interstitial cystitis, a lupus, a morphea, a multiple sclerosis (MS), a myasthenia gravis, a myopathy, a narcolepsy, a neuromyotonia, a pemphigus vulgaris, a pernicious anaemia, a primary biliary cirrhosis, a psoriasis, a recurrent disseminated encephalomyelitis, a rheumatic fever, a schizophrenia, a scleroderma, a Sjögren's syndrome, a skin disorder, a tenosynovitis, a uveitis, a vasculitis, or a vitiligo. In another embodiment, the disease associated with inflammation is an acne, an acid reflux/heartburn, an allergy, an allergic rhinitis, an Alzheimer's disease, an appendicitis, an arteritis, an arthritis, an asthma, an atherosclerosis, an autoimmune disorder, a balanitis, a blepharitis, a bronchiolitis, a bronchitis, a bursitis, a cancer, a carditis, a celiac disease, a cellulitis, a cervicitis, a cholangitis, a cholecystitis, a chorioamnionitis, a chronic obstructive pulmonary disease (COPD), a cirrhosis, a colitis, a conjunctivitis, a cystitis, a common cold, a dacryoadenitis, a dementia, a dermatitis, a dermatomyositis, an eczema, an emphysema, an encephalitis, an endocarditis, an endometritis, an enteritis, an enterocolitis, an epicondylitis, an epididymitis, a fasciitis, a fibrositis, a gastritis, a gastroenteritis, a gingivitis, a glomerulonephritis, a glossitis, a heart disease, a hepatitis, a hidradenitis suppurativa, a high blood pressure, an ileitis, an insulin resistance, an interstitial cystitis, an iritis, an ischemic heart disease, a keratitis, a keratoconjunctivitis, a laryngitis, a lupus, a mastitis, a mastoiditis, a meningitis, a metabolic syndrome (syndrome X), a migraine, a multiple sclerosis, a myelitis, a myocarditis, a myopathy, a myositis, a nephritis, a neuropathy, an obesity, an omphalitis, an oophoritis, an orchitis, an osteochondritis, an osteopenia, an osteoporosis, an osteitis, an otitis, a pancreatitis, a Parkinson's disease, a parotitis, a pelvic inflammatory disease, a pericarditis, a peritonitis, a pharyngitis, a phlebitis, a pleuritis, a pneumonitis, a proctitis, a prostatitis, a psoriasis, a pulpitis, a pyelonephritis, a pyelephlebitis, a rheumatic fever, a rhinitis, a salpingitis, a sialadenitis, a sinusitis, a spastic colon, a stomatitis, a synovitis, a tendonitis, a tendinosis, a tenosynovitis, a thrombophlebitis, a tonsillitis, a trigonitis, a tumor, an urethritis, an uveitis, a vaginitis, a vasculitis, or a vulvitis. In yet another embodiment, the neurodegenerative disease is Alexander disease, Alper's disease, Alzheimer's disease, amyloidoses, amyotrophic lateral sclerosis, anxiety, ataxia telangiectasia, attention deficit disorders, Canavan disease, central nervous system injuries, Charcot Marie Tooth disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, encephalitis (e.g., bacterial, parasitic, fungal, or viral), Friedreich's ataxia frontotemporal dementia, hereditary spastic paraparesis, Guillain-Barre syndrome (and its variants acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher syndrome), HIV/AIDS dementia complex, Huntington's disease, ischemic damage to the nervous system, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-

Joseph disease, meningitis (e.g., bacterial, parasitic, fungal, or viral), multiple sclerosis, multiple system atrophy, neural trauma, e.g., percussive brain damage, spinal cord injury and traumatic damage to the nervous system, a neuropathy such as e.g., chemotherapy-induced neuropathy, diabetes-associated neuropathy, and peripheral neuropathy, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, prion disorders, progressive supranuclear palsy, Refsum's disease, Sandhoff disease, schizophrenia, Schilder's disease, spinocerebellar atrophies, Steele-Richardson-Olszewski disease, stroke, tabes dorsalis, or vascular dementia.

[0027] In another embodiment of the use, the immunosuppressive Tat derivative polypeptide further causes the reduction of at least one symptom associated with the autoimmune disease, neurodegenerative disease, or disease associated with inflammation and therein the symptom is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, infertility or reduced sex drive (low libido), blood sugar changes, and depending on the type of autoimmune disease, an increase in the size of an organ or tissue, or the destruction of an organ or tissue.

[0028] In another embodiment of the use, the immunosuppressive Tat derivative polypeptide is administered in a plurality of doses. In another embodiment, the immunosuppressive Tat derivative polypeptide is administered daily, weekly, biweekly, monthly, or bimonthly. In yet another embodiment, the administering step comprises a repetitive administration cycle wherein each cycle comprises administering a plurality of doses of the immunosuppressive Tat derivative polypeptide in a defined time period followed by a rest period and wherein the cycle is repeated a plurality of times.

BRIEF DESCRIPTION OF DRAWINGS

[0029] FIG. 1 depicts fluorescence activated cell sorter (FACS) analysis of the results of Tat activation of monocytes. Human peripheral blood monocytes were committed to differentiate into dendritic cells (DC) through five days of culture in GM-CSF and IL-4. Committed DCs were cultured overnight either in medium alone (control), lipopolysaccharide (LPS), or Tat, after which they were stained with an anti-CD86 antibody and analyzed by FACScan for CD86, a specific marker of DC activation, induction (left panel) or generalized activation (right panel, enlargement into box R2, shown for Tat-stimulated cells).

[0030] FIG. 2 depicts the enhancement of antigen-specific activation of cytotoxic T lymphocytes (CTL) by Tat*-antigen (Ag) complexes. CTL activity was quantitated as the

number of γ -interferon-secreting spot-forming colonies (SFC)/ 10^6 plated cells using ELISPOT assays.

[0031] FIG. 3 depicts median fluorescence of monocytes, cultured for six days either with no stimulus (0), tumor necrosis factor-alpha (TNF- α), LPS, decreasing concentrations of C-Tat (conventional native immunosuppressive Tat from HIV), or oxidized C-Tat (ox-C-Tat) and stained with an anti-Fas ligand (FasL) monoclonal antibody (Mab) followed by a fluoresceinated goat anti-mouse polyclonal antibody.

[0032] FIG. 4A-B depict antibody titer to an immunogenic antigen in the presence of the immunosuppressive Tat (PT) or with non-immunosuppressive ox-Tat* (Ag) after two weeks (FIG. 4A) or six weeks (FIG. 4B).

[0033] FIG. 5 depicts FACS analysis of mouse peritoneal macrophages that were isolated either after *in vivo* thioglycolate stimulation (stimulated + adjuvant) or without *in vivo* stimulation (resting). Mouse peritoneal macrophages were cultured for five days either in the absence of additional stimulation (C), with LPS or with Tat. Activation was determined as percent enlarged cells (M1 fraction).

[0034] FIG. 6 depicts stable suppression of antigen-stimulated T lymphocytes by Tat-Ag complexes two weeks after immunization with immunosuppressive Tat.

[0035] FIG. 7 depicts the antigen-specificity of Tat suppression. Mice were immunized at day 0 and boosted at day 7 with an adjuvant emulsion containing either Tat (Ag+Tat), or with Ag alone as control. At day 14, draining lymph node cells were harvested and stimulated with either specific or non-specific antigen and proliferation measured by ^3H thymidine uptake (CPM) after four days of culture.

[0036] FIG. 8 depicts FACS analysis of human peripheral blood monocytes cultured for four days in control medium (control), or medium containing Tat or LPS. Harvested cells were doubly stained with a fluoresceinated anti-FasL Mab ($\alpha\text{FasL-FITC}$) and with an anti-CD14 rhodamine labeled Mab. Cells were analyzed by FACScan for activation (forward scatter), CD14 expression (% macrophages, R2), and for induction of FasL (MFI). The T cell population is labeled R1.

[0037] FIG. 9A-B depicts the regulatory and immunosuppressive characteristics of Tat-activated macrophages. (A) Human peripheral blood mononuclear cells (PBMC) from one individual (PBMCs #3) cultured for five days in either medium with tetanus antigen (Ag), antigen with the further addition of Tat (Ag+Tat) or Ag with Tat and recombinant sFas protein (Ag+Tat+sFas). The results are graphed as stimulation index (mean cpm stimulated culture/mean cpm medium control). (B) Proliferation of PBMCs cultured 6 days with either

tetanus or *Candida* antigen alone (Ag), compared with cultures in which Tat (Ag+Tat), or Tat and the antagonistic anti-Fas antibody, ZB4, were added (Ag+Tat+ α Fas).

[0038] FIG. 10 depicts stimulation of human monocytes with Tat derivatives.

[0039] FIG. 11 depicts a dose-response curve of stimulation of human monocytes with Tat derivatives.

[0040] FIG. 12A-C depicts staining of Jurkat cells with Hoechst-NucBlue and Alexa488-labeled Tat derivative SEQ ID NO:9 (FIG. 12A), Alexa488-labeled Tat derivative SEQ ID NO:11 (FIG. 12B), or control (no Tat derivative, FIG. 12C). Left column represents nuclear staining with Hoechst-NucBlue, center column represents Alexa488 staining, and the right column depicts a merge of the left and center images.

[0041] FIG. 13A-C depicts staining of U937 cells with Hoechst-NucBlue and Alexa488-labeled Tat derivative SEQ ID NO:9 (FIG. 13A), Alexa488-labeled Tat derivative SEQ ID NO:11 (FIG. 13B), or control (no Tat derivative, FIG. 13C). Left column represents nuclear staining with Hoechst-NucBlue, center column represents Alexa488 staining, and the right column depicts a merge of the left and center images.

[0042] FIG. 14A-C depicts activation of human peripheral blood mononuclear cells (PBMC), as measured by FasL expression, with no stimulus (FIG. 14A), LPS (FIG. 14B), or Tat derivative SEQ ID NO:9 (FIG. 14C).

[0043] FIG. 15 depicts proliferation of human CD14⁺ PBMCs, as measured by cell surface CD14 expression, with no stimulus, LPS, or Tat derivative SEQ ID NO:9.

[0044] FIG. 16 depicts the percent CD14⁺ cells in three day cultures of PBMCs treated with LPS, Tat derivative SEQ ID NO:9, or with no stimulus.

[0045] FIG. 17A-E depicts PBMCs expressing both FasL and CD14 after treatment with TNF-alpha (FIG. 17B), LPS (FIG. 17C), Tat derivative SEQ ID NO:9 (FIG. 17D), or with no stimulation (FIG. 17A) after five days in culture. FIG. 17E depicts the data from FIGs. 17A-D in graphical format.

DESCRIPTION

[0046] The present specification relates to compounds, compositions, and methods for treating an individual suffering from diseases associated with aberrant immune responses, such as autoimmune disorders including neurodegenerative disorders, or inflammation-associated disorders. This is accomplished by administering a therapeutically effective amount of an immunosuppressive Tat derivative polypeptide or composition comprising such polypeptides to an individual suffering from the diseases. As disclosed herein, the disclosed

immunosuppressive Tat derivative polypeptides have anti-inflammatory activities. The immunosuppressive derivative peptides within the scope of the present disclosure are immunosuppressive.

[0047] As used herein the term “aberrant immune responses” refers to increased, undesirable, excessive, or inappropriate immune responses in which the immune response to antigens, such as self antigens, is increased such that inflammation and/or autoimmune disease or neurodegenerative disease is seen. Aberrant immune responses, as used herein, are characterized by an immune cascade resulting in destruction of the body’s tissue. Typically, an aberrant immune result is not seen in a normal response to infection but can be triggered by infection.

[0048] The HIV Tat protein is a variable RNA binding peptide of 86-110 amino acids in length that is encoded on two separate exons of the HIV genome. Based on molecular analysis, the Tat protein (SEQ ID NO:2) encodes distinct and linked peptide activities. This present disclosure describes polypeptide compositions that are derivatized from the canonical HIV-1 Tat structure in at least at the first or amino terminal portion, in a manner to enhance the immunotherapeutic potential of the polypeptide. The amino terminal portion of Tat includes a short peptide region from a nuclear transcription factor (TF) typically flanked by proline residues. This region determines, at least in part, how stimulatory or how suppressive the Tat polypeptide is for cells of the immune system, particularly innate immune cells such as dendritic cells (DC) and macrophages (antigen-presenting cells or APCs). Consequently, it is predicted that modifications to the TF region can render the polypeptides more active in the therapy of disease.

[0049] Previous studies determined that HIV Tat is immunosuppressive in the majority of human HIV strains. However, in long-term non-progressors (LTNP), a subset of HIV-infected individuals with high viral loads who do not have a significant reduction in T4 cells and do not progress to Acquired Immunodeficiency Syndrome (AIDS), the HIV Tat protein is immunostimulatory. The Tat protein found in LTNP is capable of trans-activating viral RNA; however, LTNP Tat (designated herein after as “IS-Tat” for immunostimulatory Tat) does not induce apoptosis in T4 cells or macrophages and is not immunosuppressive. Moreover, T4 cells infected *ex vivo* with HIV isolated from LTNP (such cell lines are designated “Tat TcL”) overexpress IS-Tat proteins, often to the virtual exclusion of other viral proteins, that are strongly growth promoting rather than pro-apoptotic. The *tat* genes cloned from these Tat TcLs reveal sequence variations in two *tat* regions, at the amino terminus and within the first part of the second exon.

[0050] Based on molecular analysis, the HIV Tat protein (SEQ ID NO:2) contains three distinct regions of interest. The first region of interest is the transduction domain at the amino terminus of Tat (amino acids 3-19). A second region of interest is a cysteine-rich ligand binding domain (amino acids 22-37) which contains seven conserved cysteines. A third region of interest is the membrane translocation sequence (MTS) which encompasses amino acids 47-57.

[0051] The proline rich stretch near the amino terminus (amino acids 3-19) of HIV-1 and HIV-2 Tat within the transduction domain is an SH3 binding domain having significant homology to the SH3-binding domain of the mouse *hairless (hr)* gene (SEQ ID NO:72). The SH3 binding domain presents an important target for pharmaceutical development with the potential for the diagnosis, prophylaxis and treatment of undesirable cellular processes such as autoimmunity.

[0052] Unexpectedly, mice expressing the *hr* gene mutation develop an AIDS-like syndrome characterized by poor CTL function, a shift in helper T lymphocytes from those regulating cell-mediated immunity (TH1) to those regulating antibody-mediated immunity (TH2), and increased susceptibility to chemical and ultraviolet light-induced skin cancers. Additionally, variants of Tat are found in retrovirus-infected monkeys which do not develop immunodeficiency and that do not have epidemic infection. However, these variant Tat do not have the SH3 binding domain and instead substitute a different sequence, also set off by prolines at either end of the sequence, into the transduction domain. Therefore, the SH3 binding domain is central to the immunosuppressive activity of Tat. Genetic data indicates the SH3 binding domain regulates monocyte differentiation into antigen-presenting cell regulatory macrophages (AREgs). In Tat proteins which do not contain this SH3 domain, or this domain is mutated, monocyte differentiation is directed into DCs which stimulate CTL responses

[0053] The MTS region permits Tat to freely traffic across the endosomal membrane into the cytoplasm following receptor binding, where it transactivates gene expression, including but not restricted to, genes of HIV-1. The MTS has been wrongly assumed to facilitate Tat entrance into the cell, which it can only accomplish at high concentrations that have been impossible to attain *in vivo*.

[0054] Unlike the current immunosuppressive therapies, the disclosed Tat-based compositions, the immunosuppressive Tat derivative polypeptides, have the potential to suppress antigen-specific immune responses without immunocompromising the patient. They preserve the immunosuppressive activity of conventional HIV Tat in the absence of the virus and therefore the immunosuppressive Tat derivatives modulate the specificity of the

immune response, a key component to the bodies natural defense This is particularly important when chronic immunosuppressive therapy is needed, such as in autoimmune, neurodegenerative, or inflammation-associated diseases.

[0055] The immunosuppressive effects of Tat are mediated by macrophages. When stimulated by Tat, either by natural HIV-1 infection or by Tat uptake, macrophages induce the Fas ligand (FasL), which in turn induces the programmed cell death (apoptosis) of antigen-reacting, Fas-expressing helper T cells (FIG. 3). Tat enhances the viability of cultured murine macrophages as long as the macrophages were first activated *in vivo* compared with no prior activation and stimulated with relatively high concentrations of Tat. By comparison, LPS promotes the viability of murine macrophages independently from *in vivo* stimulation, and at the same concentration effective for human macrophages. Certain of the Tat-based compositions disclosed herein produce a stable suppression of mouse lymphocyte proliferation and may also serve to suppress an antigen-specific immune response to a variety of antigens.

[0056] The macrophages responsible for these responses have been identified as antigen presenting cell regulatory macrophages (AREgs). AREgs are also known as “alternatively activated” macrophages. AREgs are stable macrophages expressing FasL and secreting the cytokines IL-10 and IL-6. AReg are stable and respond in an autocrine and paracrine manner to these two cytokines, as well as in a paracrine manner to IL-4. These cytokines accumulate and switch the immune response from TH1 (based on helper T lymphocytes) to TH2 (based on suppressive T lymphocytes). As these cytokines build up, they overwhelm and suppress the immune response and explain why immune responses are normally self-limiting in an antigen-specific manner.

[0057] An unexpected observation is that 1,000 fold lower concentrations of Tat (500 pM) trigger this effect on the macrophages, as compared with the concentration required to initiate direct apoptosis of CD4+ T cells (approximately 500 nM). Therefore, at concentrations of Tat achievable as a systemically administered immunomodulator, the macrophage effect will preferentially occur over the T cell effect.

[0058] The Tat-mediated antigen-specific suppression is mediated through trans-(intracellular) activation of a CD14+ FasL+ macrophage. Tat-activated macrophages are immunosuppressive AREgs. At low concentrations of Tat (50 nM), Tat-induced immunosuppression was not only fully reversed by the addition of soluble Fas, but under these conditions, Tat actually became slightly stimulatory (relative to antigen treatment alone). Antibodies to FasL reversed Tat immunosuppression of tetanus responses and enhanced the *Candida* response relative to Tat treatment alone. Suppression could be fully

reversed (>95% of control) with the further addition of anti-IL-10 and anti-IL-6 antibodies to the cultures, both cytokines deriving from macrophages under these culture conditions. A portion of Tat-induced immunosuppression is contributed by induction of FasL, although other Tat-induced factors can participate in suppressing T cell proliferative responses, especially at higher concentrations of Tat.

[0059] The complete amino acid sequence of HIV-1 Tat encoded by exons 1 and 2 of the Tat gene is listed below:

ATG	GAG	CCC	GTG	GAC	CCT	CGC	CTG	GAG	CCC	TGG	AAG	CAC	CCG	GGC	AGC	
Met	Glu	<u>Pro</u>	Val	Asp	Pro	Arg	Leu	Glu	Pro	Trp	Lys	His	Pro	Gly	Ser	
1			5					10/30					15			
CAG	CCC	AAG	ACC	GCC	TGC	ACC	ACA	TGT	TACT	GC	AAG	AAG	TGC	TGC	TTC	
<u>Gln</u>	<u>Pro</u>	<u>Lys</u>	Thr	Ala	Cys	Thr	Thr	Cys	Tyr	Cys	Lys	Lys	Cys	Cys	Phe	
			20/60					25					30/90			
CAC	TGC	CAG	GTG	TGC	TTC	ACC	AAG	AAG	GCC	TTG	GGC	ATC	AGC	TAC	GGC	
His	Cys	Gln	Val	Cys	Phe	Thr	Lys	Lys	Ala	Leu	Gly	Ile	Ser	Tyr	Gly	
		35					40/120					45				
CGC	AAG	AAG	CGC	CGG	CAG	CGC	CGC	CGG	GCC	CCT	GAG	GAC	AGC	CAG	ACC	
Arg	Lys	Lys	Arg	Arg	Gln	Arg	Arg	Arg	Ala	Pro	Glu	Asp	Ser	Gln	Thr	
	50/150					55					60/180					
CAC	CAG	GTG	AGC	CCT	CCC	AAG	CAG	CCC	GCT	CCA	CAG	TTC	CGC	GGC	GAC	
His	Gln	Val	Ser	Pro	Pro	Lys	Gln	Pro	Ala	Pro	Gln	Phe	Arg	Gly	Asp	
65					70/210			75						80/240		
CCT	ACC	GGT	CCC	AAG	GAG	AGC	AAG	AAG	AAG	GTG	GAG	CGC	GAG	ACC	GAG	
Pro	Thr	Gly	Pro	Lys	Glu	Ser	Lys	Lys	Lys	Val	Glu	Arg	Glu	Thr	Glu	
			85					90/270					95			
ACC	CAT	CCC	GTC	GAC												
Thr	His	Pro	Val	Asp												
			100/300													

SEQ ID NO:1

SEQ ID NO:2

[0060] Tat has a proline (P) rich segment near the amino terminus (amino acids 3-19, underlined above). This highly conserved region of HIV-1 Tat is a canonical SH3 binding domain also referred to herein as a nuclear transcription factor (TF) domain. The mouse hairless (*hr*) gene also has an SH3 binding motif (TF, amino acids 176-196 of *hr*, SEQ ID NO:72). Homology exists between the human Tat SH3 binding domain (SEQ ID NO:4) and the SH3 binding domain of the mouse *hr* gene:

Human	3	Pro	Val	Arg	Pro	Asn	Leu	Glu	Pro	Trp	Lys	His	Pro	Gly	Ser	Gln	Pro
	18																
Mouse	180	Pro	Leu	Thr	Pro	Asn	-----	Pro	Trp	Val	Tyr	Ser	Gly	Ser	Gln	Pro	
	193																

[0061] Variants of Tat found in simian retroviruses, which do not cause immunodeficiency, do not have an SH3 binding domain but instead have the following proline-flanked sequence:

Pro Leu Arg Glu Gln Glu Asn Ser Leu Glu Ser Ser Asn Glu Arg Ser Ser Cys Ile Leu Glu Ala
Asp Ala Thr Thr Pro (SEQ ID NO:3)

[0062] The human equivalent of the simian sequence (SEQ ID NO:3) above is:

Ser Asn Glu Arg Ser Ser Cys Glu Leu Glu Val (SEQ ID NO. 4)

[0063] Another region of interest is a cysteine-rich proposed ligand binding domain (amino acids 22-37) which contains seven cysteines.

Cys Thr Thr Cys Tyr Cys Lys Lys Cys Cys Phe His Cys Gln Val Cys (SEQ ID NO:5)

[0064] Derivatives of Tat, generated through modulating the signal transduction motif defined by the SH3 binding domain, drive differentiation predominantly to dendritic cells or immunosuppressive AReg. AReg are also critical contributors to invasion of gastric, pancreas, and ductal infiltrating breast tumors, as well as components of tolerance in organ transplantation. The two external prolines at positions 3 and 18 flanking the SH3 domain are maintained in order to facilitate the proper structure for SH3 binding. In addition, the transduction domain from a non-immunosuppressive human variant Tat, or the domain from the *hr* mutation, can replace amino acids 3-19 of Tat, although the *hr* sequence is predicted to increase suppression. In addition, the stimulatory simian form of Tat (SEQ ID NO:3), or its human equivalent sequence (SEQ ID NO:4), can be substituted at this domain. Additional chemical modifications, such as ox-Tat (chemically oxidized Tat as disclosed in US 2006/0160183, incorporated by reference for all it contains regarding Tat derivatives), can be used for stimulation of dendritic/CTL responses.

[0065] In one embodiment disclosed herein, the immunosuppressive Tat derivative comprises a Tat peptide in which amino acids 3-19 are altered. These alterations include replacement of individual amino acids with alternate amino acids or replacement of all of amino acids 3-19 with another sequence. Tat peptides suitable for use in constructing the disclosed immunosuppressive Tat derivatives include Tat from HIV-1 variants, HIV-2 variants, and SIV variants. SIV variants can be from any species of primate that is infected with SIV as listed in Table 4. Also useful are immunosuppressive lentiviral Tat sequences from non-primate species including, but not limited to, feline (Tat from feline immunodeficiency virus, FIV), bovine, (Tat from bovine immunodeficiency virus, BIV), or equine (Tat from equine infectious anemia virus, EIAV). For the purposes of the instant

disclosure, the term “variants” refers to peptides corresponding to the sequence of different strains, naturally occurring or mutated, of the indicated viruses.

[0066] SH3 binding proteins contain a series of internal prolines required for nuclear transcription factor (TF) function. In certain embodiments, the internal prolines are each substituted by alanine, rendering the SH3-binding site inactive.

[0067] Exemplary immunosuppressive Tat derivatives within the scope of the present disclosure are presented in Table 1. In general, an immunosuppressive Tat derivative polypeptide for the treatment of inflammation, autoimmune disorders, and neurodegeneration comprises three regions. The first region is a derivatized TF, the second region is a cysteine-rich region, and the third region is a C-terminal Tat region.

[0068] The TF region, cysteine-rich region, and a C-terminal region are arranged in the Tat derivative polypeptide in that order. The TF region may be derived from a source including, but not limited to, HIV-1 Tat, HIV-2 Tat, SIV Tat, the hairless gene, or an artificial immunosuppressive sequences. The cysteine-rich region may be from a lentivirus Tat, or cysteine rich defensin molecule. The C-terminal region may be derived from lentivirus Tat. Additionally, the Tat derivative C-terminal regions may contain therein an arginine-rich region from HIV-1 Tat, HIV-2 Tat, or SIV Tat (also referred to as the membrane translocation sequence).

[0069] As used herein, the term “defensin molecule” refers to small cysteine-rich cationic proteins found in both vertebrates and invertebrates. Defensins comprise 18-45 amino acids including six to eight conserved cysteine residues. Defensins are classified in three groups, α -defensins, β -defensins and θ -defensins.

[0070] In another embodiment, the TF region further contains a repeat sequence including, but not limited to, (PVDPRLEPWKHPGSQP)_n (SEQ ID NO:12) wherein n=2-10 at the N-terminus. Furthermore, the repeat sequence can be separated from the N-terminus of an immunosuppressive Tat derivative polypeptide by one or more amino acids acting as a spacer.

[0071] In another embodiment, the amino acid sequence of the TF region is one of SEQ ID NOs:36, 39, 44, 48, 50, 54, 59, 60, or 61. In another embodiment, the amino acid sequence of the cysteine-rich region is one of SEQ ID NOs:37, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 58, 62, 63, 64 or 70. In another embodiment, the amino acid sequence of the C-terminal region is one of SEQ ID NOs:38, 42, 46, 47, 49, 52, 53, 68 or 71. In yet another embodiment, both the cysteine-rich region and the C-terminal region are from the same source and the amino acid sequence of the cysteine-rich/C-terminal region is one of SEQ ID NO:47, 49, or 53.

[0072] In additional embodiments, one or more amino acids, including but not limited to proline, in the TF domain is deleted or substituted with a conservative amino acid substitution.

[0073] In additional embodiments the use of conservatively modified variants of the immunosuppressive Tat derivatives is provided. The variants described herein maintain the biological activity of the parent or source molecule.

Table 1.

