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(54) **ANTI-HUMAN NICOTINAMIDE
PHOSPHORIBOSYLTRANSFERASE (NAMPT)
ANTIBODIES**

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7, 2019.

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(21) Appl. No.: **17/941,741**

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C07K 2317/76 (2013.01); **C07K 2317/24**
(2013.01); **A61K 2039/505** (2013.01)

(57) **ABSTRACT**

Anti-nicotinamide phosphoribosyltransferase (NAMPT) antibodies, or antigen binding fragments thereof, are described, as well as methods for treating a subject having a (NAMPT)-associated local and/or systemic inflammatory disorder.

Specification includes a Sequence Listing.

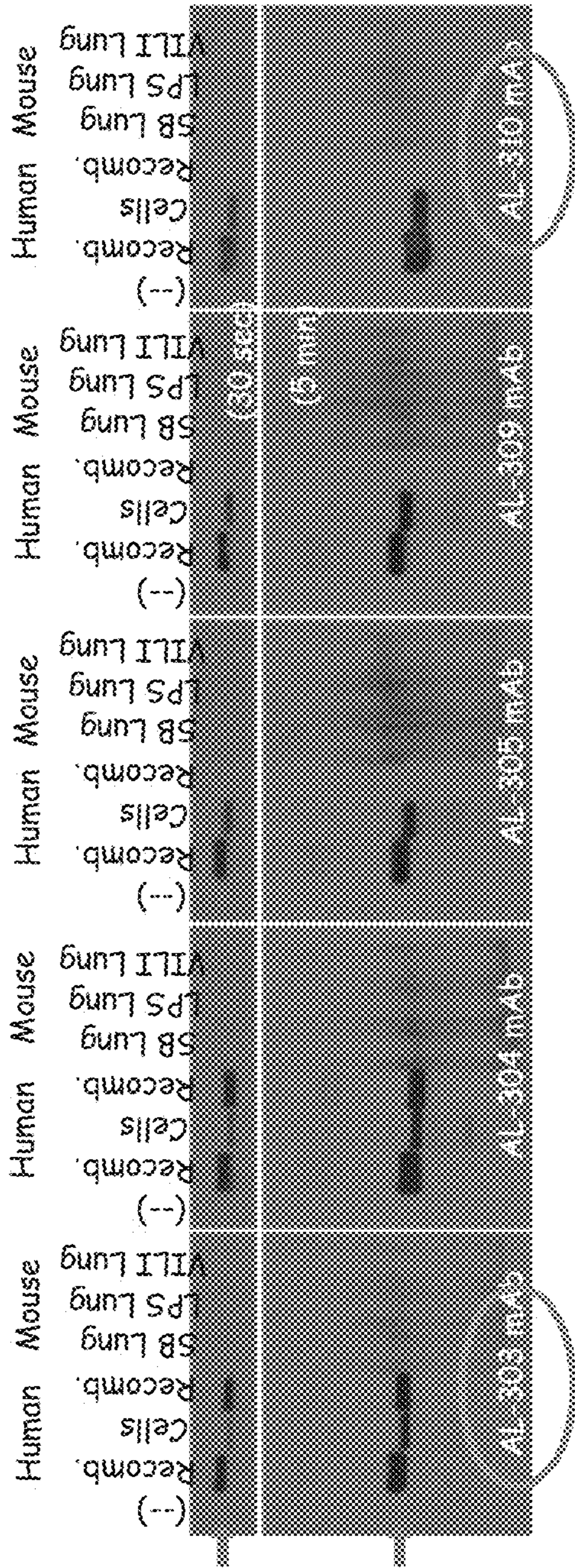


FIG. 1

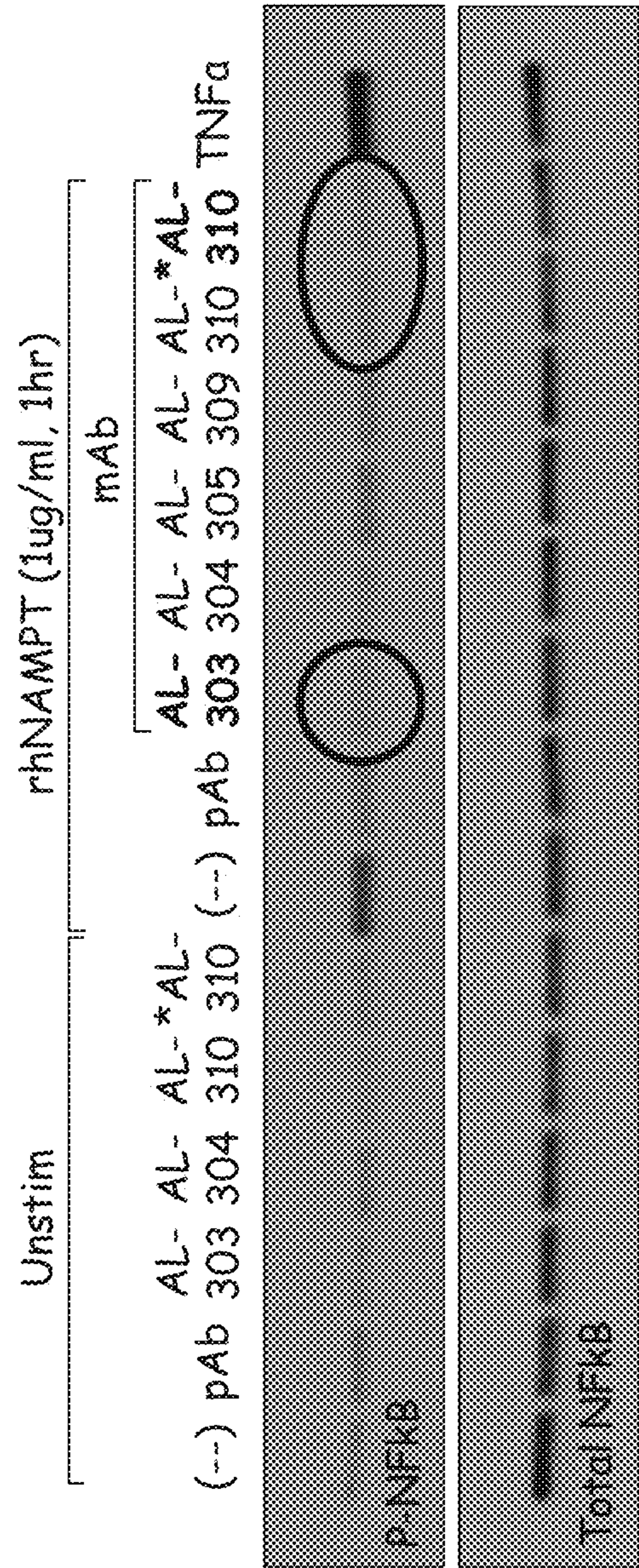


FIG. 2