SEQ ID NO.	Amino Acid Sequence	Source† (SEQ ID NO:)		
		TF region	cysteine-rich region	C-terminal region
6 (Nani-P1)	MEPVDANLEAWKHAGSQPRKTACTTCYCKKCCFHCQVCFTKGL GISYGRKKRRQRRRAPQDSQTHQASLSKQPASQSRGDPTGPTES KKKVERETETDPFD	HIV-1 SEQ ID NO:59	HIV-1 SEQ ID NO:62	HIV-1 SEQ ID NO:42
7 (Nani-P2)	MDPKGEEDQDVSHQDLIKQYRKPRTACNNCYCKKCCFHCYACFL RKGLGITYHAFRTRRKIASADRI PV PQQSISIRGRDSQTTQESQK KVEEQAKANLRISRKNLGDTRGPVGAGN	SIVagm ^a SEQ ID NO:60	HIV-1 SEQ ID NO:63	SIVagm SEQ ID NO:68
8 (Nani-P3)	METPLKEQENSLESCREHSSSISEVDVPTPVSLRKGGRCWNRCI GNTRQIGSCGVPFLKCCKRKPFTRKGLGISYGRKKRRQRRRAPQ DSQTHQASLSKQPASQSRGDPTGPTESKKKVERETETDPFD	SIVsmm ^b SEQ ID NO:61	Murine β - defensin-3 SEQ ID NO:64	HIV-1 SEQ ID NO:42
9	MDPIDPDLEPWKHPGSQPETACNNCFCKKCSYHCLVCFQKKGLG ISHGRKKRRQRRSAPPSSDHQNLISKQPIPTQGDQTGSEESKK KVESKTETDPFD	SIVcpz ^c SEQ ID NO:39	HIV-1 SEQ ID NO:65	HIV-1 SEQ ID NO:42
10	MEPLTPHPWVYSGGQPKVPTTACSKCYCKICWHCQLCLKKGLG ISYGRKKRRQRRRAPQDSQTHQASLSKQPASQSRGDPTGPTESK KKVERETETDPFD	Human <i>hr</i> gene SEQ ID NO:48	HIV-1 SEQ ID NO:66	HIV-1 SEQ ID NO:42
11	MAGPHPVIVITGPHEEPRKTACTTCYCKKCCFHCQVCFTKGLGIS YGRKKRRQRRRAPQDSQTHQASLSKQPASQSRGDPTGPTESKK KVERETETDPFD	VIVIT ^d SEQ ID NO:50	HIV-1 SEQ ID NO:67	HIV-1 SEQ ID NO:42
13	MDPTDPELPPWQQPGSQPPTPRKTACTTCYCKKCCFHCQVCFL QKGLGITYARPRKRAARSISED SAPTEPYGPEGPRQTRRRRRR QWRQRRTQRLYLQQRIFEAFGSRTAALED SLQQLQISD	SIVgor ^e SEQ ID NO:36	HIV-1 SEQ ID NO:37	SIVsyk ^f SEQ ID NO:38
14	MDPIDPDLEPWKHPGSQPETACNNCFCKKCSYHCLVCFQKGLGI TYARPRKRAARSISED SAPTEPYGPEGPRQTRRRRRRQWRQ RRTQRLYLQQRIFEAFGSRTAALED SLQQLQISD	SIVcpz SEQ ID NO:39	HIV-1 SEQ ID NO:40	SIVsyk SEQ ID NO:38
15	MDPIDPDLEPWKHPGSQPACYCRIPACIAGERRYGTCTYQGRLLWA FCCFHCQVCFTKGLGISYGRKKRRQRRRAPQDSQTHQASLSKQ PASQSRGDPTGPTESKKKVERETETDPFD	SIVcpz SEQ ID NO:39	Human α - defensin-1 SEQ ID NO:41	HIV-1 SEQ ID NO:42
16	MDPIDPDLEPWKHPGSQPGIDPVTCLKSGAICHVPFCPRRYKQI GTCGLPGTKCCKKPFHCQVCFTKGLGISYGRKKRRQRRRAPQD SQTHQASLSKQPASQSRGDPTGPTESKKKVERETETDPFD	SIVcpz SEQ ID NO:39	Human β - defensin-2 SEQ ID NO:43	HIV-1 SEQ ID NO:42
17	MEPVDPRLEPWKHPGSQPKTACNNCHCKVCCYHCVCFTKKGL GISYGRKKRRRPARTADKDQDNQDPVSKQSLAGTRSQQE	HIV-1 SEQ ID NO:44	SIVcpz SEQ ID NO:45	SIVgor SEQ ID NO:46

SEQ ID NO.	Amino Acid Sequence	Source† (SEQ ID NO:)		
		TF region	cysteine-rich region	C-terminal region
18	MDPIDPDLEPWKHPGSQPTTACSKCYCKICCWHCQLCLKKGLGIS YGRKKRKHRRGTPQSSKDHQNPQEQPLPIIRGNPTDPKESKKEV ASKAETDPFD	SIVcpz SEQ ID NO:39	HIV-1 SEQ ID NO:47	
19	MEPLTPHPWVYSGGQPKVPETACNNCFCKKCSYHCLVCFQKKGL GISHGRKKRRQRRSAPPSSDHQNLISKQPIPRQTQGDQTGSEESK KKVESKTETDPFD	Human <i>hr</i> gene SEQ ID NO:48	HIV-1 SEQ ID NO:49	
20	MAGPHPVIVITGPHEEPTTACSKCYCKICCWHCQLCLKKGLGISY RKKRKHRRGTPQSSKDHQNPQEQPLPIIRGNPTDPKESKKEVAS KAETDPFD	VIVIT SEQ ID NO:50	HIV-1 SEQ ID NO:47	
21	MAGPHPVIVITGPHEEPETACNNCFCKKCSYHCLVCFQKKGLGIS HGRKKRRQRRSAPPSSDHQNLISKQPIPRQTQGDQTGSEESKKK VESKTETDPFD	VIVIT SEQ ID NO:50	HIV-1 SEQ ID NO:49	
22	MEPLTPHPWVYSGGQPKVPRTCHCRSRCLRRESNSGSCNINGR SSLCCFLKKGLGISYEKSHRRRRTPKKAKANTSSASNEPIPNRIRL CQPKKAKKETVEAAVATAPGLGR	Human <i>hr</i> gene SEQ ID NO:48	Myeloid α - defensin-9 ⁹ SEQ ID NO:51	SIVmac ⁿ SEQ ID NO:52
23	MAGPHPVIVITGPHEEPRTCHCRSRCLRRESNSGSCNINGRIS SLCCFLKKGLGISYEKSHRRRRTPKKAKANTSSASNEPIPNRIRL CQPKKAKKETVEAAVATAPGLGR	VIVIT SEQ ID NO:50	Myeloid α - defensin-9 SEQ ID NO:51	SIVmac SEQ ID NO:52
24	MDPIDPDLEPWKHPGSQPRRTCHCRSRCLRRESNSGSCNINGRIS SLCCFLKKGLGISYEKSHRRRRTPKKAKANTSSASNEPIPNRIRLC QPKKAKKETVEAAVATAPGLGR	SIVcpz SEQ ID NO:39	Myeloid α - defensin-9 SEQ ID NO:51	SIVmac SEQ ID NO:52
25	MEPLTPHPWVYSGGQPKVPLEACYNKCYCKRCCYHCQHCFLKK GLGICYEQRRRTPKTKANTSSASDKSLRRARNCQPKKEKKET VEAEVATDLGLGR	Human <i>hr</i> gene SEQ ID NO:48	SIVsmm SEQ ID NO:53	
26	MAGPHPVIVITGPHEEPLACYNKCYCKRCCYHCQHCFLKKGLGI CYEQRRRTPKTKANTSSASDKSLRRARNCQPKKEKKETVEA EVATDLGLGR	VIVIT SEQ ID NO:50	SIVsmm SEQ ID NO:53	
27	MDPIDPDLEPWKHPGSQPLEACYNKCYCKRCCYHCQHCFLKKGL GICYEQRRRTPKTKANTSSASDKSLRRARNCQPKKEKKETVE AEVATDLGLGR	SIVcpz SEQ ID NO:39	SIVsmm SEQ ID NO:53	
28	MMEPVDPDLPKEQHPPATPRCESCKLGRGRCRKECLENKPDG RCRLNFLCCFHCQVCFTRKGLGISYGRKKRRQRRRAPQDSQTHQ ASLSKQPASQSRGDPTGPTESKKKVERETETDPFD	SIVmon ^l SEQ ID NO:54	β -defensin-105 ^l SEQ ID NO:55	HIV-1 SEQ ID NO:42

SEQ ID NO.	Amino Acid Sequence	Source† (SEQ ID NO:)		
		TF region	cysteine-rich region	C-terminal region
29	MEPLTPHPWWYSGGQPKVPCESCKLGRGRCRKECLENKPDGR CRLNFLCCFHCQVCFTRKGLGISYGRKKRRQRRRAPQDSQTHQA SLSKQPASQSRGDPTGPTESKKKVERETETDPFD	Human <i>hr</i> gene SEQ ID NO:48	β -defensin-105 SEQ ID NO:55	HIV-1 SEQ ID NO:42
30	MDPIDPDLEPWKHPGSQPCESCKLGRGRCRKECLENKPDGRC RLNFLCCFHCQVCFTRKGLGISYGRKKRRQRRRAPQDSQTHQAS LSKQPASQSRGDPTGPTESKKKVERETETDPFD	SIVcpz SEQ ID NO:	β -defensin-105 SEQ ID NO:55	HIV-1 SEQ ID NO:42
31	MAGPHPVIVITGPHEEPCESCKLGRGRCRKECLENKPDGRCRLN FLCCFHCQVCFTRKGLGISYGRKKRRQRRRAPQDSQTHQASLSK QPASQSRGDPTGPTESKKKVERETETDPFD	VIVIT SEQ ID NO:50	β -defensin-105 SEQ ID NO:55	HIV-1 SEQ ID NO:42
32	MEPVDPRLEPWKHPGSQPPEPVDPRLEPWKHPGSQPKTACNNC HCKVCCYHCVYCFHCQVCFTRKGLGISYGRKKRRQRRRAPQDS QTHQASLSKQPASQSRGDPTGPTESKKKVERETETDPFD	HIV-1 SEQ ID NO:56	SIVcpz SEQ ID NO:57	HIV-1 SEQ ID NO:42
33	MEPLTPHPWWYSGGQPKVPLRCICRRGICRLLQRRYGSCAFPGR LYRICCFLKKGLGICYEQRRRTPKKTKANTSSASDKSLSRRARN CQPKKEKKETVEAEVATDLGLGR	Human <i>hr</i> gene SEQ ID NO:48	Θ -defensin ^k SEQ ID NO:58	SIVsmm SEQ ID NO:52
34	MAGPHPVIVITGPHEEPLRCICRRGICRLLQRRYGSCAFPGRLYRI CCFLKKGLGICYEQRRRTPKKTKANTSSASDKSLSRRARNCQPK KEKKETVEAEVATDLGLGR	VIVIT SEQ ID NO:50	Θ -defensin SEQ ID NO:58	SIVsmm SEQ ID NO:52
35	MDPIDPDLEPWKHPGSQPLRCICRRGICRLLQRRYGSCAFPGRLY RICCFLKKGLGICYEQRRRTPKKTKANTSSASDKSLSRRARNCQ PKKEKKETVEAEVATDLGLGR	SIVcpz SEQ ID NO:39	Θ -defensin SEQ ID NO:58	SIVsmm SEQ ID NO:52
69	MEPLTPHPWWYSGGQPKVPLEACYNKCYCKRCCYHCQHCFSSK GLGISYERKGRRRRTPRKTKTPSPSAPDKSISTRGTGDSQPTKEQK KTSEATVWTCGLGQ	Human <i>hr</i> gene SEQ ID NO:48	SIVsmm SEQ ID NO:70	HIV-2 SEQ ID NO:71

^a agm = African Green Monkey; ^b smm = sooty mangabey monkey; ^c cpz = chimpanzee; ^d VIVIT = artificial TF sequence; ^e gor = gorilla; ^f syk = Sykes monkey; ^g from *Macaca mulatta*; ^h mac = macaque; ⁱ mon = Mona monkey; ^j from *Chlorocebus aethiops*; ^k from *Pongo abelli*.

[0074] As used herein the term "conservatively modified variants" refers to variant peptides which have the same or similar biological activity of the original peptides. For example, conservative amino acid changes may be made, which although they alter the primary sequence of the protein or peptide, do not alter its function. A conservative variant has at least one amino acid substituted by another amino acid or an amino acid analog that has at least one property similar to that of the original amino acid from an exemplary reference peptide. Examples of properties include, without limitation, similar size, topography, charge, hydrophobicity, hydrophilicity, lipophilicity, covalent-bonding capacity, hydrogen-bonding capacity, a physicochemical property, of the like, or any combination thereof. A conservative substitution can be assessed by a variety of factors, such as, e.g., the physical properties of the amino acid being substituted (Table 2) or how the original amino acid would tolerate a substitution (Table 3). The selections of which amino acid can be substituted for another amino acid in a peptide disclosed herein are known to a person of ordinary skill in the art. A conservative variant can function in substantially the same manner as the exemplary reference peptide, and can be substituted for the exemplary reference peptide in any aspect of the present specification.

Table 2. Amino Acid Properties

Property	Amino Acids
Aliphatic	G, A, I, L, M, P, V
Aromatic	F, H, W, Y
C-beta branched	I, V, T
Hydrophobic	C, F, I, L, M, V, W
Small polar	D, N, P
Small non-polar	A, C, G, S, T
Large polar	E, H, K, Q, R, W, Y
Large non-polar	F, I, L, M, V
Charged	D, E, H, K, R
Uncharged	C, S, T
Negative	D, E
Positive	H, K, R
Acidic	D, E
Basic	K, R
Amide	N, Q

Table 3. Amino Acid Substitutions

Amino Acid	Favored Substitution	Neutral Substitutions	Disfavored substitution
A	G, S, T	C, E, I, K, M, L, P, Q, R, V	D, F, H, N, Y, W
C	F, S, Y, W	A, H, I, M, L, T, V	D, E, G, K, N, P, Q, R
D	E, N	G, H, K, P, Q, R, S, T	A, C, I, L,
E	D, K, Q	A, H, N, P, R, S, T	C, F, G, I, L, M, V, W, Y
F	M, L, W, Y	C, I, V	A, D, E, G, H, K, N, P, Q, R, S, T
G	A, S	D, K, N, P, Q, R	C, E, F, H, I, L, M, T, V, W, Y
H	N, Y	C, D, E, K, Q, R, S, T, W	A, F, G, I, L, M, P, V
I	V, L, M	A, C, T, F, Y	D, E, G, H, K, N, P, Q, R, S, W
K	Q, E, R	A, D, G, H, M, N, P, S, T	C, F, I, L, V, W, Y
L	F, I, M, V	A, C, W, Y	D, E, G, H, K, N, P, Q, R, S, T
M	F, I, L, V	A, C, R, Q, K, T, W, Y	D, E, G, H, N, P, S
N	D, H, S	E, G, K, Q, R, T	A, C, F, I, L, M, P, V, W, Y
P	—	A, D, E, G, K, Q, R, S, T	C, F, H, I, L, M, N, V, W, Y
Q	E, K, R	A, D, G, H, M, N, P, S, T	C, F, I, L, V, W, Y
R	K, Q	A, D, E, G, H, M, N, P, S, T	C, F, I, L, V, W, Y
S	A, N, T	C, D, E, G, H, K, P, Q, R, T	F, I, L, M, V, W, Y
T	S	A, C, D, E, H, I, K, M, N, P, Q, R, V	F, G, L, W, Y
V	I, L, M	A, C, F, T, Y	D, E, G, H, K, N, P, Q, R, S, W
W	F, Y	H, L, M	A, C, D, E, G, I, K, N, P, Q, R, S, T, V
Y	F, H, W	C, I, L, M, V	A, D, E, G, K, N, P, Q, R, S, T

Matthew J. Betts and Robert, B. Russell, Amino Acid Properties and Consequences of Substitutions, pp. 289-316, In Bioinformatics for Geneticists, (eds Michael R. Barnes, Ian C. Gray, Wiley, 2003).

Table 4. SIV strain abbreviations useful in Tat derivative peptides

SIV host designation	SIV Host Species	Latin designation
SIVagmVer	(African Green Monkey) Vervet	<i>Chlorocebus pygerythrus</i>
SIVagmGri	(African Green Monkey) Grivet	<i>Chlorocebus aethiops</i>
SIVagmTan	(African Green Monkey) Tantalus	<i>Chlorocebus tantalus</i>
SIVagmSab	(African Green Monkey) Sabeus	<i>Chlorocebus sabaesus</i>
SIVrcm	Red-capped Mangabey	<i>Cercocebus torquatus torquatus</i>
SIVsyk	Sykes Monkey	<i>Cercopithecus albogularis</i>
SIVagi	Agile Mangabey	<i>Cercocebus agilis</i>
SIVsun	Sun-tailed Monkey	<i>Cercopithecus solatus</i>
SIVlho	L'Hoests Monkey	<i>Cercopithecus lhoesti</i>
SIVstm	Stump-tail Macaque	<i>Macaca arctoides</i>
SIVmac	Macaque	<i>Macaca mulatta</i>
SIVsmm	Sooty mangabey monkey	<i>Cercocebus atys atys</i>
SIVmnd	Mandrill	<i>Mandrillus sphinx</i>
SIVdrl	Drill Monkey	<i>Mandrillus leucophaeus</i>
SIVtal	Talapoin Monkey	<i>Miopithecus talapoin</i>
SIVmus	Mustached Monkey	<i>Cercopithecus cephus</i>
SIVdeb	De Brazza's Monkey	<i>Cercopithecus neglectus</i>
SIVden	Dent's Monkey	<i>Cercopithecus denti</i>
SIVmon	Mona Monkey	<i>Cercopithecus mona</i>
SIVgor	Gorilla	<i>Gorilla gorilla</i>
SIVwrc	Western Red Colobus	<i>Procolobus verus</i>
SIVcpzPtt	Pan Troglodytes Troglodytes	<i>Pan troglodytes troglodytes</i>
SIVcpzPts	Pan Troglodytes Schweinfurthi	<i>Pan troglodytes schweinfurthii</i>
SIVmne	Pig-tail Macaque	<i>Macaca nemestrina</i>
SIVasc	Red-tailed Guenon	<i>Cercopithecus ascanius schmidtii</i>
SIVbab	Yellow Baboon	<i>Papio spp.</i>
SIVblc	Bioko Black Colobus Monkey	<i>Cercopithecus satanas satanas</i>
SIVbkm	Black Mangabey	<i>Lophocebus aterrimus</i>
SIVblu	Blue Monkey	<i>Cercopithecus mitis</i>
SIVcol	Colobus Monkey	<i>Colobus guereza</i>
SIVolc	Olve Colobus Monkey	<i>procolobus verus</i>
SIVgsn	Greater Spot-nosed Monkey	<i>Cercopithecus nictitans</i>
SIVkrc	Kibale Red Colobus Moneky	<i>Procolobus [Piliocolobus] rufomitratu tephrosceles</i>
SIVpat	Patas Monkey	<i>Erythrocebus patas</i>
SIVpre	Preussis Monkey	<i>Cercopithecus preussi</i>
SIVreg	Red-eared Guenon	<i>Cercopithecus erythrotis erythrotis</i>
SIVtrc	Tshuapa Red Colobus	<i>Piliocolobus tholloni</i>

SIV host designation	SIV Host Species	Latin designation
SIVwcm	White-crowned Mangabey	<i>Cercocebus torquatus lunulatus</i>
SIVwol	Wolf's Monkey	<i>Cercopithecus wolfi</i>

[0075] In one embodiment, an immunosuppressive Tat derivative polypeptide is a peptide disclosed in Table 1. An immunosuppressive Tat derivative polypeptide can also comprise conservative variants to a Tat derivative polypeptide. In an embodiment, a conservative variant of an immunosuppressive Tat derivative polypeptide is a conservative variant of an immunosuppressive Tat derivative polypeptide disclosed herein. In aspects of this embodiment, a conservative variant of an immunosuppressive Tat derivative polypeptide can be, for example, an amino acid sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 98%, or at least 99% amino acid sequence identity to an immunosuppressive Tat derivative polypeptide. In other aspects of this embodiment, a conservative variant of an immunosuppressive Tat derivative polypeptide can be, for example, an amino acid sequence having at most 50%, 55%, 60%, 65%, 70%, 75%, at most 80%, at most 85%, at most 90%, at most 95%, at most 97%, or at most 98%, or at most 99% amino acid sequence identity to an immunosuppressive Tat derivative polypeptide.

[0076] In other aspects of this embodiment, a conservative variant of an immunosuppressive Tat derivative polypeptide can be, for example, an immunosuppressive Tat derivative polypeptide having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30 or more conservative substitutions, to the amino acid sequence of an immunosuppressive Tat derivative polypeptide. In other aspects of this embodiment, a conservative variant of an immunosuppressive Tat derivative polypeptide can be, for example, an amino acid sequence having at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, or at least 25 conservative substitutions to the amino acid sequence of an immunosuppressive Tat derivative polypeptide. In yet other aspects of this embodiment, a conservative variant of an immunosuppressive Tat derivative polypeptide can be, for example, an amino acid sequence having at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 20, at most 25, or at most 30 conservative substitutions to the amino acid sequence of an immunosuppressive Tat derivative polypeptide.

[0077] Modifications (which do not normally alter primary sequence) include *in vivo*, or *in vitro*, chemical derivatization of polypeptides, e.g., acetylation, or carboxylation. Also included are modifications of glycosylation, e.g., those made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing or in further processing steps; e.g. by exposing the polypeptide to enzymes which affect glycosylation, e.g., mammalian glycosylating or deglycosylating enzymes. Also embraced are sequences which have phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

[0078] Also included are immunosuppressive Tat derivative polypeptides which have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties. Analogs of such polypeptides include those containing residues other than naturally occurring L-amino acids, e.g., D-amino acids or non-naturally occurring synthetic amino acids. The peptides disclosed herein are not limited to products of any of the specific exemplary processes listed herein.

[0079] In addition to substantially full length polypeptides, the present disclosure also provides for biologically active fragments of the immunosuppressive Tat derivative polypeptides.

[0080] As used herein, amino acid sequences which are substantially the same typically share more than 95% amino acid identity. It is recognized, however, that proteins (and DNA or mRNA encoding such proteins) containing less than the above-described level of identity arising as splice variants or that are modified by conservative amino acid substitutions (or substitution of degenerate codons) are contemplated to be within the scope of the present disclosure. As readily recognized by those of skill in the art, various ways have been devised to align sequences for comparison, e.g., Blosun 62 scoring matrix, as described by Henikoff and Henikoff in Proc. Natl. Acad. Sci. USA 89:10915 (1992). Algorithms conveniently employed for this purpose are widely available (see, for example, Needleman and Wunsch in J. Mol. Bio. 48:443 (1970)).

[0081] Therefore, disclosed herein are amino acid sequences 85%, 90%, 95%, 98%, 99% or 100% identical to the immunosuppressive Tat derivatives disclosed in Table 1.

[0082] An immunosuppressive Tat derivative comprises an altered Tat peptide. In an aspect of this embodiment, an immunosuppressive Tat derivative comprises a Tat peptide in which amino acids 3-19 are altered. In another aspect of this embodiment, an immunosuppressive Tat derivative comprises a Tat peptide in which amino acids 3-19 of SEQ ID NOs:6-11, 13-35, or 69 are altered.

[0083] In other aspects of this embodiment, an immunosuppressive Tat derivative has, e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, or at least 99% amino acid identity with SEQ ID NOs: 6-11, 13-35, or 69. In yet other aspects of this embodiment, an immunosuppressive Tat derivative has, e.g., at most 70%, at most 75%, at most 80%, at most 85%, at most 90%, at most 93%, at most 95%, at most 97%, or at most 99% amino acid identity with SEQ ID NOs: 6-11, 13-35, or 69.

[0084] In other aspects of this embodiment, an immunosuppressive Tat derivative has, e.g., at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine or at least ten contiguous amino acid substitutions, deletions, and/or additions relative to SEQ ID NOs:6-11, 13-35, or 69. In yet other aspects of this embodiment, an immunosuppressive Tat derivative has, e.g., at most one, at most two, at most three, at most four, at most five, at most six, at most seven, at most eight, at most nine or at most ten contiguous amino acid substitutions, deletions, and/or additions relative to SEQ ID NOs:6-11, 13-35, or 69.

[0085] In other aspects of this embodiment, an immunosuppressive Tat derivative has, e.g., at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine or at least ten non-contiguous amino acid substitutions, deletions, and/or additions relative to SEQ ID NOs:6-11, 13-35, or 69. In yet other aspects of this embodiment, an immunosuppressive Tat derivative has, e.g., at most one, at most two, at most three, at most four, at most five, at most six, at most seven, at most eight, at most nine or at most ten non-contiguous amino acid substitutions, deletions, and/or additions relative to SEQ ID NOs:6-11, 13-35, or 69.

[0086] Furthermore, the peptides disclosed herein can self-associate into multimers, including but not limited to, dimers, trimers, and tetramers, in addition to existing in the monomer form. Multimerization of peptides can occur spontaneously or can be facilitated by subjecting the peptides to conditions conducive to multimerization. These conditions are known to persons of ordinary skill in peptide chemistry. The compositions disclosed herein can include monomers or multimers of the peptides, or a mixture of monomers and multimers.

[0087] The following expression systems are suitable for use in expressing the disclosed immunosuppressive Tat derivatives: mammalian cell expression systems such as, but not limited to, insect cell expression systems such as, but not limited to, Bac-to-Bac expression system, baculovirus expression system, and DES expression systems; and *E. coli* expression systems including, but not limited to, pET, pSUMO and GST expression systems. In another

embodiment, the Tat derivatives are expressed with a histidine tag useful for isolation of the polypeptide. Histidine tag purification systems are known to persons of ordinary skill in the art. Furthermore, the immunosuppressive Tat derivatives can be synthesized by conventional chemical synthesis techniques known to persons of ordinary skill in the art.

[0088] As used herein, the terms “treating” or “treatment” when used in reference to a disorder include preventing at least one symptom of the condition, *i.e.*, causing a clinical symptom to not significantly develop in a subject that may be exposed to, or predisposed to, the disease but does not yet experience or display symptoms of the disease, inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its symptoms, or relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms. Treatment, prevention, and ameliorating a condition, as used herein, can include, for example decreasing or eradicating a deleterious or harmful condition associated with inflammation, an autoimmune disorder, or a neurodegenerative disease.

[0089] “Therapeutically effective amount” is intended to qualify the amount required to achieve a therapeutic effect.

[0090] The present disclosure is also directed to pharmaceutical compositions comprising the above-described immunosuppressive Tat derivative polypeptides. Dosages and desired drug concentrations of the disclosed pharmaceutical compositions may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mardenti, J. and Chappell, W. “The use of interspecies scaling in toxicokinetics” In Toxicokinetics and New Drug Development, Yacobi et al, Eds., Pergamon Press, New York 1989, pp. 42-96. In one embodiment, the disease is present. In another embodiment, the life of a cell or an individual is prolonged due to the methods described herein.

[0091] Accordingly, the compositions designed for oral, nasal, lingual, sublingual, buccal, intrabuccal, intravenous, subcutaneous, intramuscular and pulmonary administration can be made without undue experimentation by means well known in the art, for example with an inert diluent or with an pharmaceutically acceptable carrier. For the purpose of therapeutic administration, the pharmaceutical compositions may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, solutions, syrups, and the like. A “pharmaceutically acceptable carrier” means any of the standard pharmaceutical carriers.

Examples of suitable carriers are well known in the art and may include but are not limited to any of the standard pharmaceutical carriers like phosphate buffered saline solutions, phosphate buffered saline containing Polysorb 80, water, emulsions such as oil/water emulsion, and various types of wetting agents. Other carriers may also include sterile solutions, tablets, coated tablets, and capsules. Typically such carriers contain excipients like starch, milk, sugar, certain types of clay, gelatin, stearic acid or salts thereof, magnesium or calcium stearate, talc, vegetable fats or oils, gums, glycols, or other known excipients. Compositions comprising such carriers are formulated by well known conventional methods.

[0092] The immunosuppressive Tat derivative polypeptide compositions can easily be administered parenterally such as for example, by intravenous, intramuscular, intrathecal or subcutaneous injection. Parenteral administration can be accomplished by incorporating the compounds into a solution or suspension. Such solutions or suspensions may also include sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents. Parenteral formulations may also include antibacterial agents such as for example, benzyl alcohol or methyl parabens, antioxidants such as for example, ascorbic acid or sodium bisulfite and chelating agents such as EDTA. Buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose may also be added. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

[0093] Transdermal administration includes percutaneous absorption of the composition through the skin. Transdermal formulations include patches, iontophoresis devices, ointments, creams, gels, salves and the like.

[0094] The composition may include various materials which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials which form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule or cachet.

[0095] The immunosuppressive Tat derivative polypeptide compositions of the present disclosure may be administered in a therapeutically effective amount, according to an appropriate dosing regimen. As understood by a skilled artisan, the exact amount required may vary from subject to subject, depending on the subject's species, age and general condition, the severity of the disease, the particular agent(s) and the mode of administration. In some embodiments, about 0.0001 mg/kg to about 50 mg/kg, of the composition based on the

subject's body weight is administered, one or more times a day, to obtain the desired therapeutic effect. In other embodiments, about 0.001 mg/kg to about 50 mg/kg, about 0.01 mg/kg to about 50 mg/kg, about 0.1 mg/kg to about 50 mg/kg, about 1 mg/kg to about 50 mg/kg, about 10 mg/kg to about 50 mg/kg, about 0.0001 mg/kg to about 25 mg/kg, about 0.0001 mg/kg to about 10 mg/kg, about 0.0001 mg/kg to about 5 mg/kg, about 0.0001 mg/kg to about 1 mg/kg, about 1 mg/kg to about 45 mg/kg, about 1 mg/kg to about 40 mg/kg, about 1 mg/kg to about 35 mg/kg, about 1 mg/kg to about 30 mg/kg, about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 15 mg/kg, about 1 mg/kg to about 10 mg/kg, or about 1 mg/kg to about 5 mg/kg of the composition based on the subject's body weight is administered, one or more times a day, to obtain the desired therapeutic effect.

[0096] The total daily dosage of the compositions will be determined by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient or subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient or subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and other factors well known in the medical arts.

[0097] The disclosed compositions may also be employed in combination therapies. That is, the compositions presently disclosed can be administered concurrently with, prior to, or subsequent to, one or more other desired compositions, therapeutics, treatments or medical procedures. The particular combination of therapies administered will be determined by the attending physician and will take into account compatibility of the treatments and the desired therapeutic effect to be achieved. It will be appreciated that therapeutically active agents utilized in combination may be administered together in a single composition, treatment or procedure, or alternatively may be administered separately. Suitable therapeutic agents include, but are not limited to, immunosuppressive agents, anti-inflammatory agents, chemotherapeutic agents, immunomodulatory agents, biologic agents, and small molecules.

[0098] In another embodiment, repetitive, or frequent, dosing of the disclosed immunosuppressive Tat derivatives is contemplated. Frequent dosing is one procedure used for example in allergy therapy that can support immunological tolerance to an agent.

[0099] The number of repeated doses of the immunosuppressive Tat derivatives can be established by the medical professional based on the response of the patient to the doses. In one embodiment, the immunosuppressive Tat derivative is administered once every three days for 3 doses in a ten day period. This administration scheme is then repeated for a plurality of cycles. The present disclosure envisions a variety of different administration schemes wherein the immunosuppressive Tat derivative is administered multiple times within a selected time frame and then the administration scheme is repeated for a plurality of cycles. In another embodiment, administration of the immunosuppressive Tat derivative can be alternated with administration of one or more other therapeutic agents.

[0100] Aspects of the present specification provide, in part, a composition comprising an immunosuppressive Tat derivative polypeptide. An immunosuppressive Tat derivative polypeptide includes the compounds disclosed herein. The compositions disclosed herein may, or may not, comprise any number and combination of compounds disclosed herein. For instance, a composition can comprise two or more compounds disclosed herein or three or more compounds disclosed herein.

[0101] A compound disclosed herein, or a composition comprising such a compound, is generally administered to an individual as a pharmaceutical composition. Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound as disclosed herein as an active ingredient, with conventional acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for therapeutic use. As used herein, the term "pharmaceutical composition" and refers to a therapeutically effective concentration of an active compound, such as, *e.g.*, any of the compounds disclosed herein. Preferably, the pharmaceutical composition does not produce an adverse, allergic, or other untoward or unwanted reaction when administered to an individual. A pharmaceutical composition disclosed herein is useful for medical and veterinary applications. A pharmaceutical composition may be administered to an individual alone, or in combination with other supplementary active compounds, agents, drugs or hormones. The pharmaceutical compositions may be manufactured using any of a variety of processes, including, without limitation, conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, and lyophilizing. The pharmaceutical composition can take any of a variety of forms including, without limitation, a sterile solution, suspension, emulsion, lyophilizate, powder, syrup, elixir, or any other dosage form suitable for administration.

[0102] Liquid dosage forms suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethyleneglycol (PEG), glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. In liquid formulations, a therapeutically effective amount of a compound disclosed herein may be between about 0.0001% (w/v) to about 50% (w/v), about 0.001% (w/v) to about 10.0% (w/v), or about 0.01% (w/v) to about 1.0% (w/v).

[0103] A pharmaceutical composition disclosed herein can optionally include a pharmaceutically acceptable carrier that facilitates processing of an active compound into pharmaceutically acceptable compositions. As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio. As used herein, the term "pharmacologically acceptable carrier" is synonymous with "pharmacological carrier" and refers to any carrier that has substantially no long term or permanent detrimental effect when administered and encompasses terms such as "pharmacologically acceptable vehicle, stabilizer, diluent, additive, auxiliary, or excipient." Such a carrier generally is mixed with an active compound or permitted to dilute or enclose the active compound and can be a solid, semi-solid, or liquid agent. It is understood that the active compounds can be soluble or can be delivered as a suspension in the desired carrier or diluent. Any of a variety of pharmaceutically acceptable carriers can be used including, without limitation, aqueous media such as, e.g., water, saline, glycine, hyaluronic acid and the like; solid carriers such as, e.g., starch, magnesium stearate, mannitol, sodium saccharin, talcum, cellulose, glucose, sucrose, lactose, trehalose, magnesium carbonate, and the like; solvents; dispersion media; coatings; antibacterial and antifungal agents; isotonic and absorption delaying agents; or any other inactive ingredient. Selection of a pharmacologically acceptable carrier can depend on the mode of administration. Except insofar as any pharmacologically acceptable carrier is incompatible with the active compound, its use in pharmaceutically acceptable compositions is contemplated. Non-limiting examples of specific uses of such pharmaceutical carriers can be

found in Pharmaceutical Dosage Forms and Drug Delivery Systems (Howard C. Ansel et al., eds., Lippincott Williams & Wilkins Publishers, 7th ed. 1999); Remington: The Science and Practice of Pharmacy (Alfonso R. Gennaro ed., Lippincott, Williams & Wilkins, 20th ed. 2000); Goodman & Gilman's The Pharmacological Basis of Therapeutics (Joel G. Hardman et al., eds., McGraw-Hill Professional, 10th ed. 2001); and Handbook of Pharmaceutical Excipients (Raymond C. Rowe et al., APhA Publications, 4th edition 2003). These protocols are routine and any modifications are well within the scope of one skilled in the art and from the teaching herein.

[0104] A pharmaceutical composition disclosed herein can optionally include, without limitation, other pharmaceutically acceptable components (or pharmaceutical components), including, without limitation, buffers, preservatives, tonicity adjusters, salts, antioxidants, osmolality adjusting agents, physiological substances, pharmacological substances, bulking agents, emulsifying agents, wetting agents, sweetening or flavoring agents, and the like. Various buffers and means for adjusting pH can be used to prepare a pharmaceutical composition disclosed herein, provided that the resulting preparation is pharmaceutically acceptable. Such buffers include, without limitation, acetate buffers, borate buffers, citrate buffers, phosphate buffers, neutral buffered saline, and phosphate buffered saline. It is understood that acids or bases can be used to adjust the pH of a composition as needed. Pharmaceutically acceptable antioxidants include, without limitation, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, and butylated hydroxytoluene. Useful preservatives include, without limitation, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, a stabilized oxy chloro composition, such as, e.g., sodium chlorite and chelants, such as, e.g., DTPA or DTPA-bisamide, calcium DTPA, and CaNaDTPA-bisamide. Tonicity adjustors useful in a pharmaceutical composition include, without limitation, salts such as, e.g., sodium chloride, potassium chloride, mannitol or glycerin and other pharmaceutically acceptable tonicity adjustor.

[0105] A compound disclosed herein, or a composition comprising such a compound, may also be incorporated into a drug delivery platform in order to achieve a controlled compound release profile over time. Such a drug delivery platform comprises a compound disclosed herein dispersed within a polymer matrix, typically a biodegradable, bioerodible, and/or bioresorbable polymer matrix. As used herein, the term "polymer" refers to synthetic homo- or copolymers, naturally occurring homo- or copolymers, as well as synthetic modifications or derivatives thereof having a linear, branched or star structure. Copolymers can be arranged in

any form, such as, e.g., random, block, segmented, tapered blocks, graft, or triblock. Polymers are generally condensation polymers. Polymers can be further modified to enhance their mechanical or degradation properties by introducing cross-linking agents or changing the hydrophobicity of the side residues. If crosslinked, polymers are usually less than 5% crosslinked, usually less than 1% crosslinked.

[0106] Suitable polymers include, without limitation, alginates, aliphatic polyesters, polyalkylene oxalates, polyamides, polyamidoesters, polyanhydrides, polycarbonates, polyesters, polyethylene glycol, polyhydroxyaliphatic carboxylic acids, polyorthoesters, polyoxaesters, polypeptides, polyphosphazenes, polysaccharides, and polyurethanes. The polymer usually comprises at least about 10% (w/w), at least about 20% (w/w), at least about 30% (w/w), at least about 40% (w/w), at least about 50% (w/w), at least about 60% (w/w), at least about 70% (w/w), at least about 80% (w/w), or at least about 90% (w/w) of the drug delivery platform. Examples of biodegradable, bioerodible, and/or bioresorbable polymers and methods useful to make a drug delivery platform are described in, e.g., U.S. Patent 4,756,911; U.S. Patent 5,378,475; U.S. Patent 7,048,946; U.S. Patent Publication 2005/0181017; U.S. Patent Publication 2005/0244464; U.S. Patent Publication 2011/0008437; each of which is incorporated by reference in its entirety.

[0107] In aspects of this embodiment, a polymer composing the matrix is a polypeptide such as, e.g., silk fibroin, keratin, or collagen. In other aspects of this embodiment, a polymer composing the matrix is a polysaccharide such as, e.g., cellulose, agarose, elastin, chitosan, chitin, or a glycosaminoglycan like chondroitin sulfate, dermatan sulfate, keratan sulfate, or hyaluronic acid. In yet other aspects of this embodiment, a polymer composing the matrix is a polyester such as, e.g., D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, caprolactone, and combinations thereof.

[0108] One of ordinary skill in the art appreciates that the selection of a suitable polymer for forming a suitable disclosed drug delivery platform depends on several factors. The more relevant factors in the selection of the appropriate polymer(s), include, without limitation, compatibility of polymer with drug, desired release kinetics of drug, desired biodegradation kinetics of platform at implantation site, desired bioerodible kinetics of platform at implantation site, desired bioresorbable kinetics of platform at implantation site, *in vivo* mechanical performance of platform, processing temperatures, biocompatibility of platform, and patient tolerance. Other relevant factors that, to some extent, dictate the *in vitro* and *in vivo* behavior of

the polymer include the chemical composition, spatial distribution of the constituents, the molecular weight of the polymer and the degree of crystallinity.

[0109] A drug delivery platform includes both a sustained release drug delivery platform and an extended release drug delivery platform. As used herein, the term "sustained release" refers to the release of a compound disclosed herein over a period of about seven days or more. As used herein, the term "extended release" refers to the release of a compound disclosed herein over a period of time of less than about seven days.

[0110] In aspects of this embodiment, a sustained release drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., about 7 days after administration, about 15 days after administration, about 30 days after administration, about 45 days after administration, about 60 days after administration, about 75 days after administration, or about 90 days after administration. In other aspects of this embodiment, a sustained release drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., at least 7 days after administration, at least 15 days after administration, at least 30 days after administration, at least 45 days after administration, at least 60 days after administration, at least 75 days after administration, or at least 90 days after administration.

[0111] In aspects of this embodiment, a drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., about 1 day after administration, about 2 days after administration, about 3 days after administration, about 4 days after administration, about 5 days after administration, or about 6 days after administration. In other aspects of this embodiment, a drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., at most 1 day after administration, at most 2 days after administration, at most 3 days after administration, at most 4 days after administration, at most 5 days after administration, or at most 6 days after administration.

[0112] Aspects of the present disclosure provide, in part, an autoimmune disorder. An autoimmune disorder arises from an overactive immune response of the body against substances and tissues normally present in the body resulting in a break in tolerance toward self-antigens. In other words, the body actually attacks its own cells because the immune system mistakes some part of the body as a pathogen and attacks it. Characterized by the development of pathogenic T cell populations infiltrating the target organ or tissue, autoimmune disorders may be restricted to certain organs or involve a particular tissue in different places.

[0113] Aspects of the present disclosure provide, in part, an inflammation. Inflammation refers to the actual tissue response (edema, erythema, etc) to a noxious stimulus. Neurogenic inflammation refers to the fact that this tissue response is initiated and/or maintained through the release of inflammatory mediators from peripheral sensory nerve terminals (*i.e.*, an efferent function, in contrast to the normal afferent signaling to the spinal cord in these nerves). Neurogenic inflammation encompasses a series of vascular and non-vascular inflammatory responses mediated by a complex biological process that ultimately results in the local release of inflammatory mediators and sensitizing compounds from sensory neurons. Upon insult by a noxious stimulus, such as, *e.g.*, a pathogen, damage to cells, or an irritant, inflammation mediating and sensitizing molecules, such as, *e.g.*, histamine, prostaglandins, leukotrienes, serotonin, neutral proteases, cytokines, bradykinin and nitric oxide, are released from inflammation mediating cells, such as, *e.g.*, mast cells, immune cells, vascular endothelial cells, and vascular smooth muscle cells. See Richardson and Vasko, J. Pharmacol. Exp. Ther. 302:839-845, (2002), which is hereby incorporated by reference in its entirety. These inflammation mediating and sensitizing molecules act on sensory neurons to stimulate the release of inflammation inducing molecules such as, *e.g.*, neuropeptides like substance P (SP) and calcitonin gene-related peptide (CGRP), prostaglandins, and amino acids like glutamate, from the peripheral nerve endings. Upon release, these inflammation inducing molecules are responsible for eliciting an inflammatory response, typically characterized by edema (swelling secondary to plasma extravasation), hypersensitivity (secondary to alterations in the excitability of certain sensory neurons), and an erythema (redness and warmth secondary to vasodilation) which extends beyond the site of stimulation (the flare response). *Id.* Because the underlying inflammatory symptoms are triggered by the activation of primary sensory neurons and the subsequent release of inflammation inducing molecules, the response is termed neurogenic inflammation.

[0114] Inflammation includes both acute inflammation and chronic inflammation. As used herein, the term "acute inflammation" means an inflammatory response having pathophysiology effects where at least one of the underlying symptoms being treated is due to a noxious stimulus etiology, such as, *e.g.*, an antimicrobial response. As used herein, the term "chronic inflammation" means an inflammatory response having pathophysiology effects where at least one of the underlying symptoms being treated is due to a nociceptive sensory nerve-based etiology, such as, *e.g.*, the release of an inflammation inducing molecule. Chronic inflammation includes both primary neurogenic inflammation and secondary neurogenic inflammation. As used herein, the term "primary" neurogenic inflammation refers to tissue inflammation

(inflammatory symptoms) that is initiated by, or results from, the release of substances from primary sensory nerve terminals (such as C and A-delta fibers). As used herein, the term "secondary" neurogenic inflammation" refers to tissue inflammation initiated by non-neuronal sources (e.g., extravasation from vascular bed or tissue interstitium-derived, such as from mast cells or immune cells) of inflammatory mediators, such as peptides or cytokines, stimulating sensory nerve terminals and causing a release of inflammatory mediators from the nerves. These nerve-derived inflammatory mediators can, in turn, stimulate the sensory nerves as well as acting on non-neuronal targets (e.g., mast cells). The net effect of both forms (primary and secondary) of neurogenic inflammation is to have an inflammatory state that is maintained by the sensitization of the peripheral sensory nerve fibers. The physiological consequence of the resulting neurogenic inflammation depends on the tissue in question, producing, such as, e.g., cutaneous pain (allodynia, hyperalgesia), joint arthritis, visceral pain and dysfunction, pulmonary dysfunction (asthma, COPD), and bladder dysfunction (pain, overactive bladder).

[0115] Inflammation and/or autoimmune disorder symptoms include, without limitation, edema, hyperemia, erythema, bruising, tenderness, stiffness, swollenness, fever, a chill, congestion of the respiratory tract including nose, and bronchi, congestion of a sinus, a breathing problem, fluid retention, a blood clot, loss of appetite, increased heart rate, formation of granulomas, fibrinous, pus, or non-viscous serous fluid, formation of an ulcer, or pain. The actual symptoms associated with an inflammation and an autoimmune disorder disclosed herein are well known and can be determined by a person of ordinary skill in the art by taking into account factors, including, without limitation, the location of the inflammation or autoimmune disorder, the cause of the inflammation or autoimmune disorder, the severity of the inflammation or autoimmune disorder, the tissue or organ affected by inflammation or the autoimmune disorder, and the disorder associated with the inflammation.

[0116] Normally, inflammation serves as a protective mechanism by an organism to remove noxious stimuli as well as initiate the healing process for injured tissue. This acute neurogenic inflammation forms the first line of defense by maintaining tissue integrity and contributing to tissue repair. In fact, in the absence of acute neurogenic inflammation, wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. However, severe or prolonged noxious stimulation results in a chronic inflammatory response provoking injury rather than mediating repair. This inflammation has been implicated in the pathophysiology of a wide range of unrelated disorders which underlie a wide variety of human diseases.

[0117] Chronic inflammation and its associated symptoms can be associated with a large, unrelated group of disorders which underlie a variety of human diseases. Non-limiting examples of disorders exhibiting inflammation as a symptom include, without limitation, acne, acid reflux/heartburn, Alzheimer's disease, appendicitis, arteritis, arthritis, asthma, allergy, allergic rhinitis, atherosclerosis, an autoimmune disorder, balanitis, blepharitis, bronchiolitis, bronchitis, bullous pemphigoid, uritis, a cancer, carditis, celiac disease, cellulitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, chronic obstructive pulmonary disease (COPD), cirrhosis, colitis, conjunctivitis, cystitis, common cold, dacryoadenitis, dementia, dermatitis, dermatomyositis, eczema, emphysema, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, glomerulonephritis, glossitis, a heart disease, hepatitis, hidradenitis suppurativa, high blood pressure, ileitis, an inflammatory dermatologic disease, an inflammatory neuropathy, insulin resistance, interstitial cystitis, iritis, ischemic heart disease, keratitis, keratoconjunctivitis, laryngitis, mastitis, mastoiditis, a meningitis, metabolic syndrome (syndrome X), migraine, myelitis, myocarditis, myositis, nephritis, obesity, omphalitis, oophoritis, orchitis, osteochondritis, osteopenia, osteoporosis, osteitis, otitis, pancreatitis, Parkinson's disease, parotitis, pelvic inflammatory disease, pemphigus vulgaris, pericarditis, peritonitis, pharyngitis, phlebitis, pleuritis, pneumonitis, proctitis, prostatitis, a psoriasis, pulpitis, pyelonephritis, pyelophlebitis, rheumatic fever, rhinitis, salpingitis, sialadenitis, sinusitis, a spastic colon, stomatitis, synovitis, tendonitis, tendinosis, tenosynovitis, thrombophlebitis, tonsillitis, trigonitis, a tumor, urethritis, uveitis, vaginitis, vasculitis, and vulvitis.

[0118] One type of disorder exhibiting a symptom of inflammation is an arthritis. Arthritis includes a group of conditions involving damage to the joints of the body due to the inflammation of the synovium including, without limitation osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthropathies like ankylosing spondylitis, reactive arthritis (Reiter's syndrome), psoriatic arthritis, enteropathic arthritis associated with inflammatory bowel disease, Whipple's disease and Behcet's disease, septic arthritis, gout (also known as gouty arthritis, crystal synovitis, metabolic arthritis), pseudogout (calcium pyrophosphate deposition disease), and Still's disease. Arthritis can affect a single joint (monoarthritis), two to four joints (oligoarthritis) or five or more joints (polyarthritis) and can be either an autoimmune disease or a non-autoimmune disease.

[0119] Aspects of the present disclosure provide, in part, a autoimmune disorder. Autoimmune disorders also exhibit symptoms of inflammation. Autoimmune diseases can be

broadly divided into systemic and organ-specific autoimmune disorders, depending on the principal clinico-pathologic features of each disease. Systemic autoimmune diseases include, without limitation, systemic lupus erythematosus (SLE), Sjögren's syndrome, scleroderma, rheumatoid arthritis and polymyositis. Local autoimmune diseases may be endocrinologic (diabetes mellitus Type 1, Hashimoto's thyroiditis, Addison's disease etc.), dermatologic (pemphigus vulgaris), hematologic (autoimmune haemolytic anemia), neural (multiple sclerosis) or can involve virtually any circumscribed mass of body tissue. Types of autoimmune disorders include, without limitation, acute disseminated encephalomyelitis (ADEM), Addison's disease, an allergy, allergic rhinitis, Alzheimer's disease, anti-phospholipid antibody syndrome (APS), an arthritis, asthma, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, bullous pemphigoid, cardiovascular disease, celiac disease, Chagas disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus type 1 (IDDM), eczema, endometriosis, fibromyalgia, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis, hidradenitis suppurativa, idiopathic thrombocytopenic purpura, an inflammatory bowel disease, an inflammatory dermatologic disease, interstitial cystitis, a lupus (including discoid lupus erythematosus, drug-induced lupus erythematosus, lupus nephritis, neonatal lupus, subacute cutaneous lupus erythematosus and systemic lupus erythematosus), morphea, multiple sclerosis (MS), myasthenia gravis, myopathies, narcolepsy, neuromyotonia, pemphigus vulgaris, pernicious anaemia, a psoriasis, primary biliary cirrhosis, recurrent disseminated encephalomyelitis (multiphasic disseminated encephalomyelitis), rheumatic fever, schizophrenia, scleroderma, Sjögren's syndrome, tenosynovitis, vasculitis, and vitiligo.

[0120] Another type of disorder exhibiting a symptom of inflammation is an inflammatory myopathy. Inflammatory myopathies are caused by problems with the immune system attacking components of the muscle, leading to signs of inflammation in the muscle. Inflammatory myopathies include, without limitation, dermatomyositis, inclusion body myositis, and polymyositis.

[0121] Another type of disorder exhibiting a symptom of inflammation is a vasculitis. Vasculitis is a varied group of disorders featuring inflammation of a vessel wall including lymphatic vessels and blood vessels like veins (phlebitis), arteries (arteritis) and capillaries due to leukocyte migration and resultant damage. The inflammation may affect any size blood vessel, anywhere in the body. It may affect either arteries and/or veins. The inflammation may be focal, meaning that it affects a single location within a vessel; or it may be widespread, with

areas of inflammation scattered throughout a particular organ or tissue, or even affecting more than one organ system in the body. Vasculitis include, without limitation, Buerger's disease (thromboangiitis obliterans), cerebral vasculitis (central nervous system vasculitis), Churg-Strauss arteritis, cryoglobulinemia, essential cryoglobulinemic vasculitis, giant cell (temporal) arteritis, Golfer's vasculitis, Henoch-Schonlein purpura, hypersensitivity vasculitis (allergic vasculitis), Kawasaki disease, microscopic polyarteritis/polyangiitis, polyarteritis nodosa, polymyalgia rheumatica (PMR), rheumatoid vasculitis, Takayasu arteritis, Wegener's granulomatosis, and vasculitis secondary to connective tissue disorders like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), relapsing polychondritis, Behçet's disease, or other connective tissue disorders, vasculitis secondary to viral infection.

[0122] Another type of disorder exhibiting a symptom of inflammation is a skin disorder. Skin disorders include, without limitation, a dermatitis, including chronic actinic dermatitis, an eczema like atopic eczema, contact eczema, xerotic eczema, seborrheic dermatitis, dyshidrosis, discoid eczema, venous eczema, dermatitis herpetiformis, neurodermatitis, and autoeczematization, and stasis dermatitis, hidradenitis suppurativa, psoriasis including plaque psoriasis, nail psoriasis, guttate psoriasis, scalp psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermis psoriasis, rosacea and scleroderma including morphea.

[0123] Another type of disorder exhibiting a symptom of inflammation is a gastrointestinal disorder. A gastrointestinal disorder includes, without limitation, irritable bowel disease, an inflammatory bowel disease including Crohn's disease and an ulcerative colitis like ulcerative proctitis, left-sided colitis, pancolitis and fulminant colitis.

[0124] Aspects of the present disclosure provide, in part, a neurodegenerative disease. Neurodegenerative arises from the progressive loss of structure or function of neurons, including death of neurons. Non-limiting examples of a neurodegenerative diseases include, but are not limited to, Alexander disease, Alper's disease, Alzheimer's disease, amyloidoses, amyotrophic lateral sclerosis, anxiety, ataxia telangiectasia, attention deficit disorders, Canavan disease, central nervous system injuries, Charcot Marie Tooth disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, encephalitis (e.g., bacterial, parasitic, fungal, or viral), Friedreich's ataxia frontotemporal dementia, hereditary spastic paraparesis, Guillain-Barre syndrome (and its variants acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher syndrome), HIV/AIDS dementia complex, Huntington's disease, ischemic damage to the nervous system, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, meningitis (e.g., bacterial,

parasitic, fungal, or viral), multiple sclerosis, multiple system atrophy, neural trauma, e.g., percussive brain damage, spinal cord injury and traumatic damage to the nervous system, a neuropathy such as e.g., chemotherapy-induced neuropathy, diabetes-associated neuropathy, and peripheral neuropathy, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, prion disorders, progressive supranuclear palsy, Refsum's disease, Sandhoff disease, schizophrenia, Schilder's disease, spinocerebellar atrophies, Steele-Richardson-Olszewski disease, stroke, tabes dorsalis, and vascular dementia. The neurodegeneration may be associated with an auto-immune disease or a non-autoimmune disease, and the neurodegeneration may be a systemic disorder or an organ-specific disorder. Non-limiting examples of a symptom reduced by a method of treating a neurodegenerative disease disclosed herein include anxiety, aphasia, cognition, confusion, depression, pain, paralysis, spasticity, tics, and tremors.

[0125] Aspects of the present disclosure provide, in part, reducing a symptom associated with an autoimmune disorder or a neurodegenerative disease. In an aspect of this embodiment, the symptom reduced is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, infertility or reduced sex drive (low libido), blood sugar changes, and depending on the type of autoimmune disease, an increase in the size of an organ or tissue or, the destruction of an organ or tissue.

[0126] In an embodiment, the immunosuppressive Tat derivative polypeptide has activity that results in increased Fas ligand (FasL) expression in antigen presenting cell regulatory macrophages (AREgs) exposed to the immunosuppressive Tat derivative polypeptide. In aspects of this embodiment, an immunosuppressive Tat derivative polypeptide increases FasL expression in cells by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%, relative to cells not exposed to the same immunosuppressive Tat derivative polypeptide. In other aspects of this embodiment, an immunosuppressive Tat derivative polypeptide increases FasL expression in cells by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to

about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%, relative to cells not exposed to the same immunosuppressive Tat derivative. In certain embodiments, the ARegs are CD14+ macrophages.

[0127] The disclosed autoimmune, neurodegenerative, and inflammation-associated diseases are immune-mediated disorders characterized by an increase in T cell-mediated inflammation that is desired to be reduced. A therapeutic agent which increases, or induces expression of, FasL on ARegs, or dendritic cells, decreases T cell-mediated inflammation and thereby treats the autoimmune, neurodegenerative, or inflammation associated disease. Therefore, in one embodiment, the present disclosure provides a method for decreasing T cell-mediated inflammation in a subject with an autoimmune, neurodegenerative, or inflammation-associated disease by administration of one or more of the disclosed immunosuppressive Tat derivative polypeptides, thereby treating the autoimmune, neurodegenerative, or inflammation-associated disease. In another embodiment, the present disclosure provides a method of inducing the expression of FasL on ARegs in a subject with an autoimmune, neurodegenerative, or inflammation-associated disease by administration of one or more of the disclosed immunosuppressive Tat derivative polypeptides, thereby treating the autoimmune, neurodegenerative, or inflammation-associated disease.

[0128] Aspects of the present disclosure additionally provide, in part, reducing a symptom associated with inflammation. In an aspect of this embodiment, the symptom reduced is edema, hyperemia, erythema, bruising, tenderness, stiffness, swollenness, fever, a chill, congestion of the respiratory tract including nose, and bronchi, congestion of a sinus, a breathing problem, fluid retention, a blood clot, a loss of appetite, an increased heart rate, a formation of granulomas, fibrinous, pus, or non-viscous serous fluid, a formation of an ulcer, or pain.

[0129] Aspects of the present disclosure provide, in part, a mammal. A mammal includes a human, and a human can be a patient. Other aspects of the present disclosure provide, in part, an individual. An individual includes a mammal and a human, and a human can be a patient. In other embodiments, mammals include domesticated animals such as dogs, cats, horses, cattle, sheep, goats, and primates.

[0130] Aspects of the present disclosure provide, in part, administering a compound or a composition disclosed herein. As used herein, the term “administering” means any delivery

mechanism that provides a compound or a composition disclosed herein to an individual that potentially results in a clinically, therapeutically, or experimentally beneficial result.

[0131] Administration of a compound or a composition disclosed herein include a variety of enteral or parenteral approaches including, without limitation, oral administration in any acceptable form, such as, e.g., tablet, liquid, capsule, powder, or the like; topical administration in any acceptable form, such as, e.g., drops, spray, creams, gels or ointments; buccal, nasal, and/or inhalation administration in any acceptable form; rectal administration in any acceptable form; vaginal administration in any acceptable form; intravascular administration in any acceptable form, such as, e.g., intravenous bolus injection, intravenous infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the vasculature; peri- and intra-tissue administration in any acceptable form, such as, e.g., intraperitoneal injection, intramuscular injection, subcutaneous injection, subcutaneous infusion, intraocular injection, retinal injection, or sub-retinal injection or epidural injection; intravesicular administration in any acceptable form, such as, e.g., catheter instillation; and by placement device, such as, e.g., an implant, a stent, a patch, a pellet, a catheter, an osmotic pump, a suppository, a bioerodible delivery system, a non-bioerodible delivery system or another implanted extended or slow release system. An exemplary list of biodegradable polymers and methods of use are described in, e.g., *Handbook of Biodegradable Polymers* (Abraham J. Domb et al., eds., Overseas Publishers Association, 1997).

[0132] A compound or a composition disclosed herein can be administered to a mammal using a variety of routes. Routes of administration suitable for treating inflammation, an autoimmune disorder, or a neurodegenerative disease as disclosed herein include both local and systemic administration. Local administration results in significantly more delivery of a composition to a specific location as compared to the entire body of the mammal, whereas, systemic administration results in delivery of a composition to essentially the entire body of the individual. Suitable routes of administration also include both central and peripheral administration. Central administration results in delivery of a compound or a composition to essentially the central nervous system of the individual and includes, e.g., intrathecal administration, epidural administration as well as a cranial injection or implant. Peripheral administration results in delivery of a compound or a composition to essentially any area of an individual outside of the central nervous system and encompasses any route of administration other than direct administration to the spine or brain. The actual route of administration of a compound or a composition disclosed herein used can be determined by a person of ordinary

skill in the art by taking into account factors, including, without limitation, the type, location, cause and severity of inflammation or an autoimmune or neurodegenerative disorder, the duration of treatment desired, the degree of relief desired, the duration of relief desired, the particular compound or composition used, the rate of excretion of the compound or composition used, the pharmacodynamics of the compound or composition used, the nature of the other compounds to be included in the composition, the particular route of administration, the particular characteristics, history and risk factors of the individual, such as, e.g., age, weight, general health and the like, the response of the individual to the treatment, or any combination thereof. An effective dosage amount of a compound or a composition disclosed herein can thus readily be determined by the person of ordinary skill in the art considering all criteria and utilizing his best judgment on the individual's behalf.

[0133] In an embodiment, a compound or a composition disclosed herein is administered systemically to a mammal. In another embodiment, a compound or a composition disclosed herein is administered locally to a mammal. In an aspect of this embodiment, a compound or a composition disclosed herein is administered to a site of inflammation, neurodegeneration, or autoimmune disorder of a mammal. In another aspect of this embodiment, a compound or a composition disclosed herein is administered to the area surrounding an inflammation, neurodegenerative disease, or autoimmune disorder of a mammal.

[0134] Aspects of the present specification provide, in part, administering a therapeutically effective amount of a compound or a composition disclosed herein. As used herein, the term "therapeutically effective amount" is synonymous with "therapeutically effective dose" and when used in reference to treating inflammation, neurodegeneration, or an autoimmune disorder means the minimum dose of a compound or composition disclosed herein necessary to achieve the desired therapeutic effect and includes a dose sufficient to reduce a symptom associated with inflammation, neurodegeneration, or an autoimmune disorder. In aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein reduces a symptom associated with inflammation, neurodegeneration, or an autoimmune disorder by, e.g., at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 100%. In other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein reduces a symptom associated with inflammation, neurodegeneration, or an autoimmune disorder by, e.g., at most 10%, at most 20%, at most 30%, at most 40%, at most 50%, at most 60%, at most 70%, at most 80%, at most 90% or at most 100%. In yet other aspects of this

embodiment, a therapeutically effective amount of a compound or a composition disclosed herein reduces a symptom associated with inflammation, neurodegeneration, or an autoimmune disorder by, e.g., about 10% to about 100%, about 10% to about 90%, about 10% to about 80%, about 10% to about 70%, about 10% to about 60%, about 10% to about 50%, about 10% to about 40%, about 20% to about 100%, about 20% to about 90%, about 20% to about 80%, about 20% to about 20%, about 20% to about 60%, about 20% to about 50%, about 20% to about 40%, about 30% to about 100%, about 30% to about 90%, about 30% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%. In still other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein is the dosage sufficient to reduces a symptom associated with inflammation, neurodegeneration, or an autoimmune disorder for, e.g., at least one week, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, or at least twelve months.

[0135] The amount of active component in a compound or a composition disclosed herein for treating inflammation, neurodegeneration, or an autoimmune disorder can be varied so that a suitable dosage is obtained. The actual therapeutically effective amount of a compound or a composition disclosed herein to be administered to a mammal can be determined by a person of ordinary skill in the art by taking into account factors, including, without limitation, the type, location, cause or severity of inflammation, neurodegeneration, or an autoimmune disorder, the duration of treatment desired, the degree of relief desired, the duration of relief desired, the particular compound or composition used, the rate of excretion of the compound or composition used, the pharmacodynamics of the compound or composition used, the nature of the other compounds to be included in the composition, the particular route of administration, the particular characteristics, history and risk factors of the individual, such as, e.g., age, weight, general health and the like, the response of the individual to the treatment, or any combination thereof. An effective dosage amount of a compound or a composition disclosed herein can thus readily be determined by the person of ordinary skill in the art considering all criteria and utilizing his best judgment on the individual's behalf.

[0136] Additionally, where repeated administration of a compound or a composition disclosed herein is used, the actual effect amount of a compound or a composition disclosed herein will further depend upon factors, including, without limitation, the frequency of administration, the half-life of the compound or composition disclosed herein, or any

combination thereof. It is known by a person of ordinary skill in the art that an effective amount of a compound or a composition disclosed herein can be extrapolated from *in vitro* assays and *in vivo* administration studies using animal models prior to administration to humans. Wide variations in the necessary effective amount are to be expected in view of the differing efficiencies of the various routes of administration. For instance, oral administration generally would be expected to require higher dosage levels than administration by intravenous or intravitreal injection. Variations in these dosage levels can be adjusted using standard empirical routines of optimization, which are well-known to a person of ordinary skill in the art. The precise therapeutically effective dosage levels and patterns are preferably determined by the attending physician in consideration of the above-identified factors.

[0137] Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art. For instance, treatment of inflammation, neurodegeneration, or an autoimmune disorder may comprise a one-time administration of an effective dose of a compound or a composition disclosed herein. As a non-limiting example, an effective dose of a compound or a composition disclosed herein can be administered once to a mammal, *e.g.*, as a single injection or deposition at or near the site exhibiting a symptom of inflammation, neurodegeneration, or an autoimmune disorder or a single oral administration of the compound or a composition. Alternatively, treatment of inflammation, neurodegeneration, or an autoimmune disorder may comprise multiple administrations of an effective dose of a compound or a composition disclosed herein carried out over a range of time periods, such as, *e.g.*, daily, once every few days, weekly, monthly or yearly. As a non-limiting example, a compound or a composition disclosed herein can be administered once or twice weekly to a mammal. The timing of administration can vary from mammal to mammal, depending upon such factors as the severity of a mammal's symptoms. For example, an effective dose of a compound or a composition disclosed herein can be administered to a mammal once a month for an indefinite period of time, or until the mammal no longer requires therapy. A person of ordinary skill in the art will recognize that the condition of the mammal can be monitored throughout the course of treatment and that the effective amount of a compound or a composition disclosed herein that is administered can be adjusted accordingly.

[0138] A compound or a composition disclosed herein as disclosed herein can also be administered to a mammal in combination with other therapeutic compounds to increase the overall therapeutic effect of the treatment. The use of multiple compounds to treat autoimmune, neurodegenerative, and inflammation-associated diseases is within the scope of the present

disclosure. Additionally, the present disclosure includes the use of the disclosed peptides to treat autoimmune, neurodegenerative, and inflammation-associated diseases and the use of the disclosed peptides in the manufacture of a medicament to treat autoimmune, neurodegenerative, and inflammation-associated diseases.

EXAMPLES

[0139] The following non-limiting examples are provided for illustrative purposes only in order to facilitate a more complete understanding of representative embodiments now contemplated. These examples should not be construed to limit any of the embodiments described in the present specification, including those pertaining to the methods of treating an autoimmune disorder, inflammation, or neurodegenerative diseases using the Tat derivatives disclosed herein.

Example 1

Effects of Tat on the Dendritic Cell Lineage

[0140] Tat induces monocytes committed to the dendritic cell (DC) lineage to enlarge into activated, CD86⁺ DC APCs (FIG. 1). Human monocytes enriched from PBMCs by Percoll density gradient separation and adherence to anti-CD14 coated magnetic beads (Dynabeads M-450, Dynal Biotech) were committed to differentiate into DCs through five days of culture in GM-CSF (100 ng/mL) and IL-4 (100 ng/mL). Committed DCs were cultured overnight either in medium alone (Control), LPS (100 ng/mL), or Tat (50nM), after which they were stained with an anti-CD86 antibody (BD Pharmingen) and analyzed by FACSscan for CD86 induction (left panel) or generalized activation (right panel, enlargement into box R2, shown for Tat-stimulated cells). The MFIs for CD86 expression are 9 (Control), 30 (LPS), and 187 (Tat), CD86 being a specific determinant of DC activation.

[0141] Derivatized Tat reduces AReg differentiation and potently enhances antigen-specific activation of CTLs (FIG. 2). Tat is chemically derivatized by oxidation (Tat* or ox-Tat) so that it does not induce ARegs from monocyte APC precursors (FIG. 3). Ten micrograms of Tat/p24 Tat*-Ag conjugate (Ag-Tat*) was administered into the flanks of Balb/C mice in adjuvant on day 0 and day 7. Experimental groups were comparatively immunized in adjuvant with 5 µg of p24 in one flank and 5 µg derivatized Tat in the other flank (Ag & Tat*), or 10 µg of p24 in adjuvant (Ag). Control mice were given two injections of adjuvant. Four mice were treated in each group. At day 14, draining lymph node cells from each animal were harvested and re-stimulated overnight in cultures of irradiated Ap24 (H-2d cells stably transfected to express antigen p24) cells or control non-transfected cells. CTL activity was quantitated as the number of γ-interferon

secreting spot forming colonies (SFC)/ 10^6 plated cells using ELISPOT assays. The background with non-transfected re-stimulators, which was in all cases < 10 SFC/ 10^6 , is subtracted from each point. The results are indicative of three similar experiments.

Example 2

Tat Activation of Macrophages and Suppression of the Immune Response

[0142] Recombinant Tat protein is prepared as previously described (Li, C.J. et al. (1995), Science 268:429-31) under mildly denaturing conditions and was renatured in the presence of 0.1 mM DTT.

[0143] Tat activation of monocytes is dose-dependent and saturatable (FIG. 3). Human monocytes were cultured in increasing concentrations of recombinant Tat for six days at which time they were assayed for Fas ligand (FasL) induction as a measure of activation by using flow cytometry (FACScan, Becton Dickinson) to quantitate the intensity of staining (mean fluorescence index (MFI)) with an anti-Fas ligand monoclonal antibody (Nok 1, BD Pharmingen). Higher concentrations of Tat did not increase MFI (not shown), and T cells could not be activated with 50 nM Tat (not shown), the plateau stimulatory concentration for APCs.

[0144] Tat suppresses the antigen-specific humoral immune response to HIV-1 p24 (FIG. 4). At week 0, mice (4 in each group) were immunized with 5 μ g recombinant p24 protein (Chiron, Emeryville, CA) and either 5 μ g recombinant Tat protein (PT) or 5 μ g recombinant ox-Tat* protein (Ag) mixed in 100 μ L complete Freund's adjuvant and administered subcutaneously in the flank. Following immunization, sera were collected every other week for 10 weeks and assayed for a specific antibody response to p24 by commercially available ELISA (Abbott Laboratories, Abbott Park, IL). The p24 antibody titer at 2 weeks (FIG. 4A) was completely suppressed by the Tat protein (PT) compared with the ox-Tat* control (Ag). This response was maintained for at least 6 weeks. The antibody titers at 6 weeks are approximately ten times greater than at week 2 due to maturation of the immune response.

[0145] Tat enhances the viability of cultured murine macrophages as long as the macrophages were first activated *in vivo* compared with no prior activation and stimulated with relatively high concentrations of Tat (FIG. 5). APCs were isolated by peritoneal lavage from mice intraperitoneally injected four days earlier with either 2.9% thioglycolate (as adjuvant) or 0.85% saline solution (resting). Harvested washout cells were cultured at 10^6 cells/mL for five days in medium alone (Control, C), lipopolysaccharide (LPS, 100 ng/mL), or Tat produced as recombinant protein in *E. coli* (Tat, 500 ng/mL). Activation was determined as % enlarged cells (M1 fraction).

[0146] The immunosuppressive Tat produces a stable suppression of mouse lymphocyte proliferation (FIG. 6). Mice were immunized in quadruplicate with a Freund's adjuvant emulsion containing either 5 µg Tat/p24 (recombinant HIV-1 *gag* protein p24) tolerogen (GRP 2) or with 5 µg avidin-p24 (GRP 1) as control. At two weeks residual draining lymph node cells were harvested, pooled within each group, and cultured at 10^5 cells/microtiter well for four days in the presence of graded concentrations of recombinant p24 protein (p24, µg/mL). Proliferation was assayed as a determinant of recall T cell response by quantitating overnight ^3H thymidine uptake (CPM) in a liquid scintillation counter. This response is maintained for up to six weeks.

[0147] In addition, the immunosuppressive Tat generates an antigen-specific immune suppression (FIG. 7). Mice in quadruplicate were immunized at day 0 and boosted at day 7 with an adjuvant emulsion containing either 5 µg Tat/p24 tolerogen (Ag+Tol) or with 5 µg avidin-p24 (Ag Alone) as control. At day 14, draining lymph node cells were harvested and stimulated at 10^5 cells/microtiter culture well either with added antigen (Specific, recombinant p24, 1 µg/mL) or with added anti-T cell receptor monoclonal antibody (NonSpecific, 2C11, 10 µg/mL). Tritiated thymidine uptake (CPM) was determined by liquid scintillation at day 4 of culture. The specific Ag+Tol response is suppressed 98% relative to Ag alone, and is not distinguishable from cells cultured in the absence of stimulants.

Example 3

Tat Suppression is Mediated by ARegs

[0148] Tat mediated antigen-specific suppression is mediated through trans- (intracellular) activation of a CD14⁺ FasL⁺ macrophage (FIG. 8). In mice, Tat tolerizes at the T cell level and is maintained for at least six weeks after the initial treatment under the conditions demonstrated in FIG. 6. A human peripheral blood mononuclear cell (PBMC) population enriched for monocytes by Percoll centrifugation was cultured for four days either in medium containing 5% fetal calf serum (FCS, Control), Tat (50 nM), or LPS (100 ng/mL). Harvested cells were doubly stained with a fluoresceinated (anti-fl1) anti-FasL monoclonal antibody (Mab), (αFasL-FITC, Nok 1, BD Pharmingen) and with an anti-CD14 rhodamine labeled Mab (αCD14fl2, BD Biosciences, CD14 being a determinant specific to macrophages (MΦ). Cells were analyzed by FACScan (Becton Dickinson) for activation (Forward Scatter), CD14 expression (R2, percent MΦs), and for induction of FasL (MFI). The T cell population (R1) was CD14⁻ and did not express FasL. Similar results were obtained from cells harvested after 2, 3, 5, or 6 days of culture as for PBMCs harvested at day four.

[0149] In human cells, Tat-activated macrophages are regulatory and immunosuppressive APC macrophage regulators (AREgs) (FIG. 9). To define the pathway of Tat immunosuppression, through FasL induction on the macrophage, resulting in loss of helper T cell recall responses, T cell proliferation assays were used with recall antigens, tat and FasL antagonists. In FIG. 9A, human PBMCs from one individual were cultured in triplicate for 5 days in either medium (not shown), tetanus antigen (Ag, 0.3 Lf/mL), antigen with the further addition of 50 nM Tat (Ag+Tat) or Ag with 50 nM Tat and recombinant sFas protein (25 µg/mL) to block surface Fas L expressed on macrophages (Ag+Tat+sFas). Tritiated thymidine was added over the last 18 hours, and results are graphed as stimulation index (mean cpm stimulated culture/mean cpm medium control). Results are representative of three similar experiments. At low concentrations of Tat (50 nM), Tat-induced immunosuppression was not only fully reversed by the addition of soluble Fas, but under these conditions, Tat actually became stimulatory (141% relative to antigen treatment alone). FIG. 9B: Proliferation of PBMCs cultured 6 days with either tetanus or *Candida* antigen alone (Ag), compared with cultures in which Tat (Ag+Tat, 125 nM), or Tat (125 nM) and the antagonistic anti-Fas antibody, ZB4 (250 µg/mL, Upstate Biotechnology) also were added (Ag+Tat+αFas). Results are representative of three similar experiments.

Example 4

In Vitro Bioassay for Monocyte Differentiation

[0150] The *in vitro* ultra-sensitive monocyte Tat bioassay is used to assess the immunosuppressant or immunostimulatory activity of the Tat proteins disclosed herein. This assay utilizes fresh monocyte cells substantially purified from human peripheral blood using standard density gradient enrichment procedures or other cell isolation protocols known in the art. The substantially purified monocytes are washed and then cultured in RPMI-1640 supplemented with 10% FBS at 37°C.

[0151] The *in vitro* ultra-sensitive monocyte Tat bioassay is performed using a positive control (FasL, inducing compound) and a negative control (no active compound is added to the culture). Additional suitable positive controls include, but are not limited to, lipopolysaccharide (LPS) and or tumor necrosis factor (TNF-α) at a final concentration of 100 ng/mL and 50 ng/mL, respectively. Test samples (Tat preparations) are run at final concentrations from 50 pM to 50nM and include Tat, ox-Tat, and other Tat derivatives and mutants.

[0152] The test samples and controls are individually mixed with the substantially pure monocytes seeded at a density of 10⁶ cells/mL in round bottom tubes containing RPMI-1640

with 10% FBS (herein referred to collectively as assay cultures). The assay cultures are then incubated for a suitable period of time, preferably from five to six days, at 37°C, in a 5% CO₂ environment.

[0153] At the end of the incubation period, cells are removed from each assay culture and the presence of any induced FasL expression (for measurement of differentiation into ARegs) or CD86 expression (for differentiation in dendritic cells) is detected by staining with anti-FasL or anti-CD86 antibodies and appropriate fluorescent detection agents. After the cultures have been stained, the fluorescence is detected using a fluorescence activated cell sorter (FACS) system. Control staining is performed using the fluorescent detection system alone and subtracted from the specific anti-FasL or anti-CD86 staining seen in the assay cultures. The greater the percentage of FasL positive cells in a given assay culture, the more immunosuppressant the test sample in the assay culture is. Conversely, if the assay culture contains a predominance of CD86 positive cells, the test sample is identified to be immunostimulatory. Negative controls should always remain non-reactive with the antibodies and the positive control should fall within predetermined ranges.

Example 5

Synthesis of Tat derivatives

[0154] Synthetic peptides were assembled by standard Fmoc chemistry using a CS336X automated synthesizer (C S Bio Co., Menlo Park, CA). The peptides were cleaved from the resin using trifluoroacetic acid cleavage/deprotection cocktail compatible with the presence of seven cysteines. Purification was done using reverse phase HPLC. The final product was lyophilized from H₂O/acetonitrile. A portion of each synthesis was labeled with Alexa-488. All synthetic Tat derivatives achieved a purity of > 95%. Synthetic peptides were reconstituted in phosphate buffer in the presence of 0.1 mM dithiothreitol before use.

Example 6

In vitro activity of Tat derivatives

[0155] Human monocytes were cultured for 24-28 hours with a Tat derivative (SEQ ID NO:7, Nani-P2), (FIG. 10) or lipopolysaccharide (LPS) (FIG. 11) and the cells were then washed and stained with fluorescent-labeled CD86. The Tat derivative stimulated higher expression of CD86 than either ISS (TLR) or LPS.

Example 7

Live Cell Imaging of Tat Derivatives in T-Lymphocyte and Monocyte Cell Lines

[0156] A Jurkat cell line (Clone E6-1, American Type Culture Collection) was maintained in RPMI-1640 (GIBCO), 10% heat-inactivated FBS (GIBCO), 50 U penicillin/50 µg/ml streptomycin (GIBCO), and 2 mM L-Glutamine (GIBCO) at 37°C in 5% CO₂. U937 Cells (American Type Culture Collection) were maintained in RPMI-1640 (GIBCO), 10% heat-inactivated FBS, 50 U penicillin, 50 µg/ml streptomycin, and 2 mM L-Glutamine (GIBCO), 10 mM HEPES (GIBCO), and 0.005% β-mercaptoethanol (Sigma-Aldrich) at 37°C in 5% CO₂.

[0157] One million live Jurkat or U937 cells were incubated in complete culture medium for 60-120 minutes at 37°C in 5% CO₂, with or without addition of 5 µM Alexa-488-labeled synthetic Tat derivative. Cells were washed in PBS containing 0.1% heat-inactivated FBS, 1 mM EDTA, and stained with a HOECHST-NucBlue Live Cell Stain (Molecular Probes) by adding 2 drops/mL to the cell suspension. Cells were kept on ice until live cell imaging was performed.

[0158] Cells were placed in glass-bottom dishes (MatTek Corp.) and imaged on a Zeiss Axio Observer.Z1 microscope (Carl Zeiss) using a Plan-Neofluor 100x/1.3 objective lens. LEDs (Colibri; Carl Zeiss) at 365 nm and 470 nm were used to excite HOESCHT-stained DNA and Alexa488-labeled protein. Emission was collected with standard DAPI and FITC fluorescence filters. Fluorescence and phase-contrast images were collected with an Orca ER cooled CCD camera (Hamamatsu Photonics).

[0159] The results, depicted in FIG. 12 and 13 demonstrate the ability of synthetic Tat derivatives to enter T-lymphocyte and monocytic cell lines *in vitro*. Jurkat T-cells (FIG. 12) and U937 monocytes (FIG. 13) treated with Alexa488-labeled Tat derivatives show cellular uptake and nuclear localization of fluorescently labeled proteins, highlighting the application of these molecules as cell penetrating peptides endowed with the ability to localize within and around the nucleus.

Example 8

Fluorescence Activated Cell Sorting of Tat Derivative Treated Cells

[0160] Human peripheral blood mononuclear cells (PBMC) were isolated from whole blood by density gradient centrifugation with Histopaque separation medium using an ACCUSPIN™ centrifuge tube (Sigma-Aldrich). PBMC cultures were established in RPMI-1640, 10% heat-inactivated fetal bovine serum, 50U penicillin/50 µg/mL streptomycin, and 2 mM L-Glutamine at a cell density of 1x10⁶ cells/mL in a 12 well tissue culture plate. PBMC's were incubated in the

presence of either no stimulus, 1 µg/ml LPS (Sigma-Aldrich), 100 ng/ml TNF-α (Peprotech), or 1 µg/ml synthetic Tat derivative (SEQ ID NO:9) at 37°C in 5% CO₂. After 3-5 days, cells were harvested, washed, and stained with a mouse anti-human CD14-allophycocyanin (APC) conjugated monoclonal antibody (clone M5E2, BD Biosciences,) or a mouse anti-human Fas Ligand fluorescein (FITC) conjugated monoclonal antibody (clone SB93a, Southern Biotech). Propidium iodide was added to assess viability before fluorescence activated cell sorting (FACS) was performed on a BD LSR II Flow Cytometer (BD Biosciences).

[0161] The results, depicted in FIG. 14-17 demonstrate the ability of Tat derivatives to stimulate and increase cell surface CD14 and FasL on human PBMC's *in vitro* relative to non-stimulated controls by FACS indicating the presence AReg cells capable of suppressing a T-cell immune response.

[0162] In closing, it is to be understood that although aspects of the present specification are highlighted by referring to specific embodiments, one skilled in the art will readily appreciate that these disclosed embodiments are only illustrative of the principles of the subject matter disclosed herein. Therefore, it should be understood that the disclosed subject matter is in no way limited to a particular methodology, protocol, and/or reagent, etc., described herein. As such, various modifications or changes to or alternative configurations of the disclosed subject matter can be made in accordance with the teachings herein without departing from the spirit of the present specification. Lastly, the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims. Accordingly, the present invention is not limited to that precisely as shown and described.

[0163] Certain embodiments of the present invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the present invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described embodiments in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0164] Groupings of alternative embodiments, elements, or steps of the present invention are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other group members disclosed herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0165] Unless otherwise indicated, all numbers expressing a characteristic, item, quantity, parameter, property, term, and so forth used in the present specification and claims are to be understood as being modified in all instances by the term “about.” As used herein, the term “about” means that the characteristic, item, quantity, parameter, property, or term so qualified encompasses a range of plus or minus ten percent above and below the value of the stated characteristic, item, quantity, parameter, property, or term. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical indication should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and values setting forth the broad scope of the invention are approximations, the numerical ranges and values set forth in the specific examples are reported as precisely as possible. Any numerical range or value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Recitation of numerical ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate numerical value falling within the range. Unless otherwise indicated herein, each individual value of a numerical range is incorporated into the present specification as if it were individually recited herein.

[0166] The terms “a,” “an,” “the” and similar referents used in the context of describing the present invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein is intended merely to better illuminate the present invention and does not pose a limitation on the scope of the invention otherwise

claimed. No language in the present specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0167] Specific embodiments disclosed herein may be further limited in the claims using consisting of or consisting essentially of language. When used in the claims, whether as filed or added per amendment, the transition term “consisting of” excludes any element, step, or ingredient not specified in the claims. The transition term “consisting essentially of” limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the present invention so claimed are inherently or expressly described and enabled herein.

[0168] All patents, patent publications, and other publications referenced and identified in the present specification are individually and expressly incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the compositions and methodologies described in such publications that might be used in connection with the present invention. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

What is claimed is:

1. An immunosuppressive trans-activator of transcription (Tat) derivative polypeptide comprising an amino acid sequence comprising the following domains in the indicated order:
 - a transcription factor (TF) domain comprising a sequence from an immunosuppressive human immunodeficiency virus (HIV), SIV Tat protein, hairless or an artificial immunosuppressive sequence;
 - a cysteine-rich region from lentiviral Tat or a defensin molecule; and
 - a C-terminal region from a lentiviral Tat protein.
2. The immunosuppressive Tat derivative polypeptide of claim 1, wherein the HIV is HIV-1 or HIV-2.
3. The immunosuppressive Tat derivative polypeptide of claim 1, further comprising an arginine-rich domain from a lentiviral Tat protein.
4. The immunosuppressive Tat derivative polypeptide of claim 1, wherein at least one of the amino acids in the TF domain is modified with a conservative amino acid substitution.
5. The immunosuppressive Tat derivative polypeptide of claim 1, wherein the lentiviral Tat is from HIV-1, HIV-2, SIV, FIV, or EIAV.
6. The immunosuppressive Tat derivative polypeptide of claim 1, wherein the TF domain further comprises a repeat sequence comprising (PVDPRLEPWKHPGSQP)_n at the N-terminus, wherein n=2-10.
7. The immunosuppressive Tat derivative peptide of claim 1, wherein the TF domain comprises an amino acid sequence of one of SEQ ID NOs: 36, 39, 44, 48, 50, 54, 59, 60, or 61.
8. The immunosuppressive Tat derivative peptide of claim 1, wherein the cysteine-rich domain comprises an amino acid sequence of one of SEQ ID NOs: 37, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 58, 62, 63, 64, or 70.
9. The immunosuppressive Tat derivative peptide of claim 1, wherein the C-terminal domain comprises an amino acid sequence of one of SEQ ID NOs: 38, 42, 46, 47, 49, 52, 53, 68, or 71.
10. The immunosuppressive Tat derivative peptide of claim 1, wherein both the cysteine-rich region and the C-terminal region are from the same source and the amino acid

sequence of the combined cysteine-rich and C-terminal region is one of SEQ ID NOs:47, 49, or 53.

11. The immunosuppressive Tat derivative polypeptide of claim 1, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

12. The immunosuppressive Tat derivative polypeptide of claim 1, wherein the immunosuppressive Tat derivative polypeptide has greater than 90% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

13. The immunosuppressive Tat derivative polypeptide of claim 1, wherein the immunosuppressive Tat derivative polypeptide has greater than 95% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

14. A pharmaceutical composition comprising one or more of an immunosuppressive Tat derivative polypeptide according to claim 1 and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition according to claim 14, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one or more of SEQ ID NOs:9-11, 13-35, or 69.

16. A method of treating a disease characterized by aberrant immune responses, the method comprising:

administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptide of claim 1 to a subject in need thereof; and
thereby treating the disease by suppressing the immune system.

17. The method of claim 16, wherein the treatment increases the expression of Fas ligand on antigen presenting cell regulatory macrophages (AREgs).

18. The method of claim 17, wherein the AREgs are CD14+ macrophages.

19. The method of claim 16, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

20. The method of claim 16, wherein the disease is an autoimmune, neurodegenerative or inflammation-associated disorder.

21. The method of claim 20, wherein the autoimmune disorder is an acute disseminated encephalomyelitis (ADEM), an Addison's disease, an allergy, allergic rhinitis, an Alzheimer's disease, an anti-phospholipid antibody syndrome (APS), an arthritis, an asthma, an

autoimmune deficiency syndrome, an autoimmune hemolytic anemia, an autoimmune hepatitis, an autoimmune inner ear disease, a bullous pemphigoid, a celiac disease, a Chagas disease, a chronic obstructive pulmonary disease (COPD), a diabetes mellitus type 1 (IDDM), an eczema, an endometriosis, a gastrointestinal disorder, a Goodpasture's syndrome, a Graves' disease, a Guillain-Barré syndrome (GBS), a Hashimoto's thyroiditis, a hidradenitis suppurativa, an idiopathic thrombocytopenic purpura, an inflammatory bowel disease, an inflammatory dermatologic disease, an interstitial cystitis, a lupus, a morphea, a multiple sclerosis (MS), a myasthenia gravis, a myopathy, a narcolepsy, a neuromyotonia, a pemphigus vulgaris, a pernicious anaemia, a primary biliary cirrhosis, a psoriasis, a recurrent disseminated encephalomyelitis, a rheumatic fever, a schizophrenia, a scleroderma, a Sjögren's syndrome, a skin disorder, a tenosynovitis, a uveitis, a vasculitis, or a vitiligo.

22. The method of claim 20, wherein the disease associated with inflammation is an acne, an acid reflux/heartburn, an allergy, an allergic rhinitis, an Alzheimer's disease, an appendicitis, an arteritis, an arthritis, an asthma, an atherosclerosis, an autoimmune disorder, a balanitis, a blepharitis, a bronchiolitis, a bronchitis, a bursitis, a cancer, a carditis, a celiac disease, a cellulitis, a cervicitis, a cholangitis, a cholecystitis, a chorioamnionitis, a chronic obstructive pulmonary disease (COPD), a cirrhosis, a colitis, a conjunctivitis, a cystitis, a common cold, a dacryoadenitis, a dementia, a dermatitis, a dermatomyositis, an eczema, an emphysema, an encephalitis, an endocarditis, an endometritis, an enteritis, an enterocolitis, an epicondylitis, an epididymitis, a fasciitis, a fibrositis, a gastritis, a gastroenteritis, a gingivitis, a glomerulonephritis, a glossitis, a heart disease, a hepatitis, a hidradenitis suppurativa, a high blood pressure, an ileitis, an insulin resistance, an interstitial cystitis, an iritis, an ischemic heart disease, a keratitis, a keratoconjunctivitis, a laryngitis, a lupus, a mastitis, a mastoiditis, a meningitis, a metabolic syndrome (syndrome X), a migraine, a multiple sclerosis, a myelitis, a myocarditis, a myopathy, a myositis, a nephritis, a neuropathy, an obesity, an omphalitis, an oophoritis, an orchitis, an osteochondritis, an osteopenia, an osteoporosis, an osteitis, an otitis, a pancreatitis, a Parkinson's disease, a parotitis, a pelvic inflammatory disease, a pericarditis, a peritonitis, a pharyngitis, a phlebitis, a pleuritis, a pneumonitis, a proctitis, a prostatitis, a psoriasis, a pulpitis, a pyelonephritis, a pyelephlebitis, a rheumatic fever, a rhinitis, a salpingitis, a sialadenitis, a sinusitis, a spastic colon, a stomatitis, a synovitis, a tendonitis, a tendinosis, a tenosynovitis, a thrombophlebitis, a tonsillitis, a trigonitis, a tumor, an urethritis, an uveitis, a vaginitis, a vasculitis, or a vulvitis.

23. The method of claim 20, wherein the neurodegenerative disease is Alexander disease, Alper's disease, Alzheimer's disease, amyloidoses, amyotrophic lateral sclerosis, anxiety, ataxia telangiectasia, attention deficit disorders, Canavan disease, central nervous system injuries, Charcot Marie Tooth disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, encephalitis (e.g., bacterial, parasitic, fungal, or viral), Friedreich's ataxia frontotemporal dementia, hereditary spastic paraparesis, Guillain-Barre syndrome (and its variants acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher syndrome), HIV/AIDS dementia complex, Huntington's disease, ischemic damage to the nervous system, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, meningitis (e.g., bacterial, parasitic, fungal, or viral) multiple sclerosis, multiple system atrophy, neural trauma, e.g., percussive brain damage, spinal cord injury and traumatic damage to the nervous system, a neuropathy such as e.g., chemotherapy-induced neuropathy, diabetes-associated neuropathy, and peripheral neuropathy, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, prion disorders, progressive supranuclear palsy, Refsum's disease, Sandhoff disease, schizophrenia, Schilder's disease, spinocerebellar atrophies, Steele-Richardson-Olszewski disease, stroke, tabes dorsalis, or vascular dementia.

24. The method of claim 16, wherein the method further causes the reduction of at least one symptom associated with the autoimmune disease, neurodegenerative disease, or disease associated with inflammation and therein the symptom is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, infertility or reduced sex drive (low libido), blood sugar changes, and depending on the type of autoimmune disease, an increase in the size of an organ or tissue, or the destruction of an organ or tissue.

25. The method of claim 16, wherein the subject is not immunocompromised.

26. The method of claim 16, wherein the immune system of the subject is not compromised as a result of the administration.

27. The method of claim 16, wherein, as a result of the administration, secretion of cytokines by ARegs is decreased.

28. The method of claim 16, wherein the immunosuppressive Tat derivative polypeptide is administered in a plurality of doses.

29. The method of claim 28, wherein the immunosuppressive Tat derivative polypeptide is administered daily, weekly, biweekly, monthly, or bimonthly.

30. The method of claim 16, wherein the administering step comprises a repetitive administration cycle wherein each cycle comprises administering a plurality of doses of the immunosuppressive Tat derivative polypeptide in a defined time period followed by a rest period and wherein the cycle is repeated a plurality of times.

31. A method of increasing the expression of Fas ligand (FasL) on antigen presenting cell regulatory macrophages (AREgs), the method comprising:

administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptide of claim 1 to a subject; and
thereby increasing the expression of FasL on the AREgs.

32. The method according to claim 31, wherein the AREgs are CD14+ macrophages.

33. The method of claim 31, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

34. The method of claim 31, wherein the disease is an autoimmune, neurodegenerative or inflammation-associated disorder.

35. The method of claim 31, wherein the subject is not immunocompromised.

36. The method of claim 31, wherein the immune system of the subject is not compromised as a result of the administration.

37. The method of claim 31, wherein as a result of the administration, secretion of cytokines by AREgs is decreased.

38. A method of reducing inflammation, the method comprising:
administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptide of claim 1 to a subject in need thereof; and
thereby increasing reducing inflammation in the subject.

39. The method of claim 38, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

40. The method according to claim 38, wherein the inflammation is associated with an autoimmune, neurodegenerative or inflammation-associated disorder.

41. The method of claim 38, wherein the subject is not immunocompromised.

42. The method of claim 38, wherein the immune system of the subject is not compromised as a result of the administration.

43. Use of one or more immunosuppressive Tat derivative polypeptides in the manufacture of a medicament for treatment of a disease characterized by aberrant immune responses in a subject in need thereof; wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, and wherein administration of the immunosuppressive Tat derivative polypeptide treats the disease by suppressing the immune system in the subject.

44. The use according to claim 43, wherein the treatment increases the expression of Fas ligand on antigen presenting cell regulatory macrophages (AREgs).

45. The use according to claim 43, wherein the AREgs are CD14+ macrophages.

46. The use according to claim 43, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

47. The use according to claim 43, wherein the subject is not immunocompromised.

48. The use according to claim 43, wherein the immune system of the subject is not compromised as a result of the administration.

49. The use according to claim 43, wherein, as a result of the administration, secretion of cytokines by AREgs is decreased.

50. The use according to claim 43, wherein the disease is an autoimmune, neurodegenerative or inflammation-associated disorder.

51. The use according to claim 50, wherein the autoimmune disorder is an acute disseminated encephalomyelitis (ADEM), an Addison's disease, an allergy, allergic rhinitis, an Alzheimer's disease, an anti-phospholipid antibody syndrome (APS), an arthritis, an asthma, an autoimmune deficiency syndrome, an autoimmune hemolytic anemia, an autoimmune hepatitis, an autoimmune inner ear disease, a bullous pemphigoid, a celiac disease, a Chagas disease, a chronic obstructive pulmonary disease (COPD), a diabetes mellitus type 1 (IDDM), an eczema, an endometriosis, a gastrointestinal disorder, a Goodpasture's syndrome, a Graves' disease, a Guillain-Barré syndrome (GBS), a Hashimoto's thyroiditis, a hidradenitis suppurativa, an

idiopathic thrombocytopenic purpura, an inflammatory bowel disease, an inflammatory dermatologic disease, an interstitial cystitis, a lupus, a morphea, a multiple sclerosis (MS), a myasthenia gravis, a myopathy, a narcolepsy, a neuromyotonia, a pemphigus vulgaris, a pernicious anaemia, a primary biliary cirrhosis, a psoriasis, a recurrent disseminated encephalomyelitis, a rheumatic fever, a schizophrenia, a scleroderma, a Sjögren's syndrome, a skin disorder, a tenosynovitis, a uveitis, a vasculitis, or a vitiligo.

52. The use according to claim 50, wherein the disease associated with inflammation is an acne, an acid reflux/heartburn, an allergy, an allergic rhinitis, an Alzheimer's disease, an appendicitis, an arteritis, an arthritis, an asthma, an atherosclerosis, an autoimmune disorder, a balanitis, a blepharitis, a bronchiolitis, a bronchitis, a bursitis, a cancer, a carditis, a celiac disease, a cellulitis, a cervicitis, a cholangitis, a cholecystitis, a chorioamnionitis, a chronic obstructive pulmonary disease (COPD), a cirrhosis, a colitis, a conjunctivitis, a cystitis, a common cold, a dacryoadenitis, a dementia, a dermatitis, a dermatomyositis, an eczema, an emphysema, an encephalitis, an endocarditis, an endometritis, an enteritis, an enterocolitis, an epicondylitis, an epididymitis, a fasciitis, a fibrositis, a gastritis, a gastroenteritis, a gingivitis, a glomerulonephritis, a glossitis, a heart disease, a hepatitis, a hidradenitis suppurativa, a high blood pressure, an ileitis, an insulin resistance, an interstitial cystitis, an iritis, an ischemic heart disease, a keratitis, a keratoconjunctivitis, a laryngitis, a lupus, a mastitis, a mastoiditis, a meningitis, a metabolic syndrome (syndrome X), a migraine, a multiple sclerosis, a myelitis, a myocarditis, a myopathy, a myositis, a nephritis, a neuropathy, an obesity, an omphalitis, an oophoritis, an orchitis, an osteochondritis, an osteopenia, an osteoporosis, an osteitis, an otitis, a pancreatitis, a Parkinson's disease, a parotitis, a pelvic inflammatory disease, a pericarditis, a peritonitis, a pharyngitis, a phlebitis, a pleuritis, a pneumonitis, a proctitis, a prostatitis, a psoriasis, a pulpitis, a pyelonephritis, a pyelephlebitis, a rheumatic fever, a rhinitis, a salpingitis, a sialadenitis, a sinusitis, a spastic colon, a stomatitis, a synovitis, a tendonitis, a tendinosis, a tenosynovitis, a thrombophlebitis, a tonsillitis, a trigonitis, a tumor, an urethritis, an uveitis, a vaginitis, a vasculitis, or a vulvitis.

53. The use according to claim 50, wherein the neurodegenerative disease is Alexander disease, Alper's disease, Alzheimer's disease, amyloidoses, amyotrophic lateral sclerosis, anxiety, ataxia telangiectasia, attention deficit disorders, Canavan disease, central nervous system injuries, Charcot Marie Tooth disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, encephalitis (e.g., bacterial, parasitic, fungal, or viral), Friedreich's ataxia frontotemporal dementia, hereditary spastic paraparesis,

Guillain-Barre syndrome (and its variants acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher syndrome), HIV/AIDS dementia complex, Huntington's disease, ischemic damage to the nervous system, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, meningitis (e.g., bacterial, parasitic, fungal, or viral), multiple sclerosis, multiple system atrophy, neural trauma, e.g., percussive brain damage, spinal cord injury and traumatic damage to the nervous system, a neuropathy such as e.g., chemotherapy-induced neuropathy, diabetes-associated neuropathy, and peripheral neuropathy, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, prion disorders, progressive supranuclear palsy, Refsum's disease, Sandhoff disease, schizophrenia, Schilder's disease, spinocerebellar atrophies, Steele-Richardson-Olszewski disease, stroke, tabes dorsalis, or vascular dementia.

54. The use according to claim 43, wherein the immunosuppressive Tat derivative polypeptide further causes the reduction of at least one symptom associated with the autoimmune disease, neurodegenerative disease, or disease associated with inflammation and therein the symptom is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, infertility or reduced sex drive (low libido), blood sugar changes, and depending on the type of autoimmune disease, an increase in the size of an organ or tissue, or the destruction of an organ or tissue.

55. The use according to claim 43, wherein the immunosuppressive Tat derivative polypeptide is administered in a plurality of doses.

56. The use according to claim 55, wherein the immunosuppressive Tat derivative polypeptide is administered daily, weekly, biweekly, monthly, or bimonthly.

57. Use of one or more immunosuppressive Tat derivative polypeptides in the manufacture of a medicament for increasing the expression of Fas ligand (FasL) on antigen presenting cell regulatory macrophages (AREgs) in a subject wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, wherein administration of the immunosuppressive Tat derivative polypeptides increases the expression of FasL on the AREgs.

58. The use according to claim 57, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

59. The use according to claim 57, wherein the ARegs are CD14+ macrophages.
60. The use according to claim 57, wherein the disease is an autoimmune, neurodegenerative or inflammation-associated disorder.
61. The use according to claim 57, wherein the subject is not immunocompromised.
62. The use according to claim 57, wherein the immune system of the subject is not compromised as a result of the administration.
63. The use according to claim 57, wherein as a result of the administration, secretion of cytokines by ARegs is decreased.
64. Use of one or more immunosuppressive Tat derivative peptides in the manufacture of a medicament for reducing inflammation in a subject, wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, and wherein administration of the immunosuppressive Tat derivative polypeptides reduces inflammation in the subject.
65. The use according to claim 64, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.
66. The use according to claim 64, wherein the inflammation is associated with an autoimmune, neurodegenerative or inflammation-associated disorder.
67. The use according to claim 64, wherein the subject is not immunocompromised.
68. The use according to claim 64, wherein the immune system of the subject is not compromised as a result of the administration.
69. An immunosuppressive trans-activator of transcription (Tat) derivative polypeptide comprising an amino acid sequence comprising the following domains in the indicated order:
- a transcription factor (TF) domain comprising a sequence from an immunosuppressive human immunodeficiency virus (HIV), SIV Tat protein, hairless or an artificial immunosuppressive sequence;
 - a cysteine-rich region from lentiviral Tat or a defensin molecule; and
 - a C-terminal region from a lentiviral Tat protein.
70. The immunosuppressive Tat derivative polypeptide of claim 69, wherein the HIV is HIV-1 or HIV-2.

71. The immunosuppressive Tat derivative polypeptide of claims 69 or 70, further comprising an arginine-rich domain from a lentiviral Tat protein.

72. The immunosuppressive Tat derivative polypeptide of any one of claims 69-71, wherein at least one of the amino acids in the TF domain is modified with a conservative amino acid substitution.

73. The immunosuppressive Tat derivative polypeptide of any one of claims 69-72, wherein the lentiviral Tat is from HIV-1, HIV-2, SIV, FIV, or EIAV.

74. The immunosuppressive Tat derivative polypeptide of any one of claims 69-73, wherein the TF domain further comprises a repeat sequence comprising $(\text{PVDPRLEPWKHPGSQP})_n$ at the N-terminus, wherein $n=2-10$.

75. The immunosuppressive Tat derivative peptide of any one of claims 69-74, wherein the TF domain comprises an amino acid sequence of one of SEQ ID NOs: 36, 39, 44, 48, 50, 54, 59, 60, or 61.

76. The immunosuppressive Tat derivative peptide of any one of claims 69-75, wherein the cysteine-rich domain comprises an amino acid sequence of one of SEQ ID NOs:37, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 58, 62, 63, 64, or 70.

77. The immunosuppressive Tat derivative peptide of any one of claims 69-76, wherein the C-terminal domain comprises an amino acid sequence of one of SEQ ID NOs:38, 42, 46, 47, 49, 52, 53, 68, or 71.

78. The immunosuppressive Tat derivative peptide of any one of claims 69-77, wherein both the cysteine-rich region and the C-terminal region are from the same source and the amino acid sequence of the combined cysteine-rich and C-terminal region is one of SEQ ID NOs:47, 49, or 53.

79. The immunosuppressive Tat derivative polypeptide of any one of claims 69-78, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

80. The immunosuppressive Tat derivative polypeptide of any one of claims 69-79, wherein the immunosuppressive Tat derivative polypeptide has greater than 90% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

81. The immunosuppressive Tat derivative polypeptide of any one of claims 69-80, wherein the immunosuppressive Tat derivative polypeptide has greater than 95% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

82. A method of treating a disease characterized by aberrant immune responses, the method comprising:

administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptide of claim 1 to a subject in need thereof; and thereby treating the disease by suppressing the immune system.

83. A method of increasing the expression of Fas ligand (FasL) on antigen presenting cell regulatory macrophages (AREgs), the method comprising:

administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptide of claim 1 to a subject; and thereby increasing the expression of FasL on the AREgs.

84. A method of reducing inflammation, the method comprising:
administering a therapeutically effective amount of one or more of the immunosuppressive Tat derivative polypeptide of claim 1 to a subject in need thereof; and thereby increasing reducing inflammation in the subject.

85. The method of any one of claims 82-84, wherein the treatment increases the expression of Fas ligand on antigen presenting cell regulatory macrophages (AREgs).

86. The method of any one of claims 82-85, wherein the AREgs are CD14+ macrophages.

87. The method of any one of claims 82-86, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

88. The method of any one of claims 82-87, wherein the disease is an autoimmune, neurodegenerative or inflammation-associated disorder.

89. The method of claim 88, wherein the autoimmune disorder is an acute disseminated encephalomyelitis (ADEM), an Addison's disease, an allergy, allergic rhinitis, an Alzheimer's disease, an anti-phospholipid antibody syndrome (APS), an arthritis, an asthma, an autoimmune deficiency syndrome, an autoimmune hemolytic anemia, an autoimmune hepatitis, an autoimmune inner ear disease, a bullous pemphigoid, a celiac disease, a Chagas disease, a

chronic obstructive pulmonary disease (COPD), a diabetes mellitus type 1 (IDDM), an eczema, an endometriosis, a gastrointestinal disorder, a Goodpasture's syndrome, a Graves' disease, a Guillain-Barré syndrome (GBS), a Hashimoto's thyroiditis, a hidradenitis suppurativa, an idiopathic thrombocytopenic purpura, an inflammatory bowel disease, an inflammatory dermatologic disease, an interstitial cystitis, a lupus, a morphea, a multiple sclerosis (MS), a myasthenia gravis, a myopathy, a narcolepsy, a neuromyotonia, a pemphigus vulgaris, a pernicious anaemia, a primary biliary cirrhosis, a psoriasis, a recurrent disseminated encephalomyelitis, a rheumatic fever, a schizophrenia, a scleroderma, a Sjögren's syndrome, a skin disorder, a tenosynovitis, a uveitis, a vasculitis, or a vitiligo.

90. The method of claim 88, wherein the disease associated with inflammation is an acne, an acid reflux/heartburn, an allergy, an allergic rhinitis, an Alzheimer's disease, an appendicitis, an arteritis, an arthritis, an asthma, an atherosclerosis, an autoimmune disorder, a balanitis, a blepharitis, a bronchiolitis, a bronchitis, a bursitis, a cancer, a carditis, a celiac disease, a cellulitis, a cervicitis, a cholangitis, a cholecystitis, a chorioamnionitis, a chronic obstructive pulmonary disease (COPD), a cirrhosis, a colitis, a conjunctivitis, a cystitis, a common cold, a dacryoadenitis, a dementia, a dermatitis, a dermatomyositis, an eczema, an emphysema, an encephalitis, an endocarditis, an endometritis, an enteritis, an enterocolitis, an epicondylitis, an epididymitis, a fasciitis, a fibrositis, a gastritis, a gastroenteritis, a gingivitis, a glomerulonephritis, a glossitis, a heart disease, a hepatitis, a hidradenitis suppurativa, a high blood pressure, an ileitis, an insulin resistance, an interstitial cystitis, an iritis, an ischemic heart disease, a keratitis, a keratoconjunctivitis, a laryngitis, a lupus, a mastitis, a mastoiditis, a meningitis, a metabolic syndrome (syndrome X), a migraine, a multiple sclerosis, a myelitis, a myocarditis, a myopathy, a myositis, a nephritis, a neuropathy, an obesity, an omphalitis, an oophoritis, an orchitis, an osteochondritis, an osteopenia, an osteoporosis, an osteitis, an otitis, a pancreatitis, a Parkinson's disease, a parotitis, a pelvic inflammatory disease, a pericarditis, a peritonitis, a pharyngitis, a phlebitis, a pleuritis, a pneumonitis, a proctitis, a prostatitis, a psoriasis, a pulpitis, a pyelonephritis, a pyelephlebitis, a rheumatic fever, a rhinitis, a salpingitis, a sialadenitis, a sinusitis, a spastic colon, a stomatitis, a synovitis, a tendonitis, a tendinosis, a tenosynovitis, a thrombophlebitis, a tonsillitis, a trigonitis, a tumor, an urethritis, an uveitis, a vaginitis, a vasculitis, or a vulvitis.

91. The method of claim 88, wherein the neurodegenerative disease is Alexander disease, Alper's disease, Alzheimer's disease, amyloidoses, amyotrophic lateral sclerosis, anxiety, ataxia telangiectasia, attention deficit disorders, Canavan disease, central nervous

system injuries, Charcot Marie Tooth disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, encephalitis (*e.g.*, bacterial, parasitic, fungal, or viral), Friedreich's ataxia frontotemporal dementia, hereditary spastic paraparesis, Guillain-Barre syndrome (and its variants acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher syndrome), HIV/AIDS dementia complex, Huntington's disease, ischemic damage to the nervous system, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, meningitis (*e.g.*, bacterial, parasitic, fungal, or viral) multiple sclerosis, multiple system atrophy, neural trauma, *e.g.*, percussive brain damage, spinal cord injury and traumatic damage to the nervous system, a neuropathy such as *e.g.*, chemotherapy-induced neuropathy, diabetes-associated neuropathy, and peripheral neuropathy, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, prion disorders, progressive supranuclear palsy, Refsum's disease, Sandhoff disease, schizophrenia, Schilder's disease, spinocerebellar atrophies, Steele-Richardson-Olszewski disease, stroke, tabes dorsalis, or vascular dementia.

92. The method of any one of claims 82-91, wherein the method further causes the reduction of at least one symptom associated with the autoimmune disease, neurodegenerative disease, or disease associated with inflammation and therein the symptom is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, infertility or reduced sex drive (low libido), blood sugar changes, and depending on the type of autoimmune disease, an increase in the size of an organ or tissue, or the destruction of an organ or tissue.

93. The method of any one of claims 82-92, wherein the subject is not immunocompromised.

94. The method of any one of claims 82-93, wherein the immune system of the subject is not compromised as a result of the administration.

95. The method of any one of claims 82-94, wherein, as a result of the administration, secretion of cytokines by ARegs is decreased.

96. The method of any one of claims 82-95, wherein the immunosuppressive Tat derivative polypeptide is administered in a plurality of doses.

97. The method of any one of claims 82-96, wherein the immunosuppressive Tat derivative polypeptide is administered daily, weekly, biweekly, monthly, or bimonthly.

98. The method of any one of claims 82-97, wherein the administering step comprises a repetitive administration cycle wherein each cycle comprises administering a plurality of doses of the immunosuppressive Tat derivative polypeptide in a defined time period followed by a rest period and wherein the cycle is repeated a plurality of times.

99. Use of one or more immunosuppressive Tat derivative polypeptides in the manufacture of a medicament for treatment of a disease characterized by aberrant immune responses in a subject in need thereof; wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, and wherein administration of the immunosuppressive Tat derivative polypeptide treats the disease by suppressing the immune system in the subject.

100. Use of one or more immunosuppressive Tat derivative polypeptides in the manufacture of a medicament for increasing the expression of Fas ligand (FasL) on antigen presenting cell regulatory macrophages (AREgs) in a subject wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, wherein administration of the immunosuppressive Tat derivative polypeptides increases the expression of FasL on the AREgs.

101. Use of one or more immunosuppressive Tat derivative peptides in the manufacture of a medicament for reducing inflammation in a subject, wherein the one or more immunosuppressive Tat derivative polypeptides are at least 85% identical to an immunosuppressive Tat derivative polypeptide of claim 1, and wherein administration of the immunosuppressive Tat derivative polypeptides reduces inflammation in the subject.

102. The use according to any one of claims 99-101, wherein the treatment increases the expression of Fas ligand on antigen presenting cell regulatory macrophages (AREgs).

103. The use according to any one of claims 99-102, wherein the AREgs are CD14+ macrophages.

104. The use according to any one of claims 99-103, wherein the immunosuppressive Tat derivative polypeptide has greater than 85% sequence identity to one of SEQ ID NOs:9-11, 13-35, or 69.

105. The use according to any one of claims 99-104, wherein the subject is not immunocompromised.

106. The use according to any one of claims 99-105, wherein the immune system of the subject is not compromised as a result of the administration.

107. The use according to any one of claims 99-106, wherein, as a result of the administration, secretion of cytokines by ARegs is decreased.

108. The use according to any one of claims 99-107, wherein the disease is an autoimmune, neurodegenerative or inflammation-associated disorder.

109. The use according to claim 108, wherein the autoimmune disorder is an acute disseminated encephalomyelitis (ADEM), an Addison's disease, an allergy, allergic rhinitis, an Alzheimer's disease, an anti-phospholipid antibody syndrome (APS), an arthritis, an asthma, an autoimmune deficiency syndrome, an autoimmune hemolytic anemia, an autoimmune hepatitis, an autoimmune inner ear disease, a bullous pemphigoid, a celiac disease, a Chagas disease, a chronic obstructive pulmonary disease (COPD), a diabetes mellitus type 1 (IDDM), an eczema, an endometriosis, a gastrointestinal disorder, a Goodpasture's syndrome, a Graves' disease, a Guillain-Barré syndrome (GBS), a Hashimoto's thyroiditis, a hidradenitis suppurativa, an idiopathic thrombocytopenic purpura, an inflammatory bowel disease, an inflammatory dermatologic disease, an interstitial cystitis, a lupus, a morphea, a multiple sclerosis (MS), a myasthenia gravis, a myopathy, a narcolepsy, a neuromyotonia, a pemphigus vulgaris, a pernicious anaemia, a primary biliary cirrhosis, a psoriasis, a recurrent disseminated encephalomyelitis, a rheumatic fever, a schizophrenia, a scleroderma, a Sjögren's syndrome, a skin disorder, a tenosynovitis, a uveitis, a vasculitis, or a vitiligo.

110. The use according to claim 108, wherein the disease associated with inflammation is an acne, an acid reflux/heartburn, an allergy, an allergic rhinitis, an Alzheimer's disease, an appendicitis, an arteritis, an arthritis, an asthma, an atherosclerosis, an autoimmune disorder, a balanitis, a blepharitis, a bronchiolitis, a bronchitis, a bursitis, a cancer, a carditis, a celiac disease, a cellulitis, a cervicitis, a cholangitis, a cholecystitis, a chorioamnionitis, a chronic obstructive pulmonary disease (COPD), a cirrhosis, a colitis, a conjunctivitis, a cystitis, a common cold, a dacryoadenitis, a dementia, a dermatitis, a dermatomyositis, an eczema, an emphysema, an encephalitis, an endocarditis, an endometritis, an enteritis, an enterocolitis, an epicondylitis, an epididymitis, a fasciitis, a fibrositis, a gastritis, a gastroenteritis, a gingivitis, a glomerulonephritis, a glossitis, a heart disease, a hepatitis, a hidradenitis suppurativa, a high

blood pressure, an ileitis, an insulin resistance, an interstitial cystitis, an iritis, an ischemic heart disease, a keratitis, a keratoconjunctivitis, a laryngitis, a lupus, a mastitis, a mastoiditis, a meningitis, a metabolic syndrome (syndrome X), a migraine, a multiple sclerosis, a myelitis, a myocarditis, a myopathy, a myositis, a nephritis, a neuropathy, an obesity, an omphalitis, an oophoritis, an orchitis, an osteochondritis, an osteopenia, an osteoporosis, an osteitis, an otitis, a pancreatitis, a Parkinson's disease, a parotitis, a pelvic inflammatory disease, a pericarditis, a peritonitis, a pharyngitis, a phlebitis, a pleuritis, a pneumonitis, a proctitis, a prostatitis, a psoriasis, a pulpitis, a pyelonephritis, a pyelephlebitis, a rheumatic fever, a rhinitis, a salpingitis, a sialadenitis, a sinusitis, a spastic colon, a stomatitis, a synovitis, a tendonitis, a tendinosis, a tenosynovitis, a thrombophlebitis, a tonsillitis, a trigonitis, a tumor, an urethritis, an uveitis, a vaginitis, a vasculitis, or a vulvitis.

111. The use according to claim 108, wherein the neurodegenerative disease is Alexander disease, Alper's disease, Alzheimer's disease, amyloidoses, amyotrophic lateral sclerosis, anxiety, ataxia telangiectasia, attention deficit disorders, Canavan disease, central nervous system injuries, Charcot Marie Tooth disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, encephalitis (*e.g.*, bacterial, parasitic, fungal, or viral), Friedreich's ataxia frontotemporal dementia, hereditary spastic paraparesis, Guillain-Barre syndrome (and its variants acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher syndrome), HIV/AIDS dementia complex, Huntington's disease, ischemic damage to the nervous system, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, meningitis (*e.g.*, bacterial, parasitic, fungal, or viral), multiple sclerosis, multiple system atrophy, neural trauma, *e.g.*, percussive brain damage, spinal cord injury and traumatic damage to the nervous system, a neuropathy such as *e.g.*, chemotherapy-induced neuropathy, diabetes-associated neuropathy, and peripheral neuropathy, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, prion disorders, progressive supranuclear palsy, Refsum's disease, Sandhoff disease, schizophrenia, Schilder's disease, spinocerebellar atrophies, Steele-Richardson-Olszewski disease, stroke, tabes dorsalis, or vascular dementia.

112. The use according to any one of claims 99-111, wherein the immunosuppressive Tat derivative polypeptide further causes the reduction of at least one symptom associated with the autoimmune disease, neurodegenerative disease, or disease associated with inflammation and therein the symptom is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in

muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, infertility or reduced sex drive (low libido), blood sugar changes, and depending on the type of autoimmune disease, an increase in the size of an organ or tissue, or the destruction of an organ or tissue.

113. The use according to any one of claims 99-112, wherein the immunosuppressive Tat derivative polypeptide is administered in a plurality of doses.

114. The use according to any one of claims 99-113, wherein the immunosuppressive Tat derivative polypeptide is administered daily, weekly, biweekly, monthly, or bimonthly.

115. The use according to any one of claims 99-114, wherein the administering step comprises a repetitive administration cycle wherein each cycle comprises administering a plurality of doses of the immunosuppressive Tat derivative polypeptide in a defined time period followed by a rest period and wherein the cycle is repeated a plurality of times.

FIG. 1A

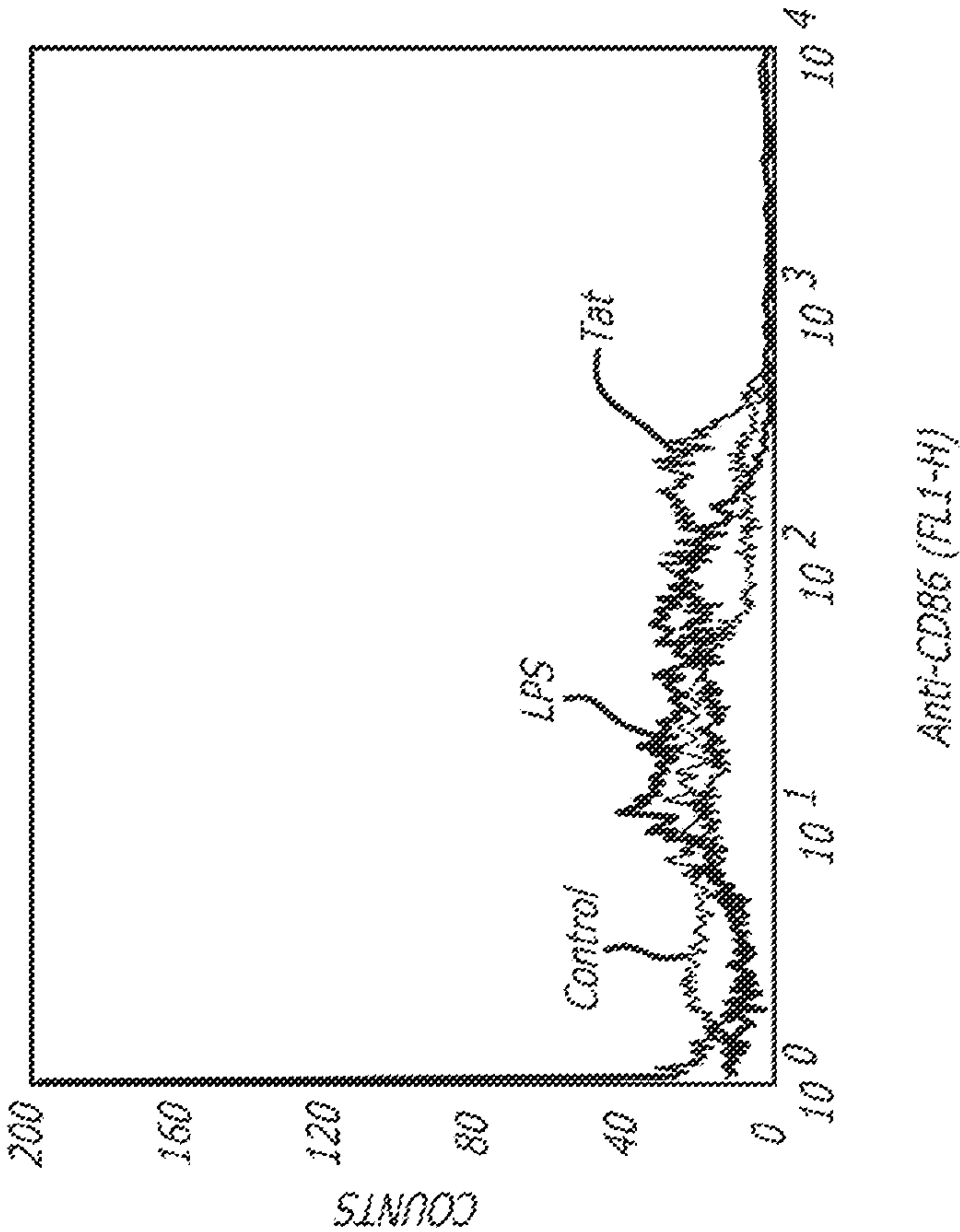
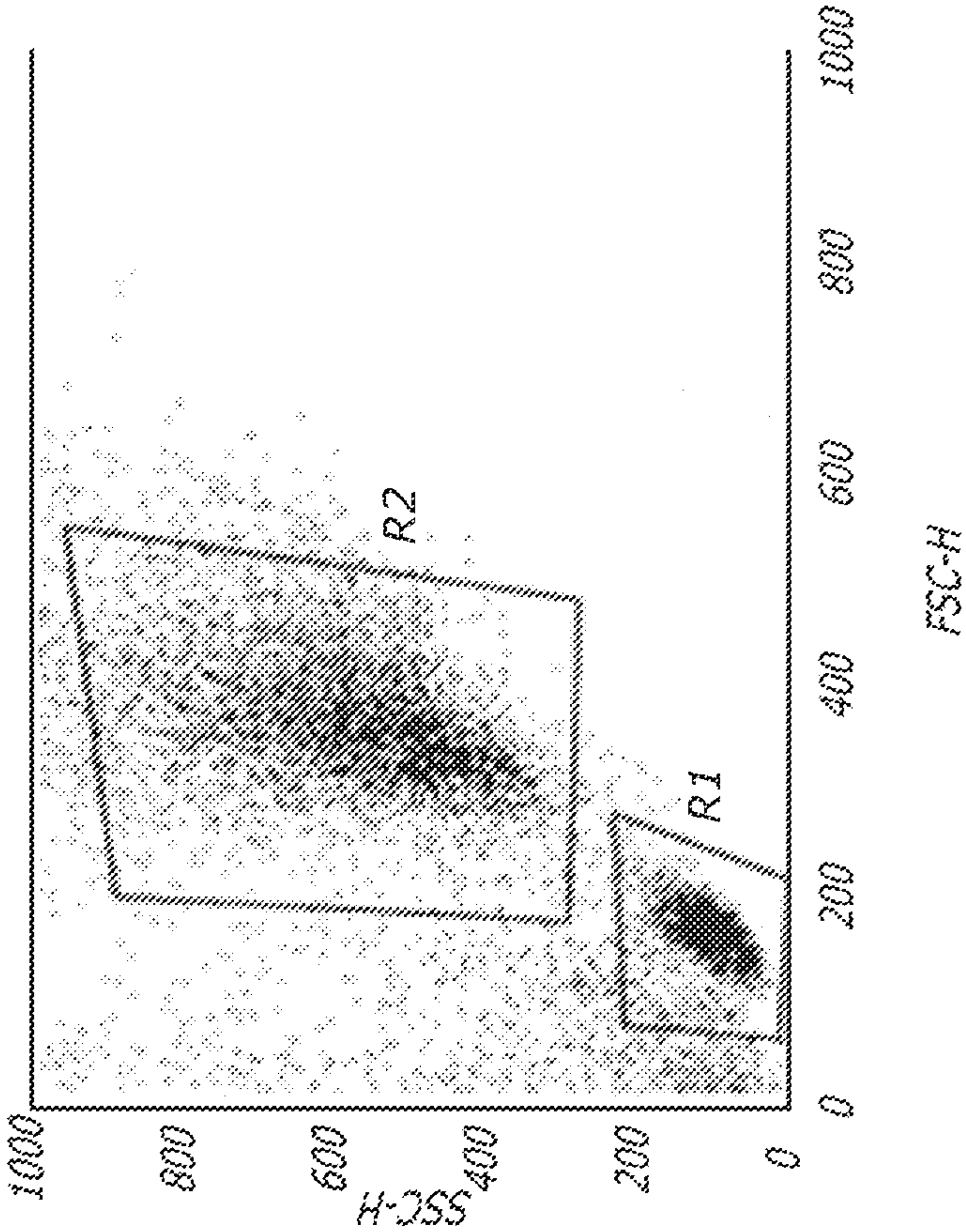
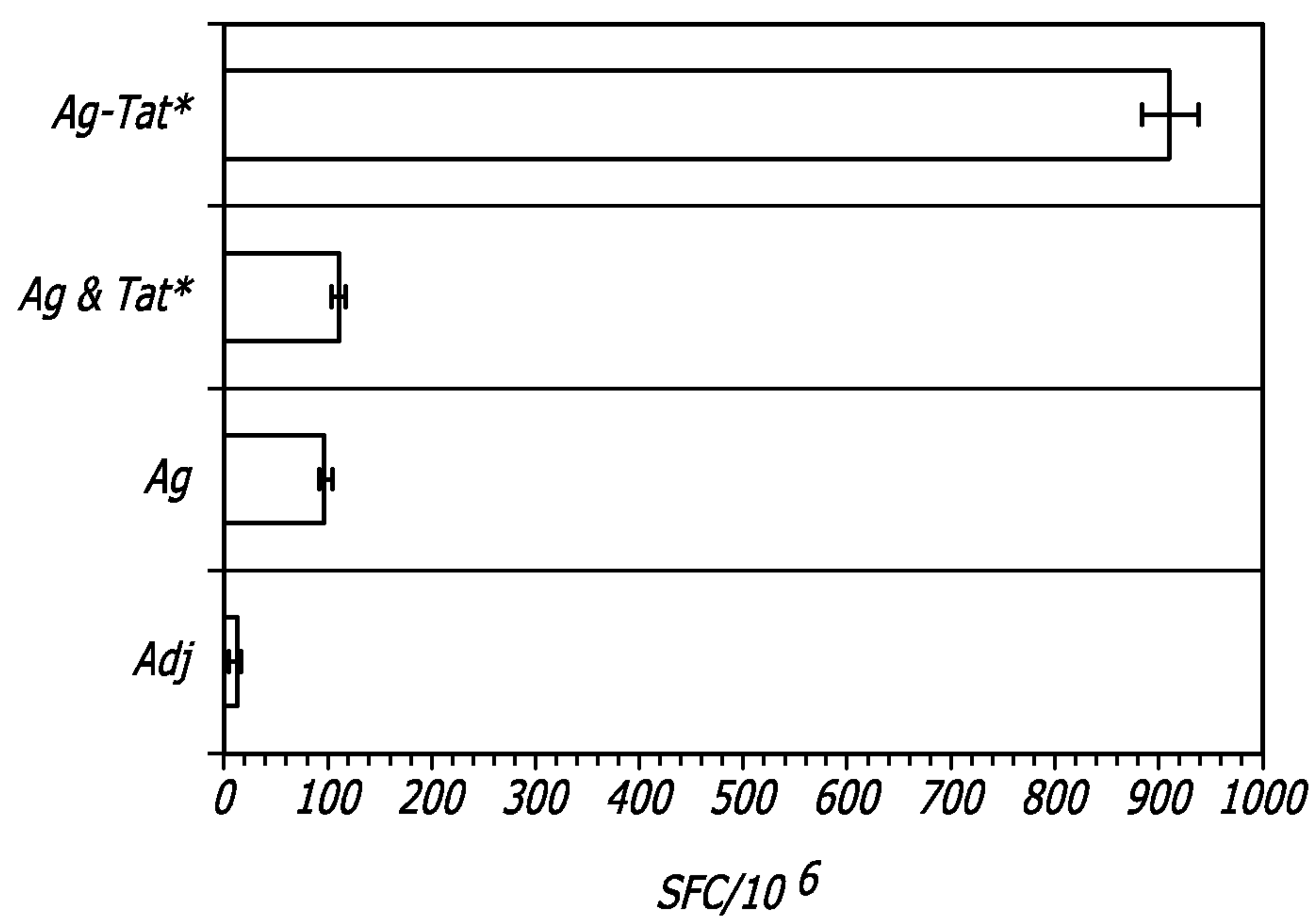
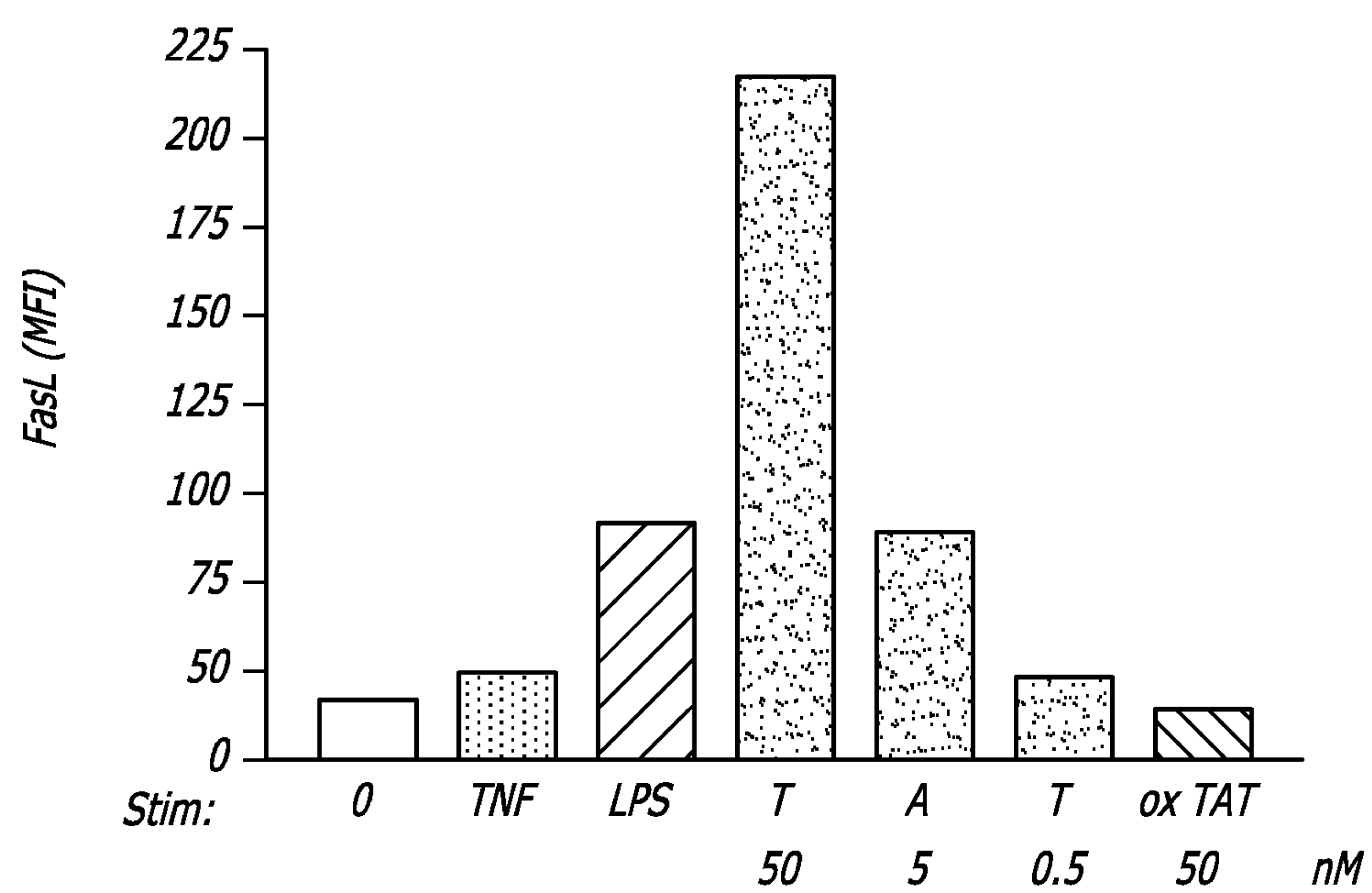
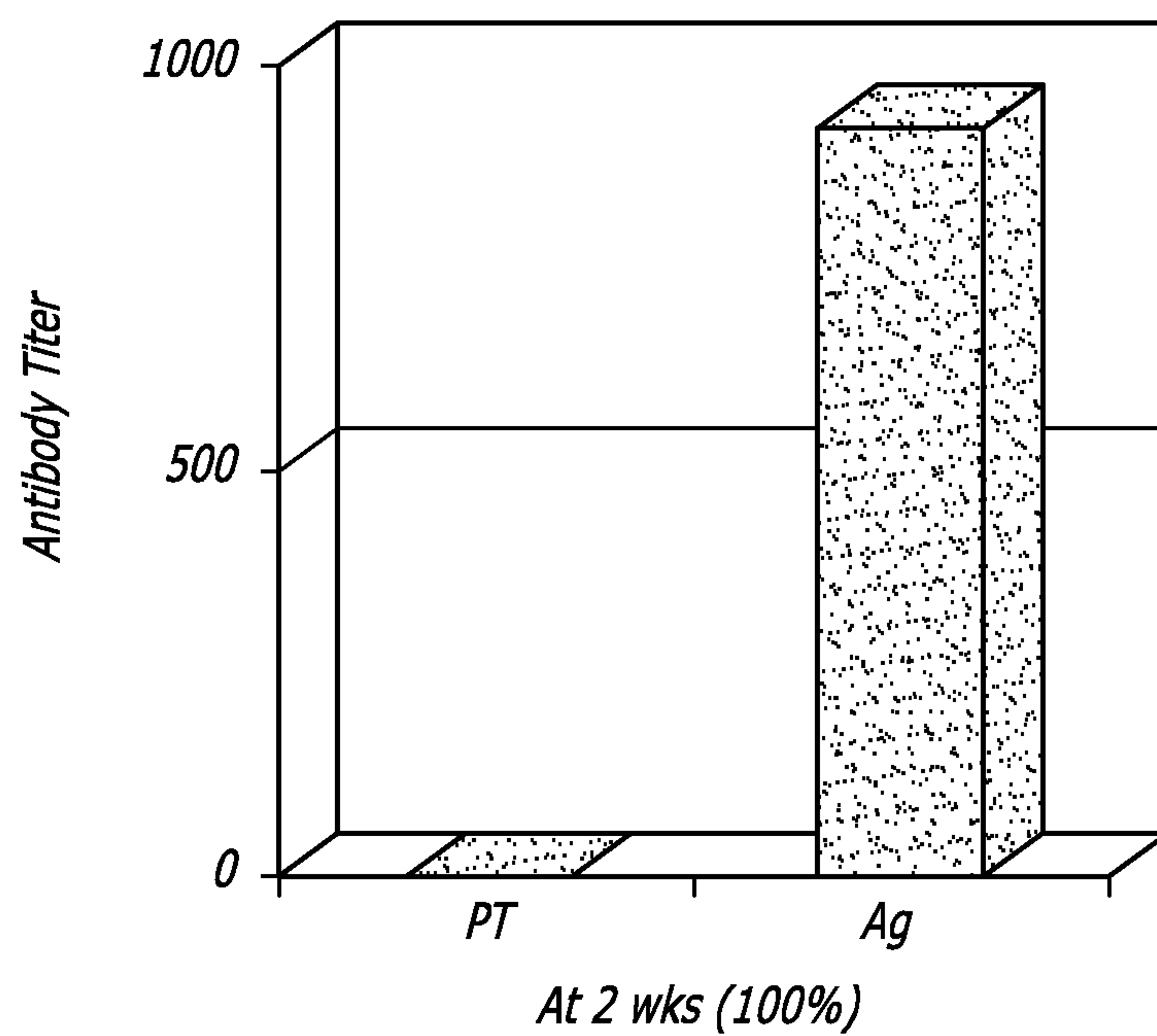
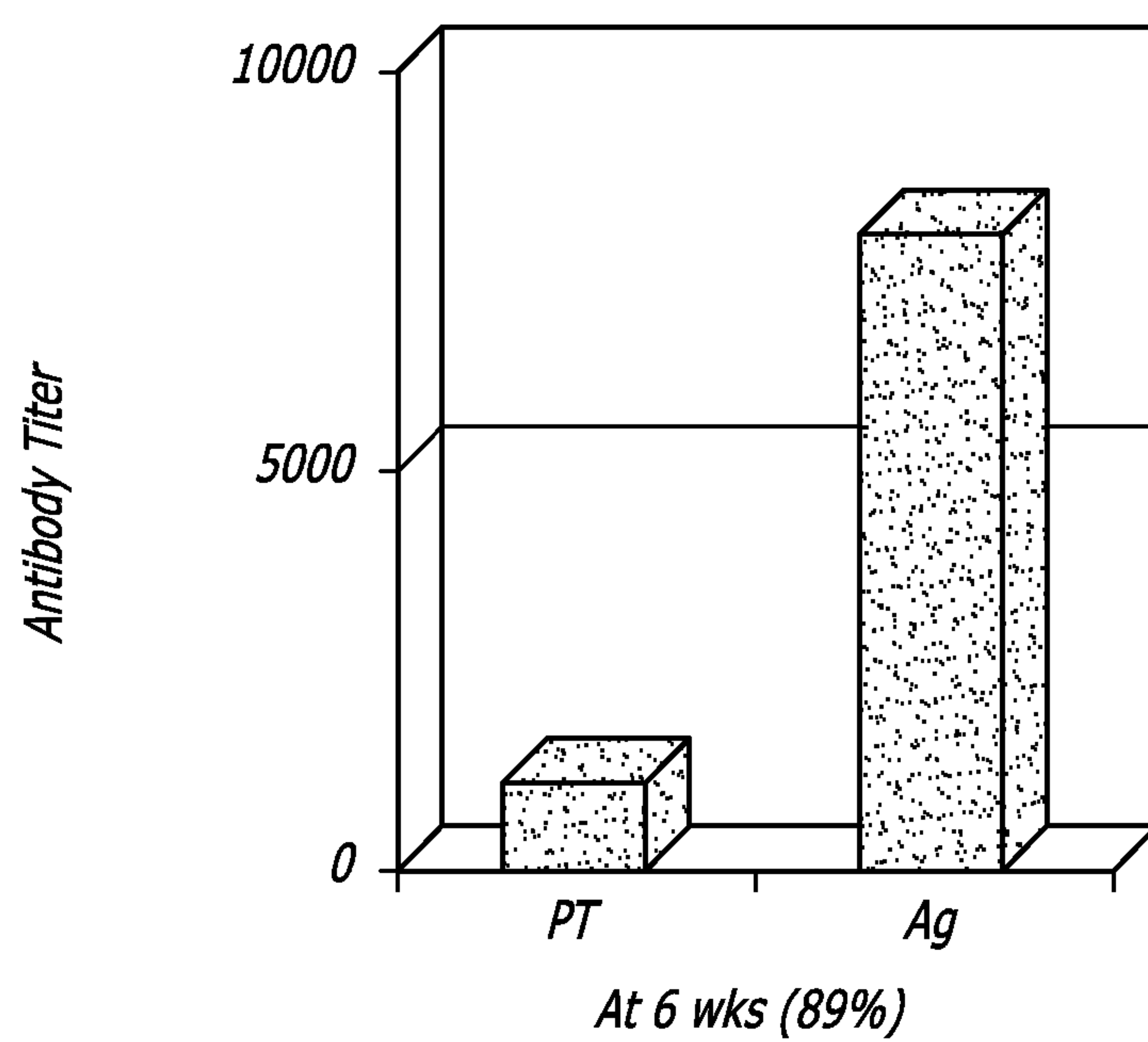


FIG. 1B



**FIG. 2****FIG. 3**

**FIG. 4A****FIG. 4B**

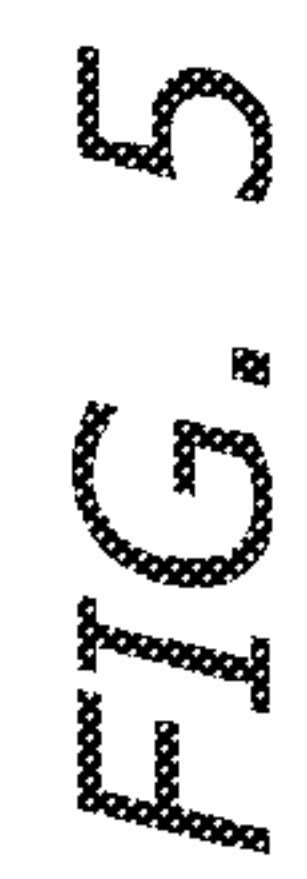
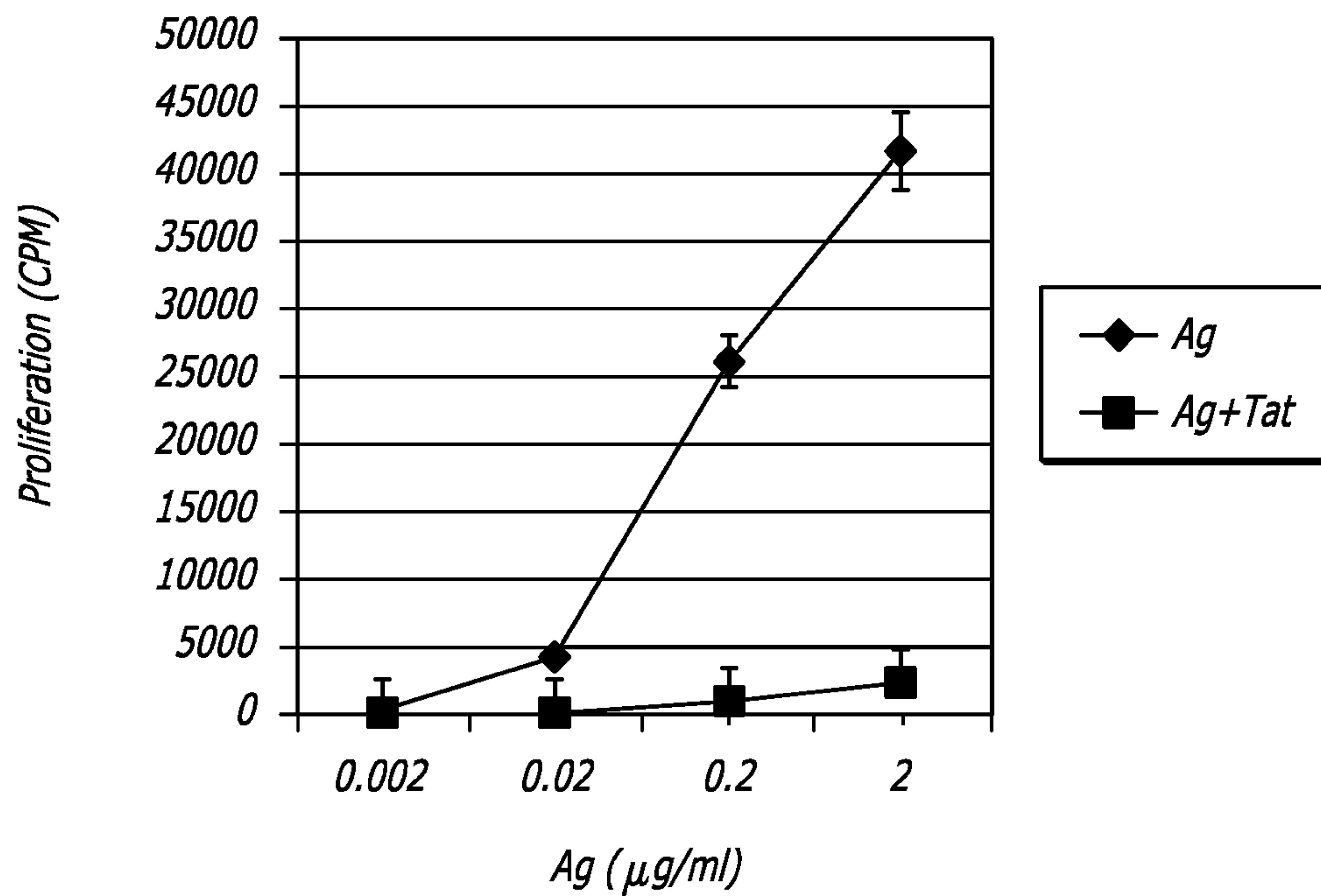
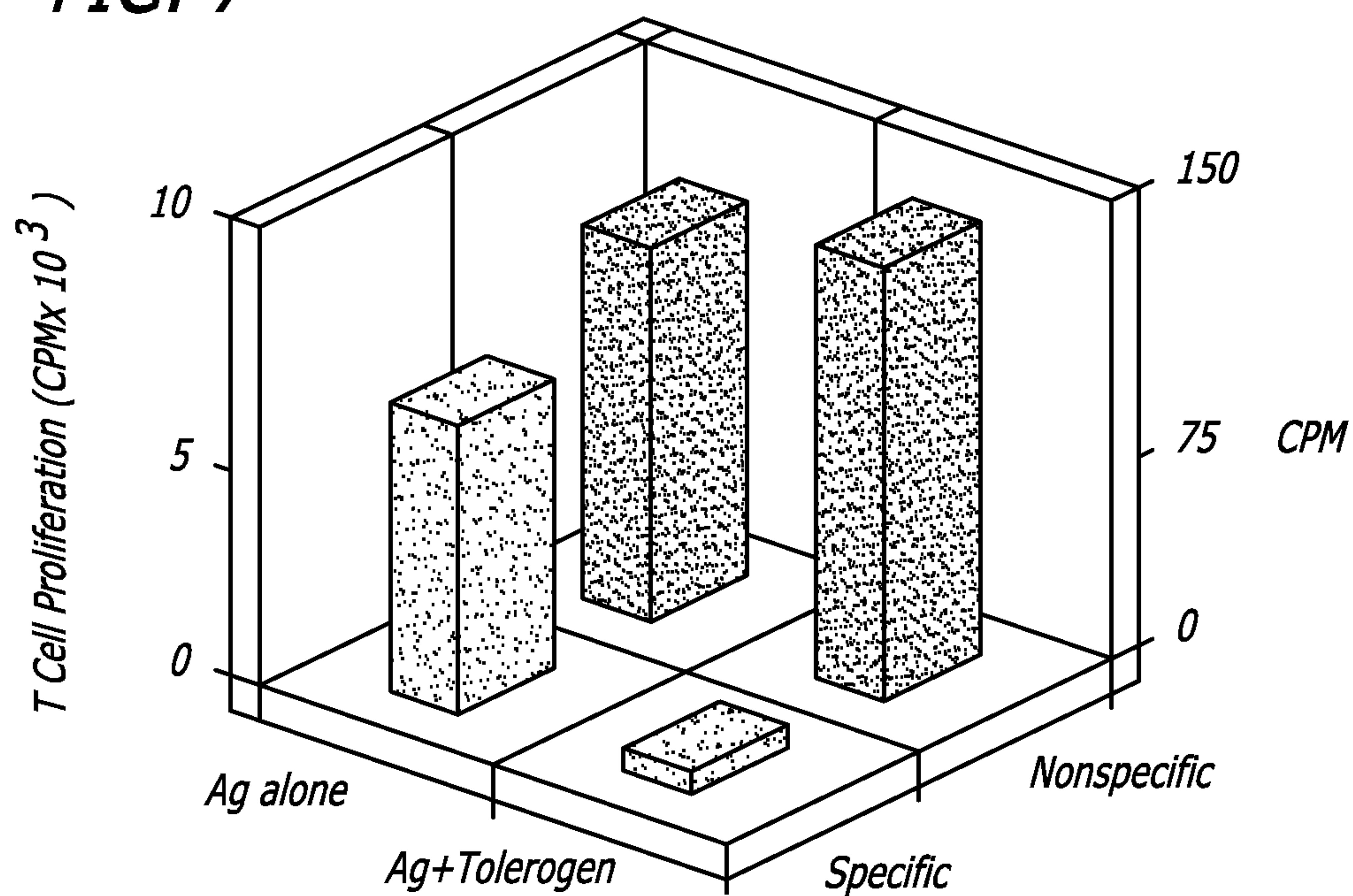


FIG. 6**FIG. 7**

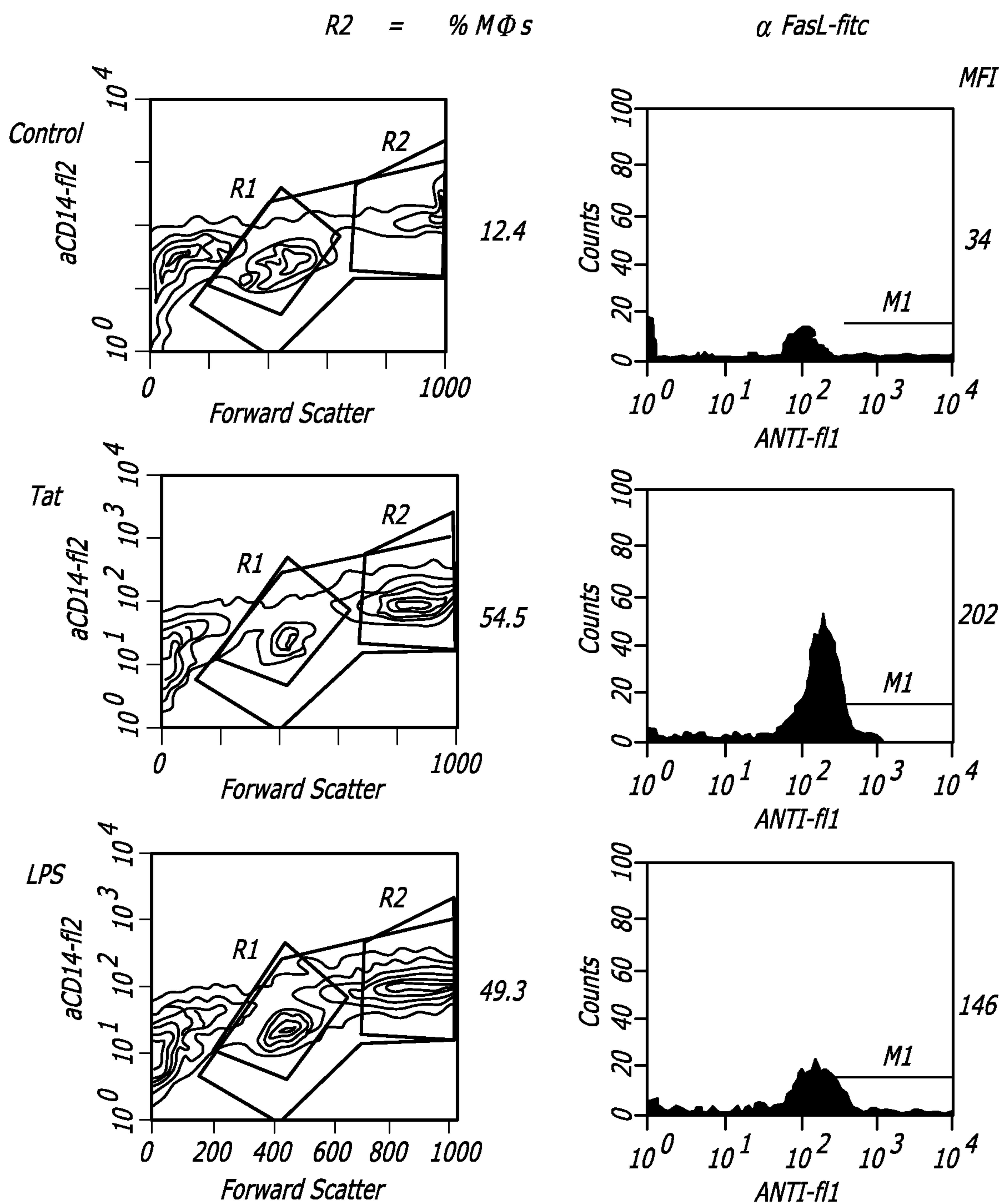


FIG. 8

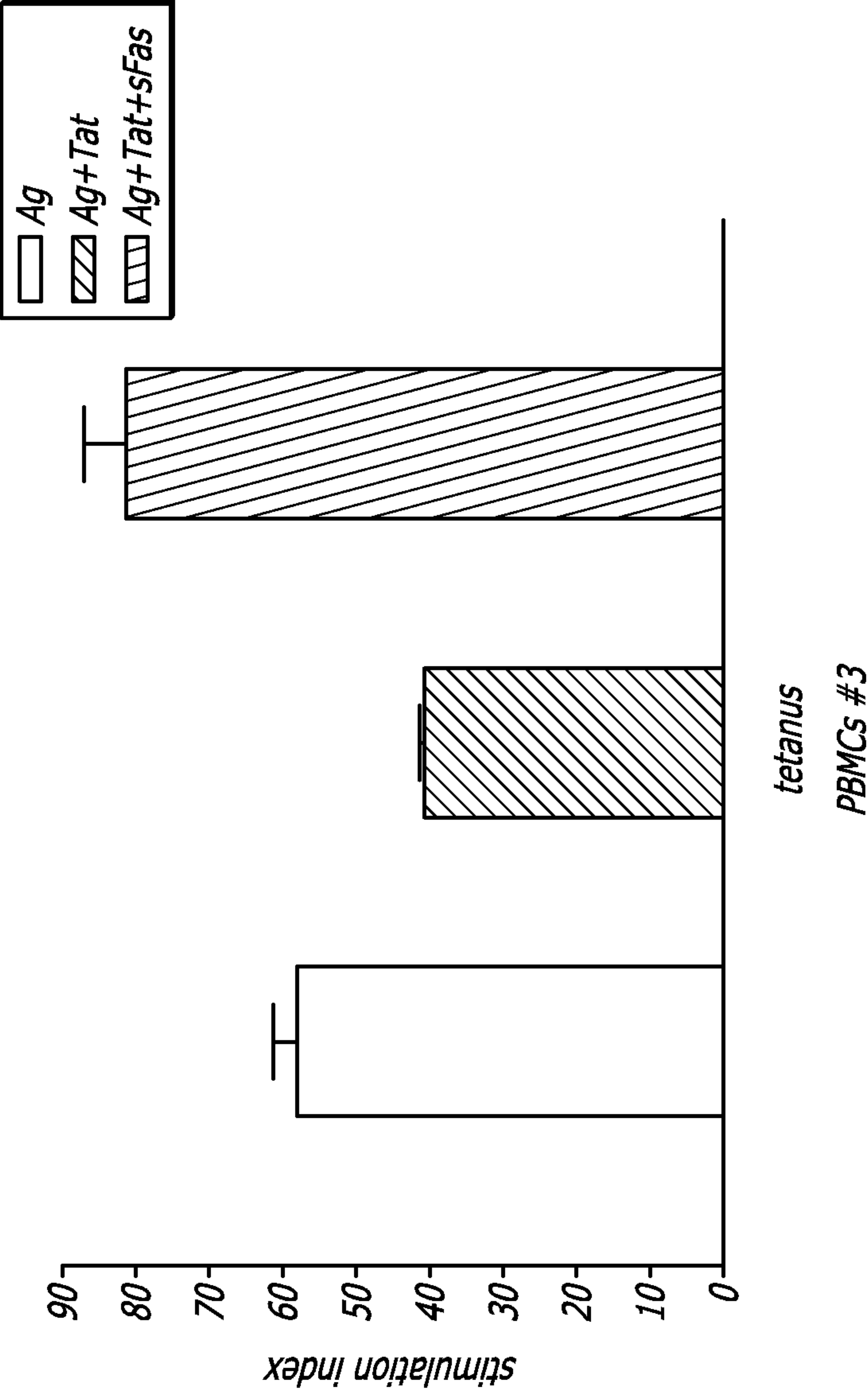


FIG. 9A

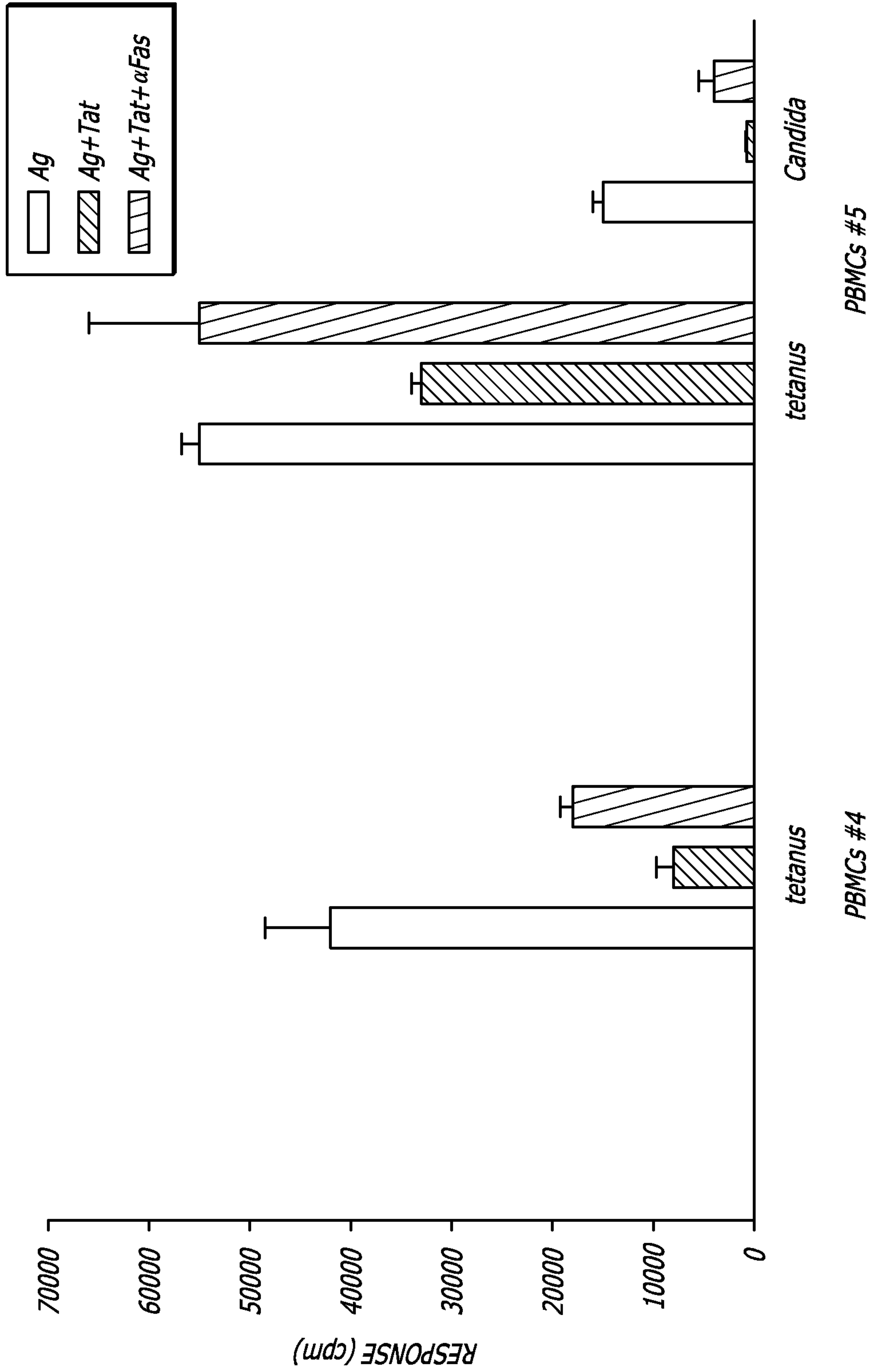


FIG. 9B

FIG. 10

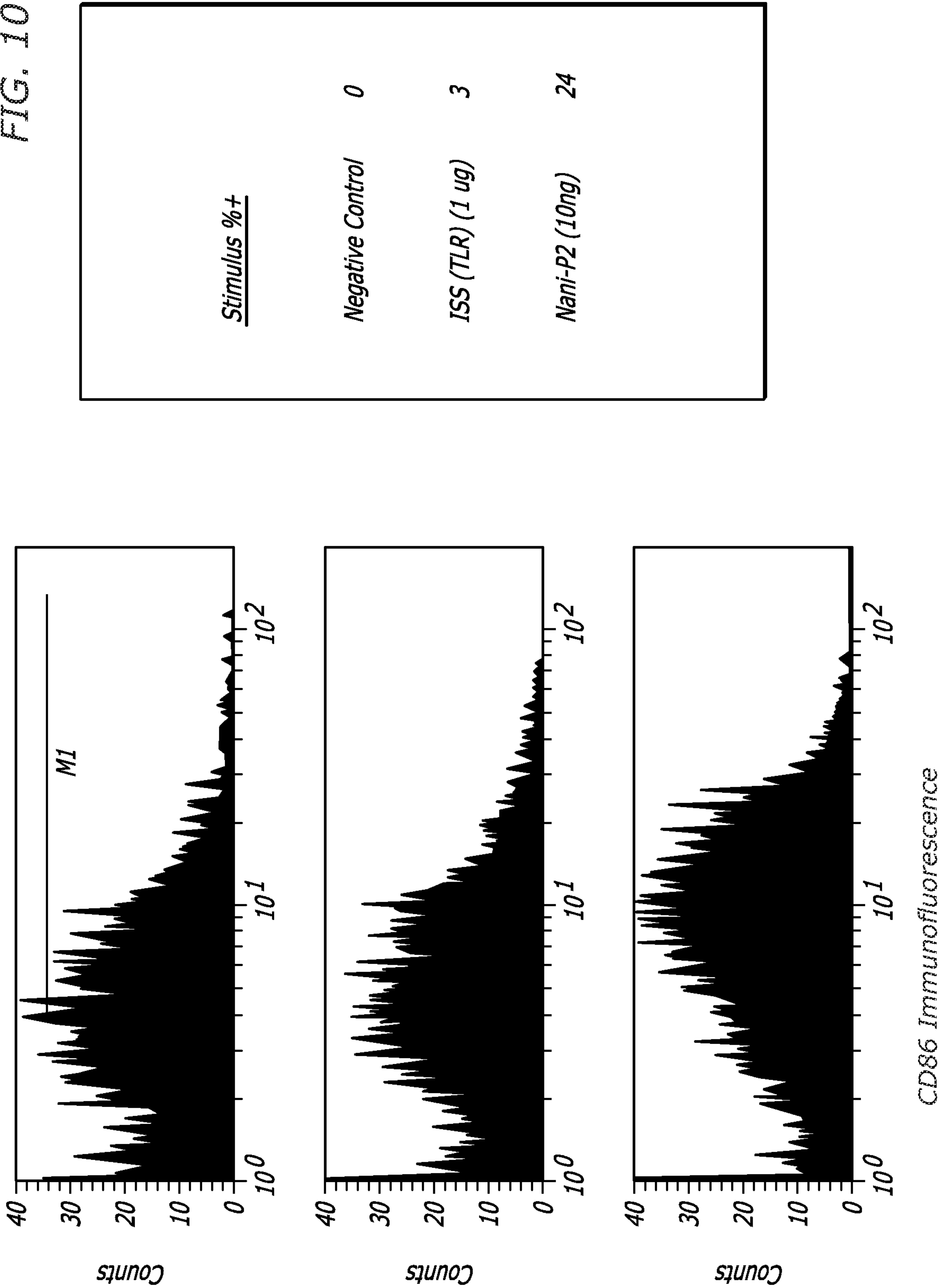
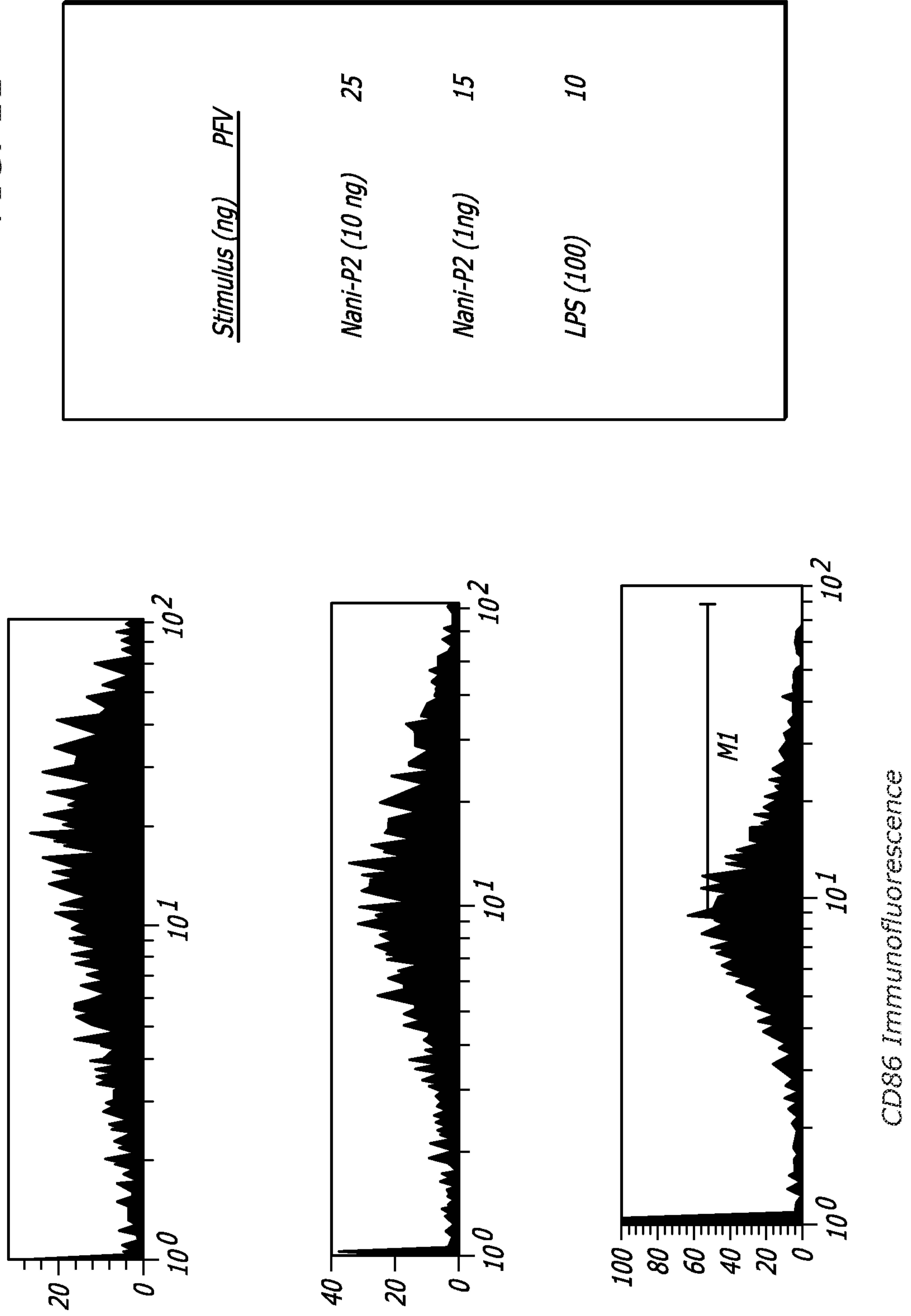
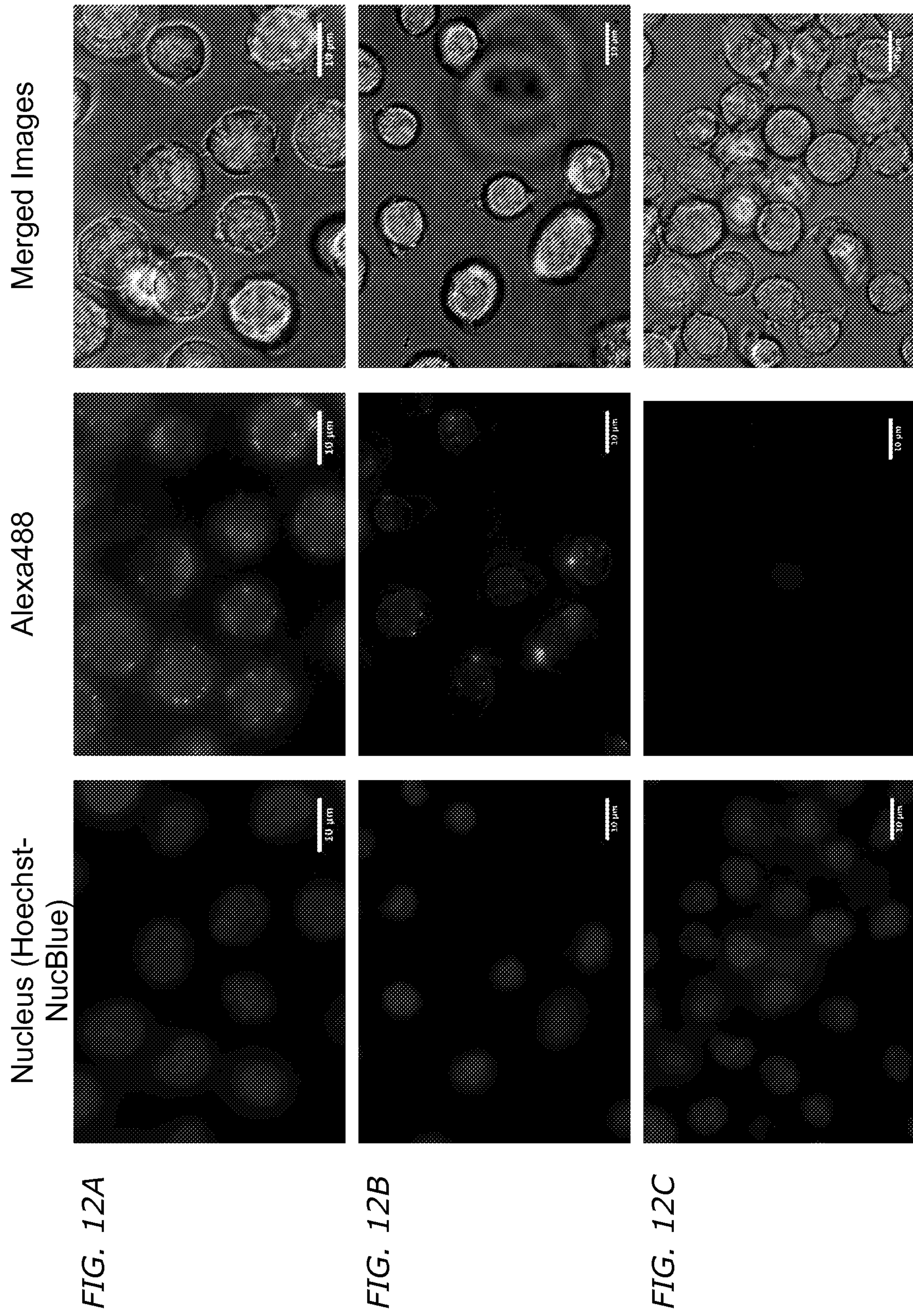


FIG. 11





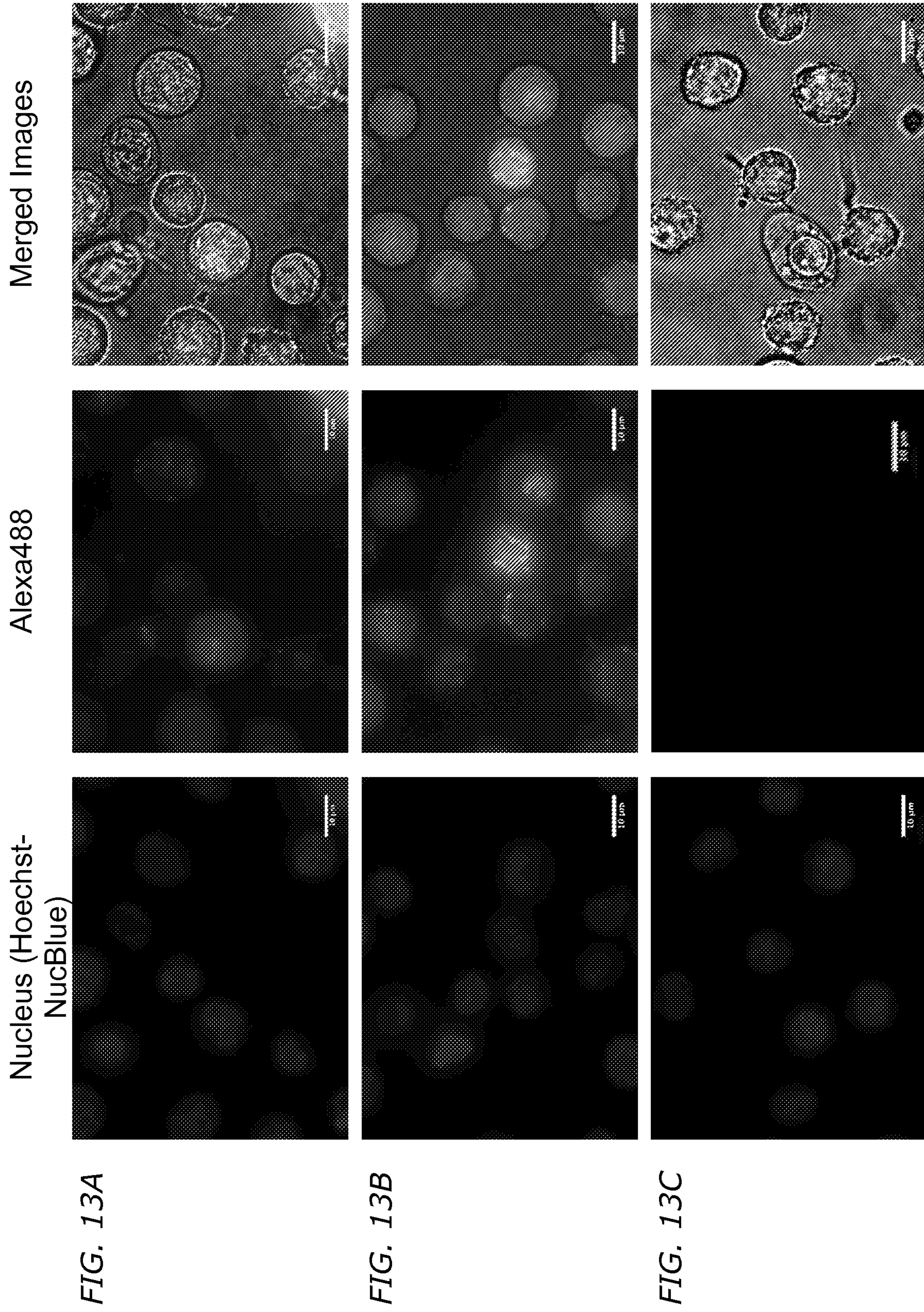


FIG. 14A

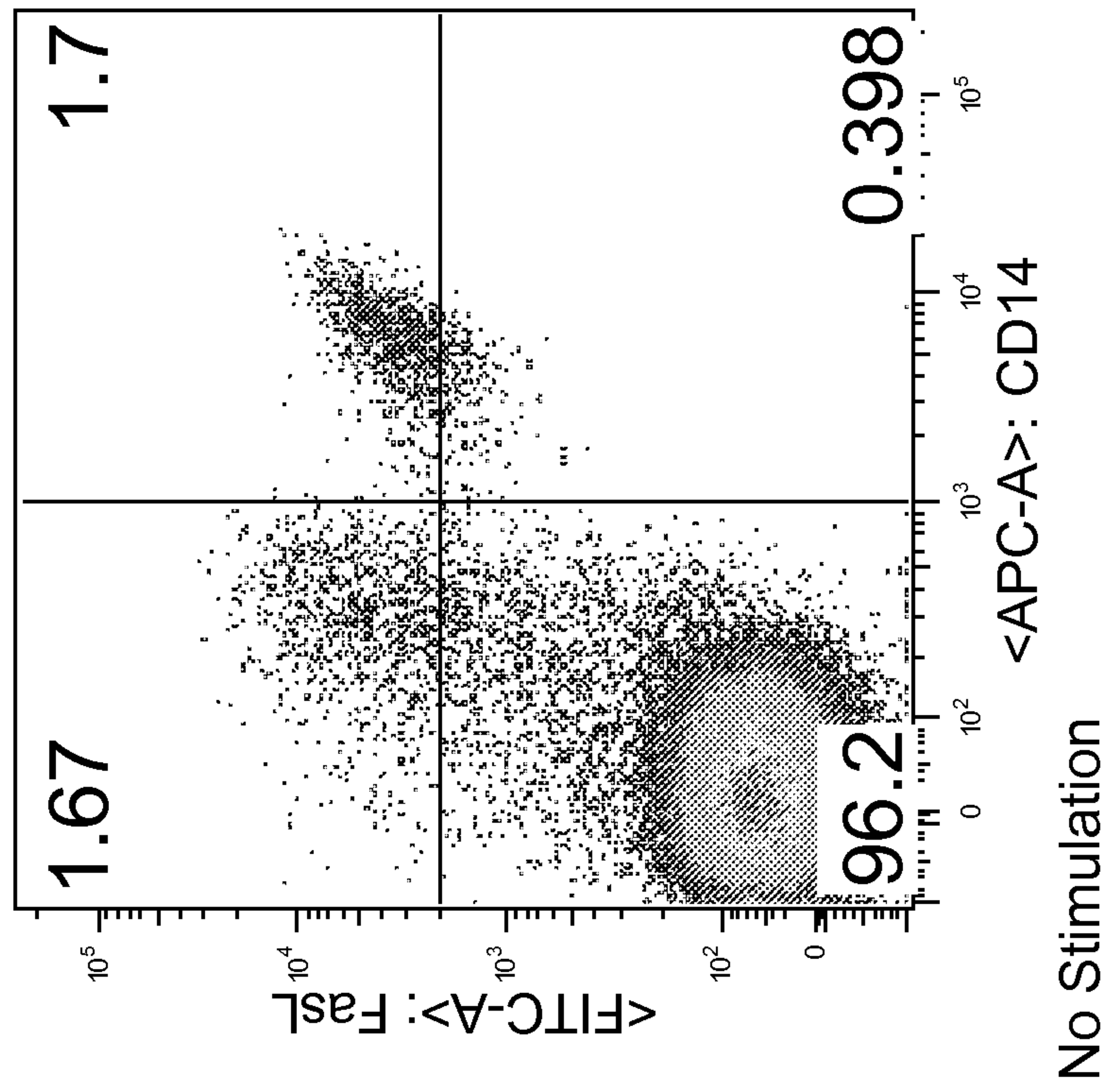


FIG. 14B

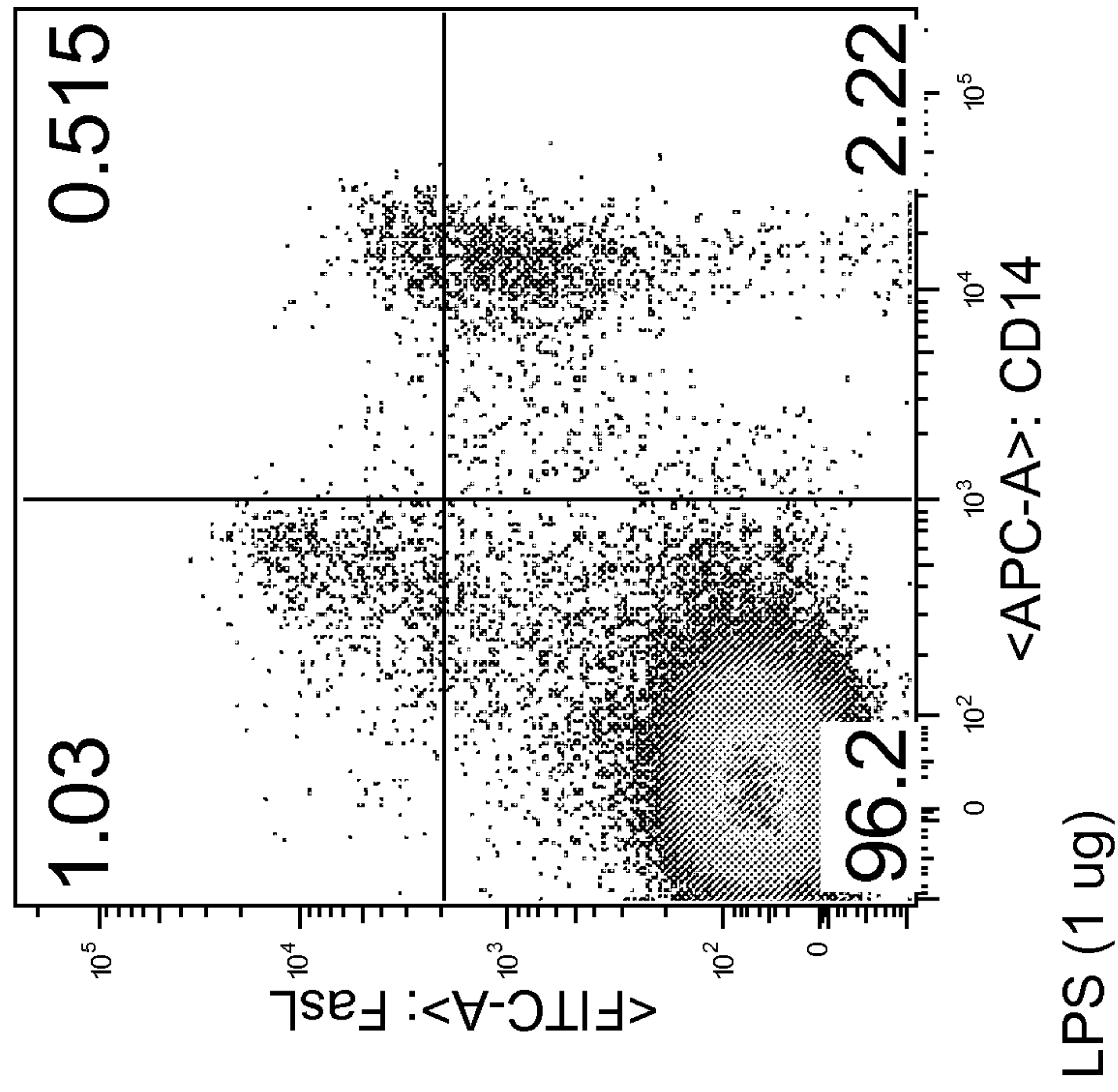
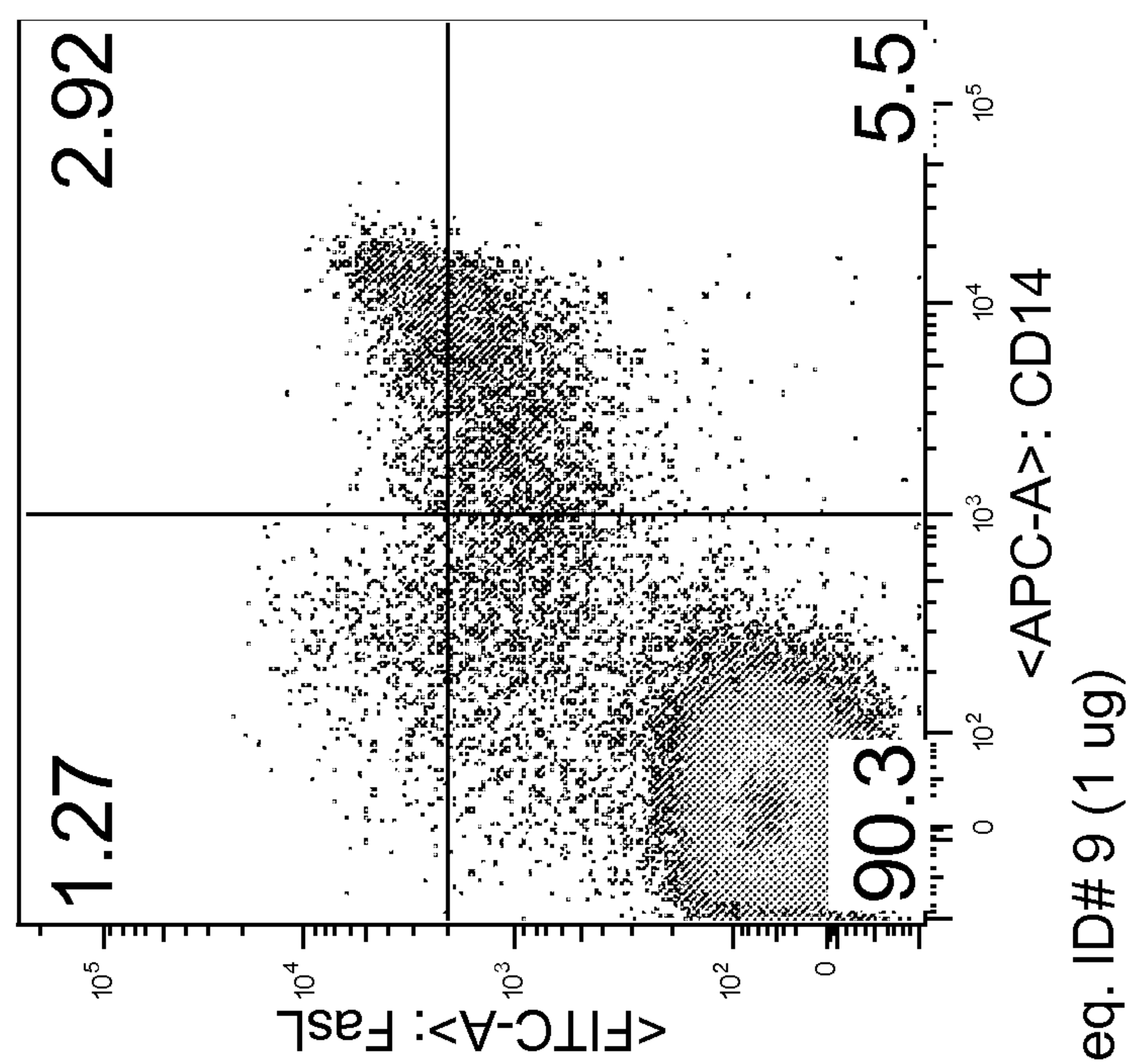


FIG. 14C



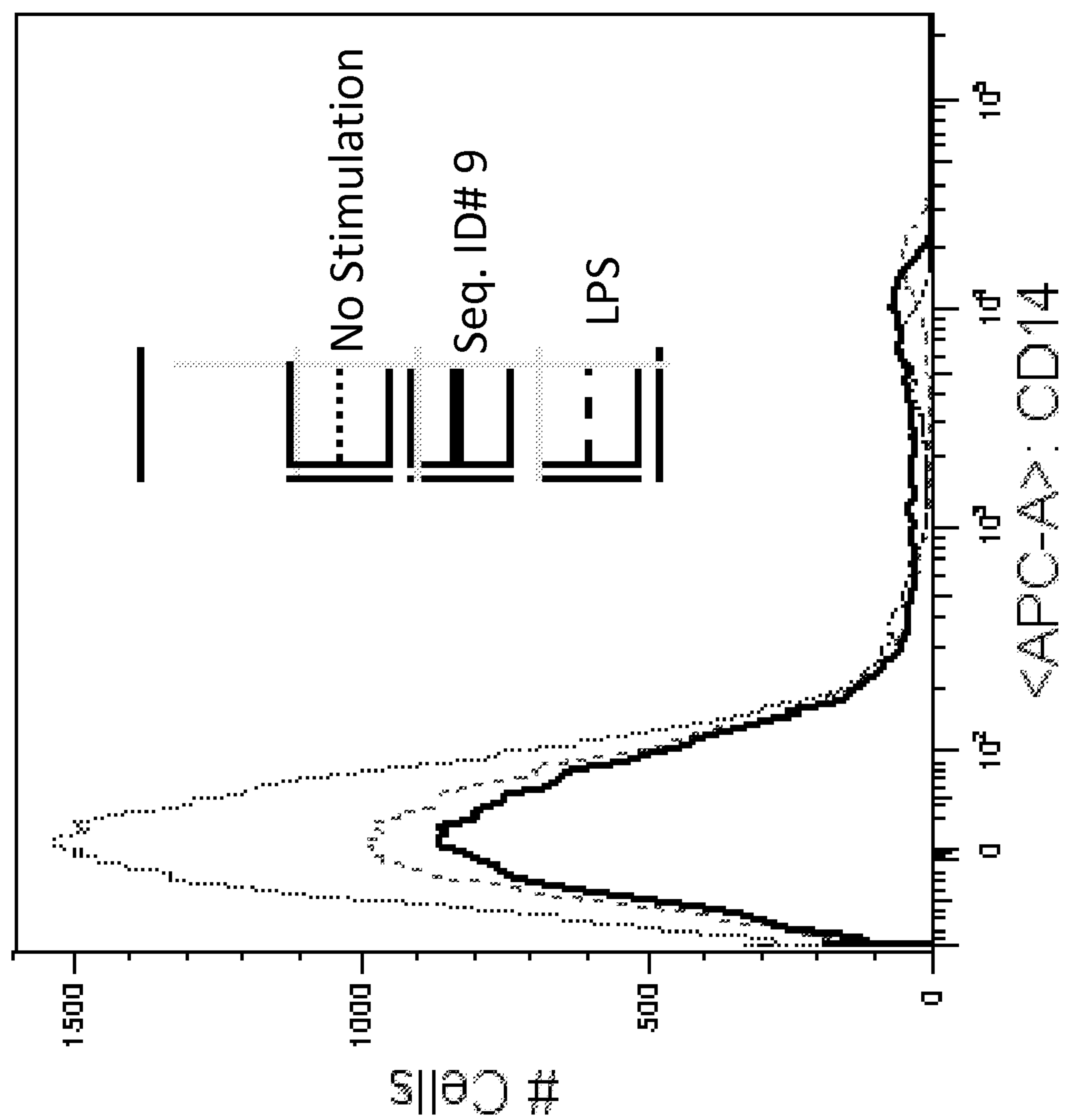


FIG. 15

FIG. 16

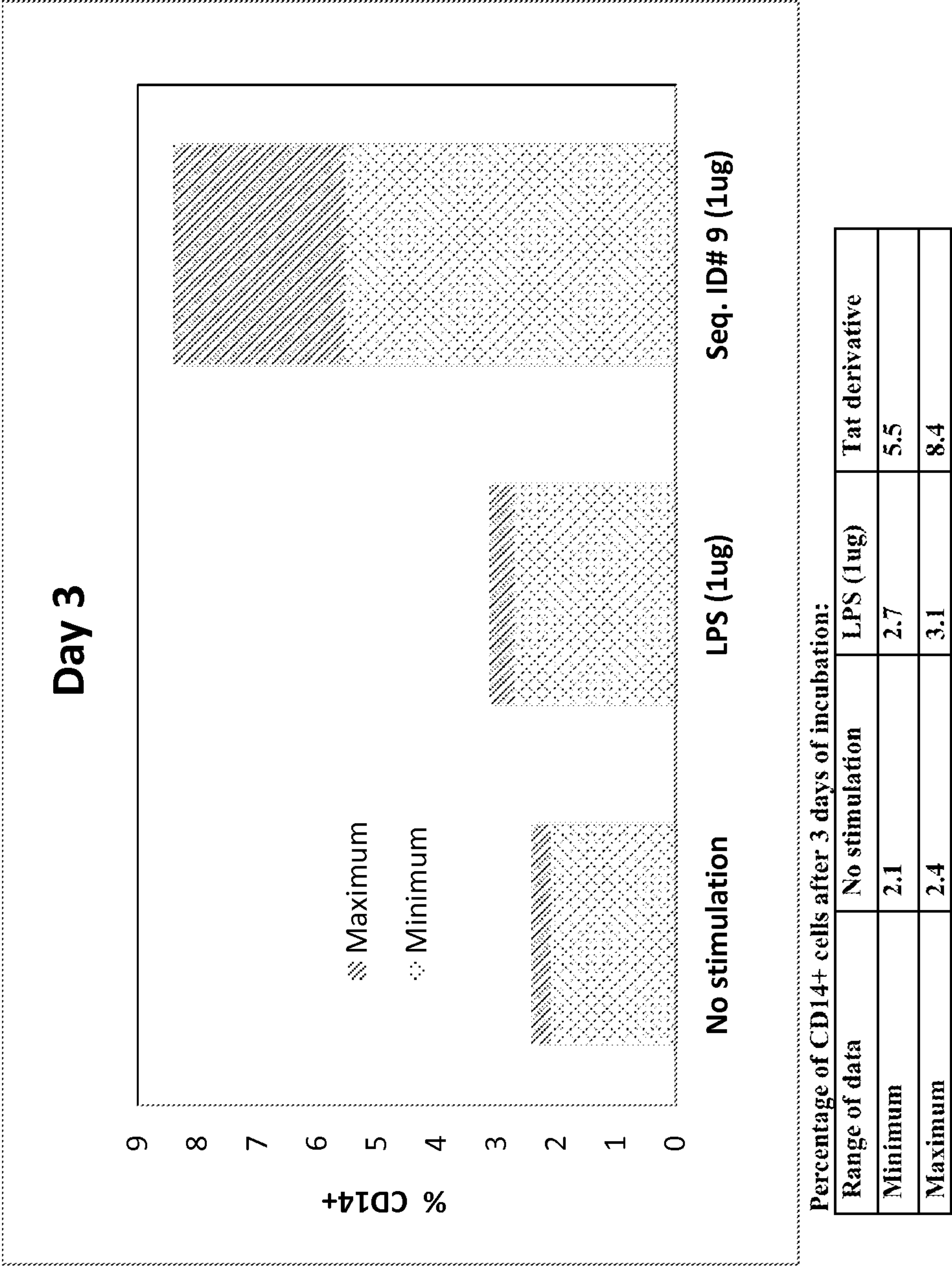


FIG. 17A

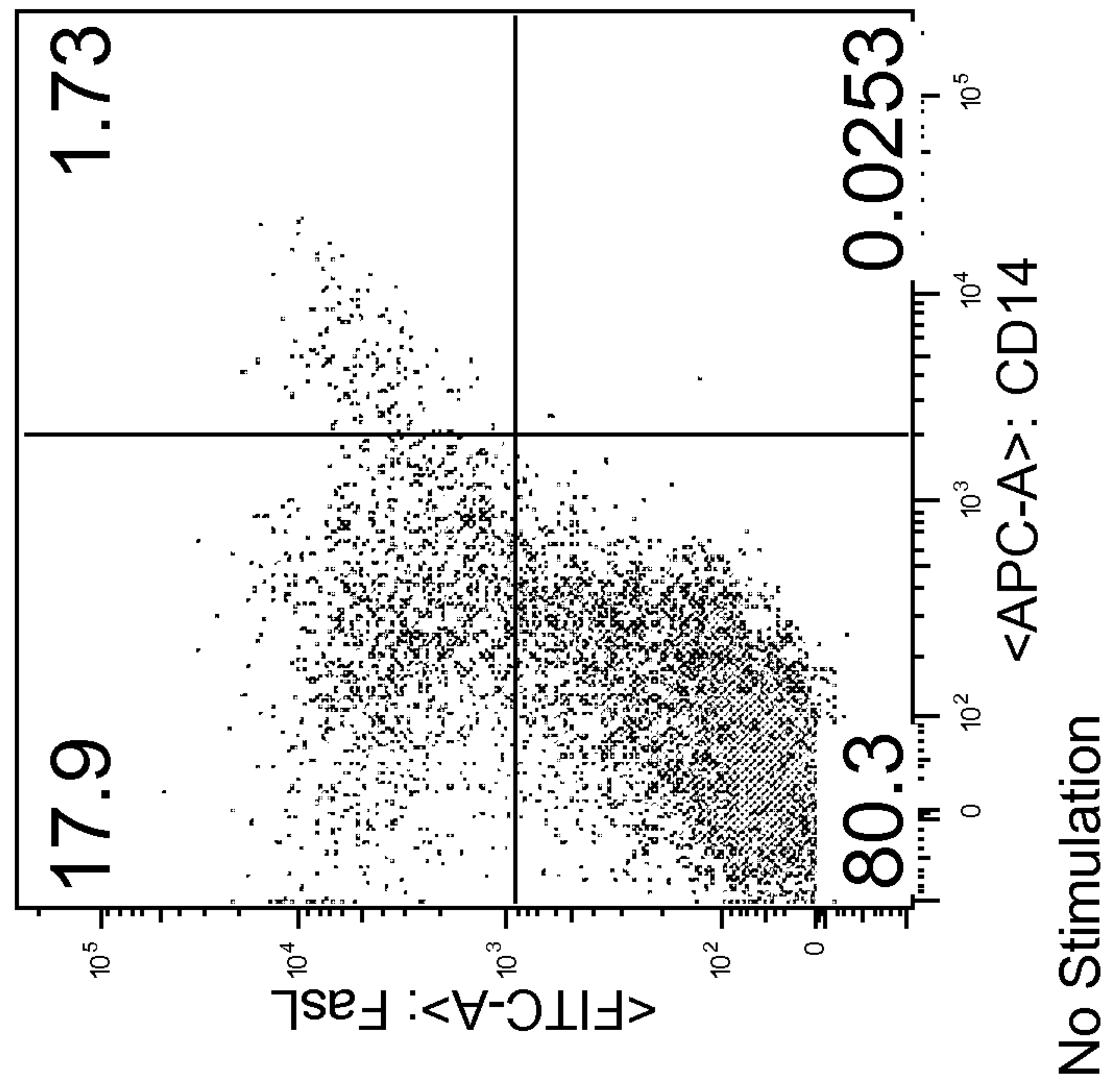


FIG. 17B

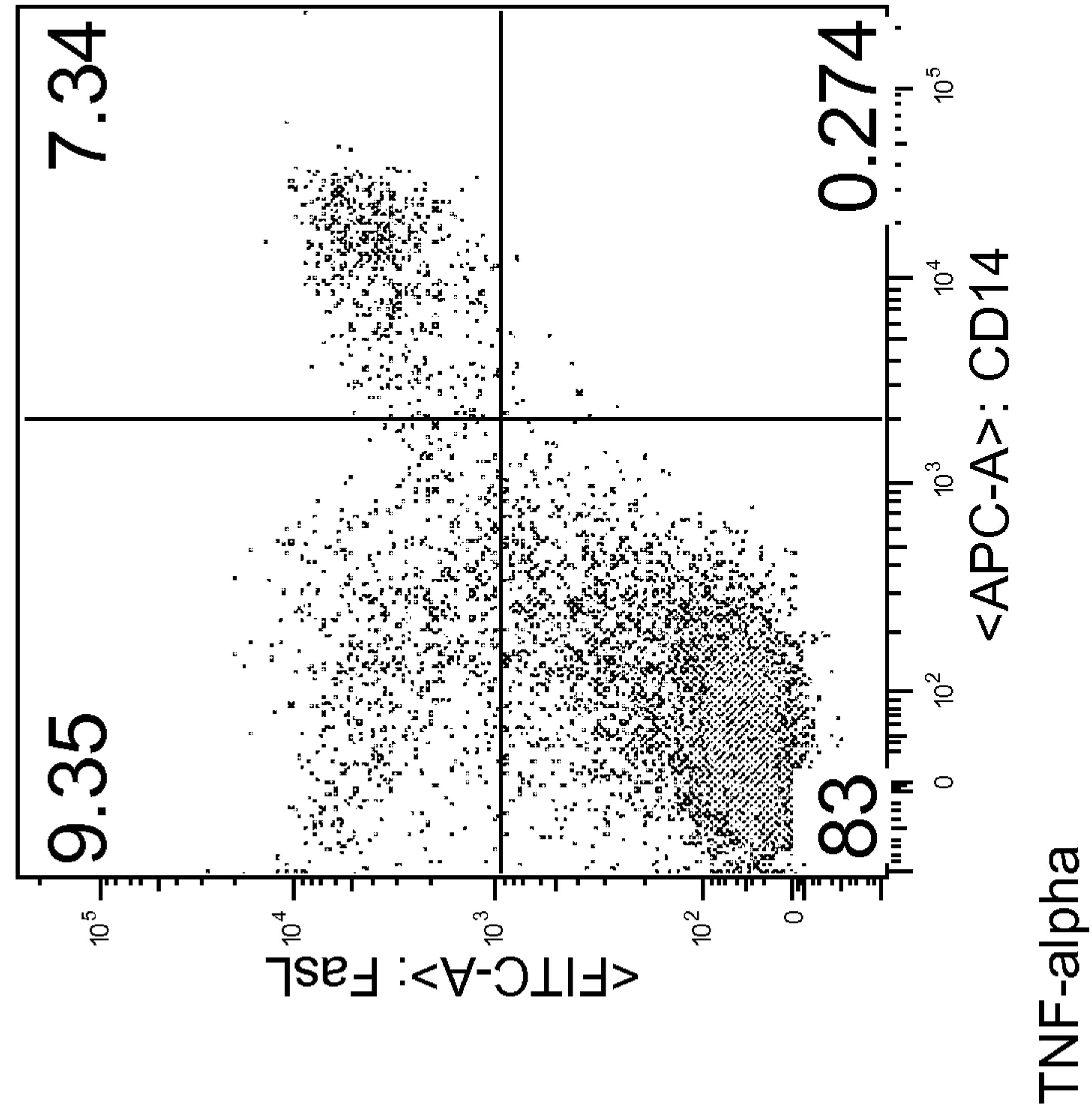


FIG. 17C

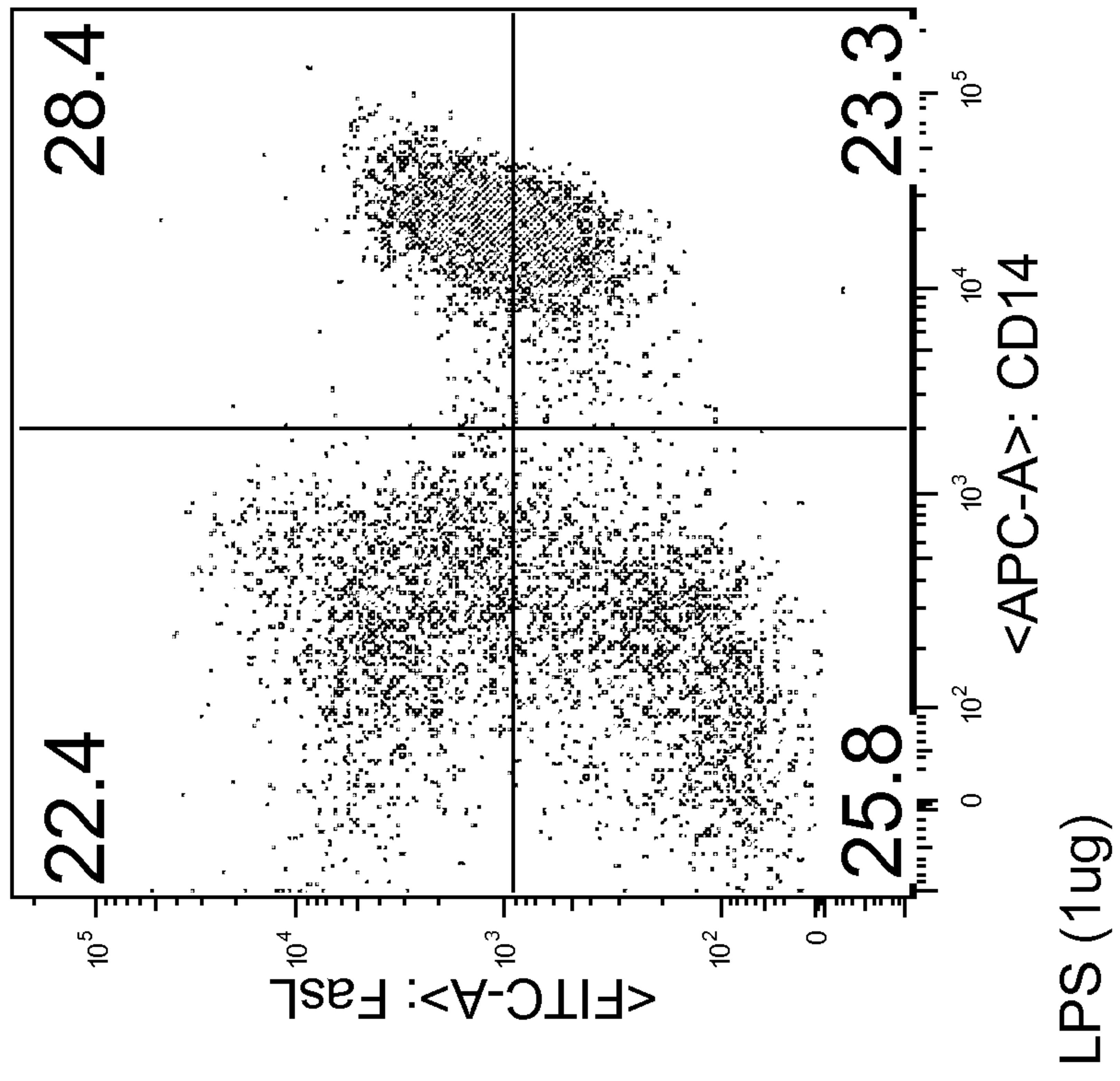


FIG. 17D

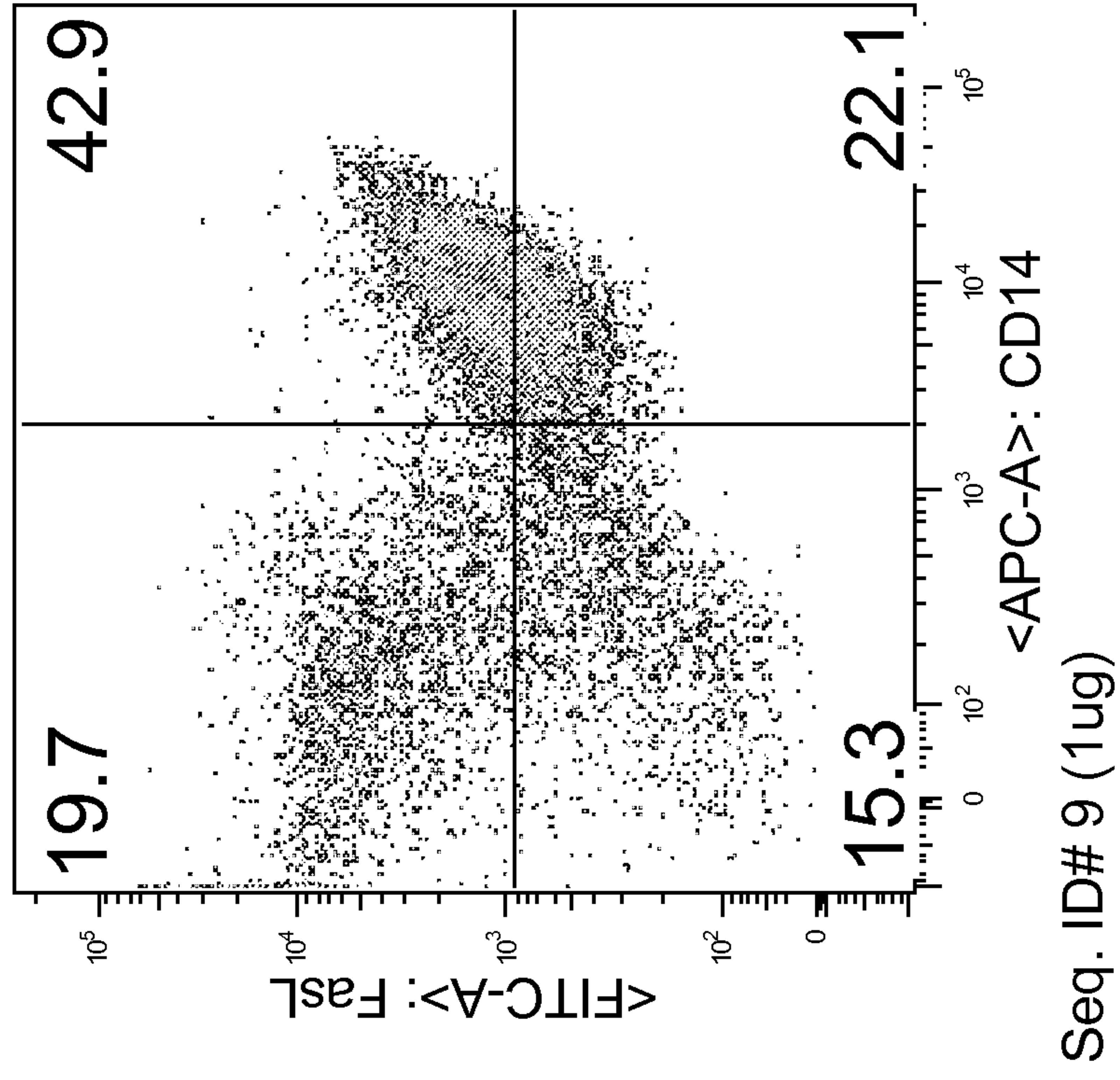
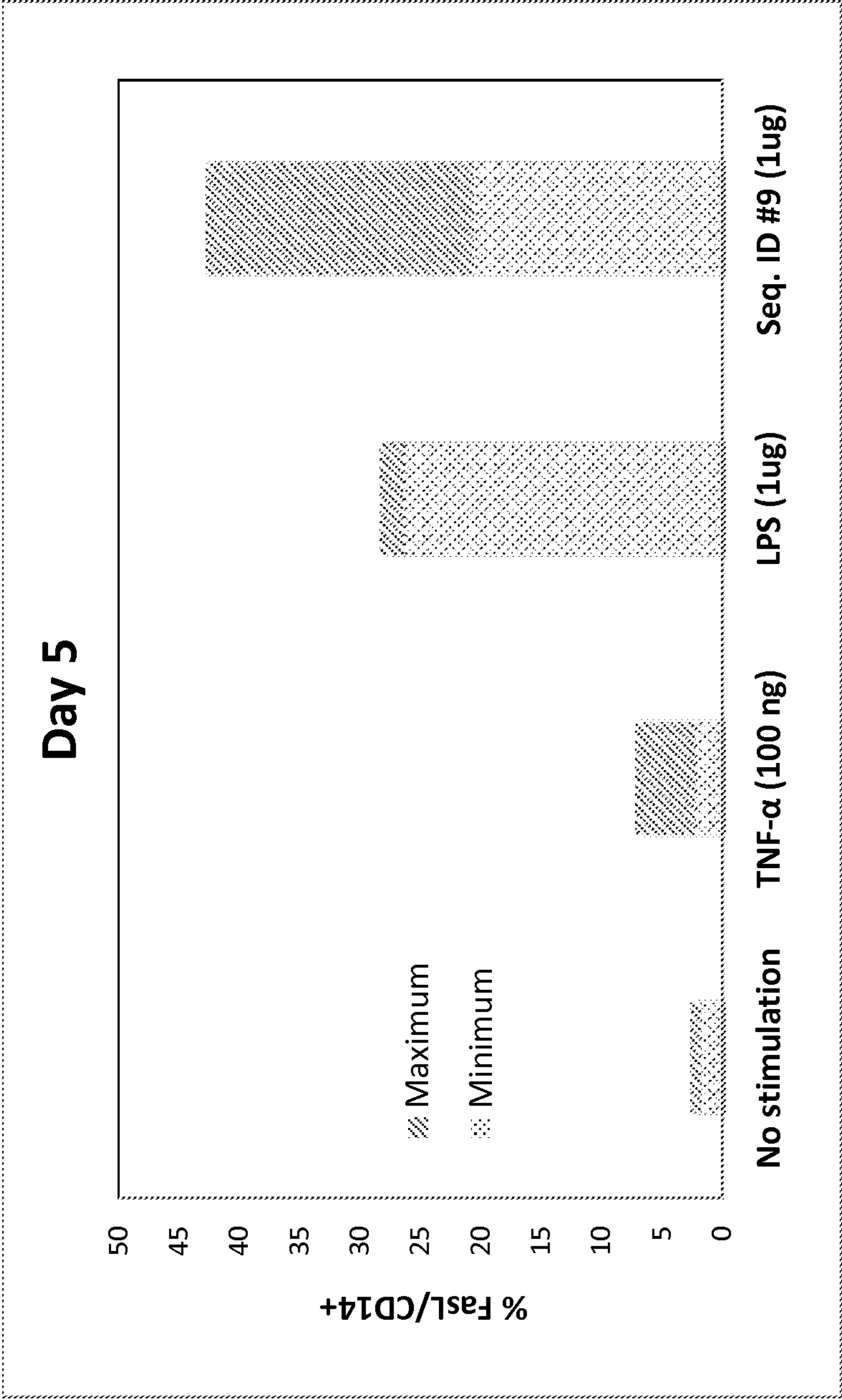


FIG. 17E



Percentage of FasL/CD14+ cells after 5 days of incubation:

Range of data	No stimulation	TNF- α (100 ng)	LPS (1ug)	Tat derivative
Minimum	1.73	2.26	26.8	28.6
Maximum	2.75	7.34	28.4	42.9