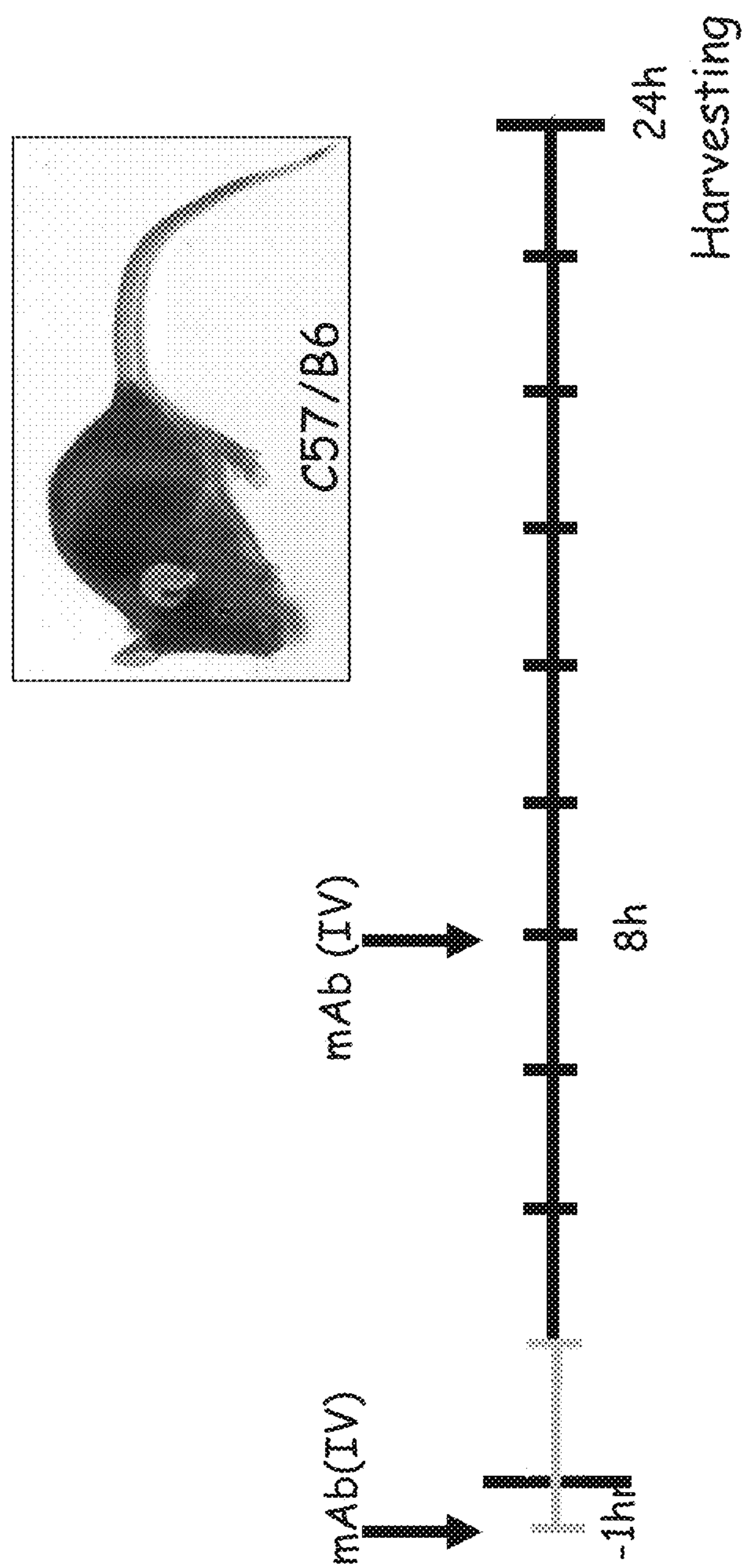


FIG. 3

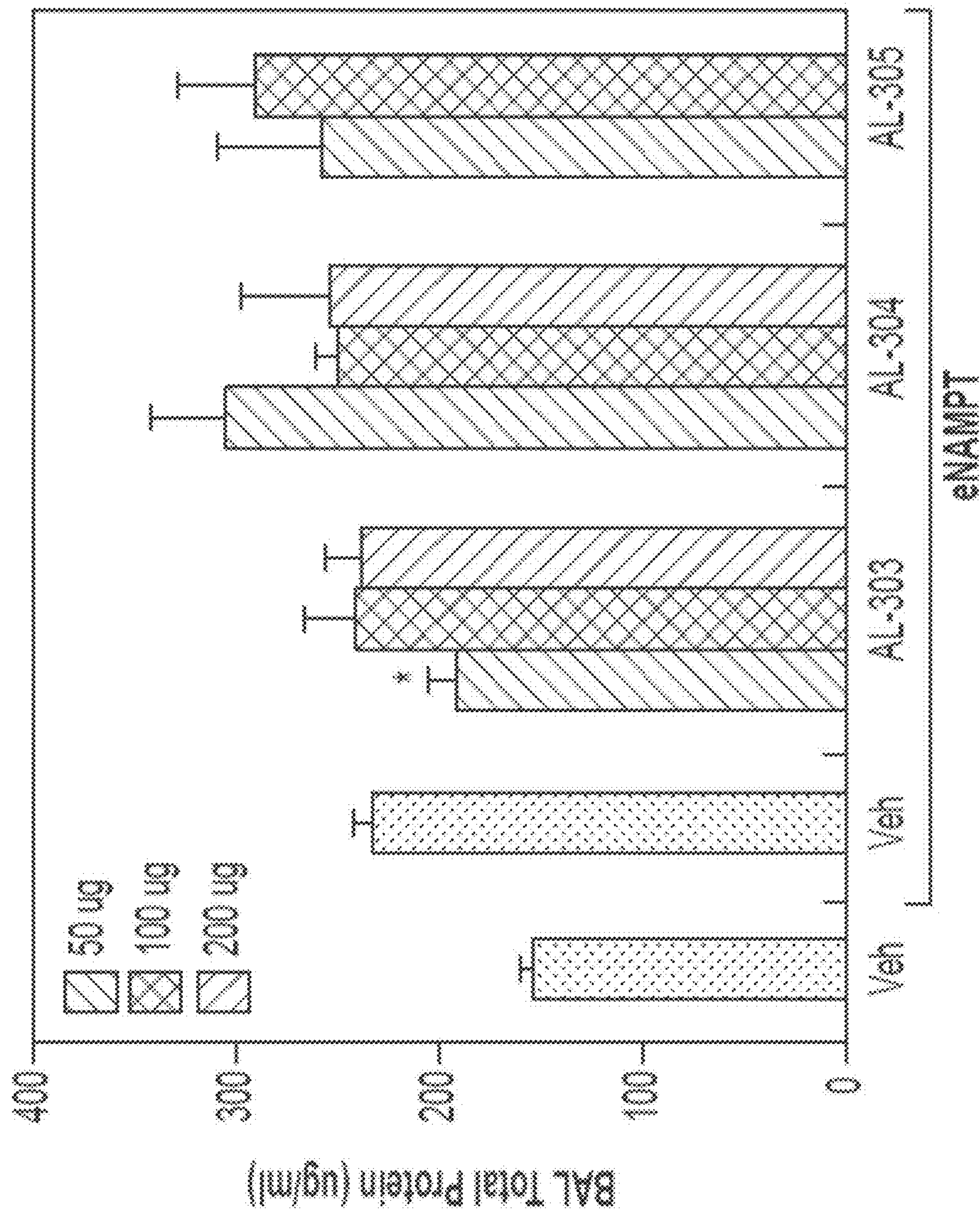


FIG. 4A

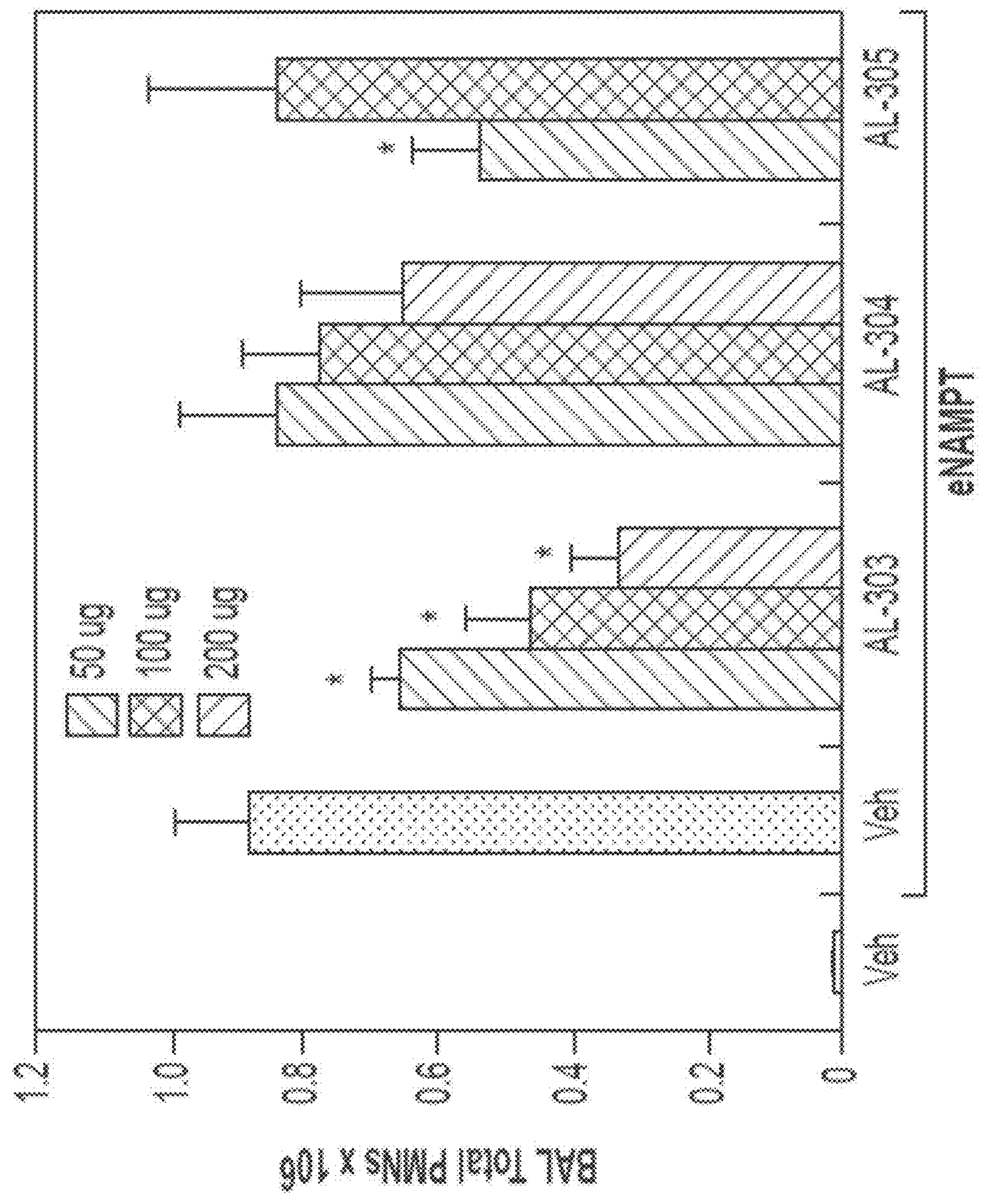


FIG. 4B

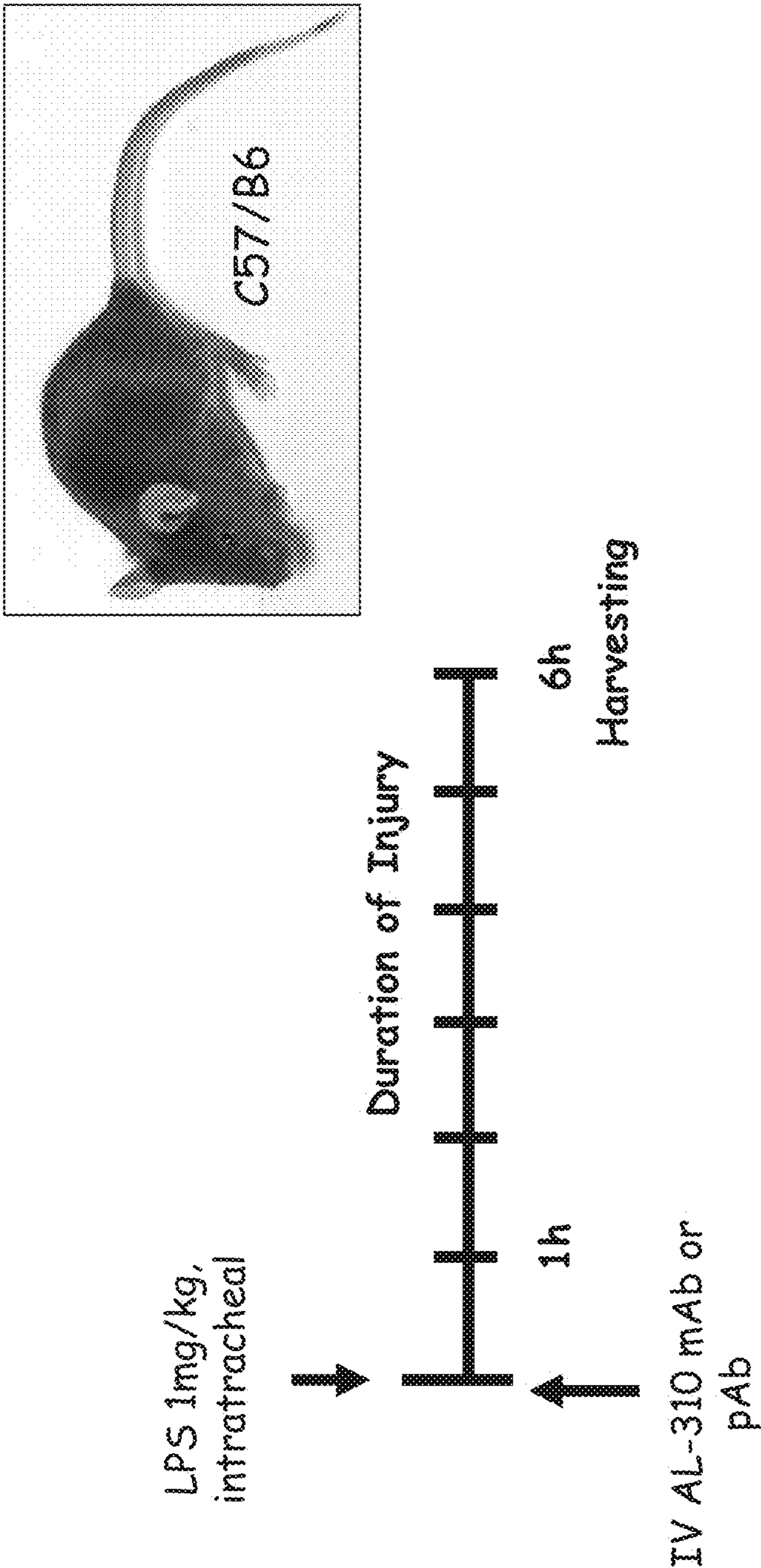


FIG. 5

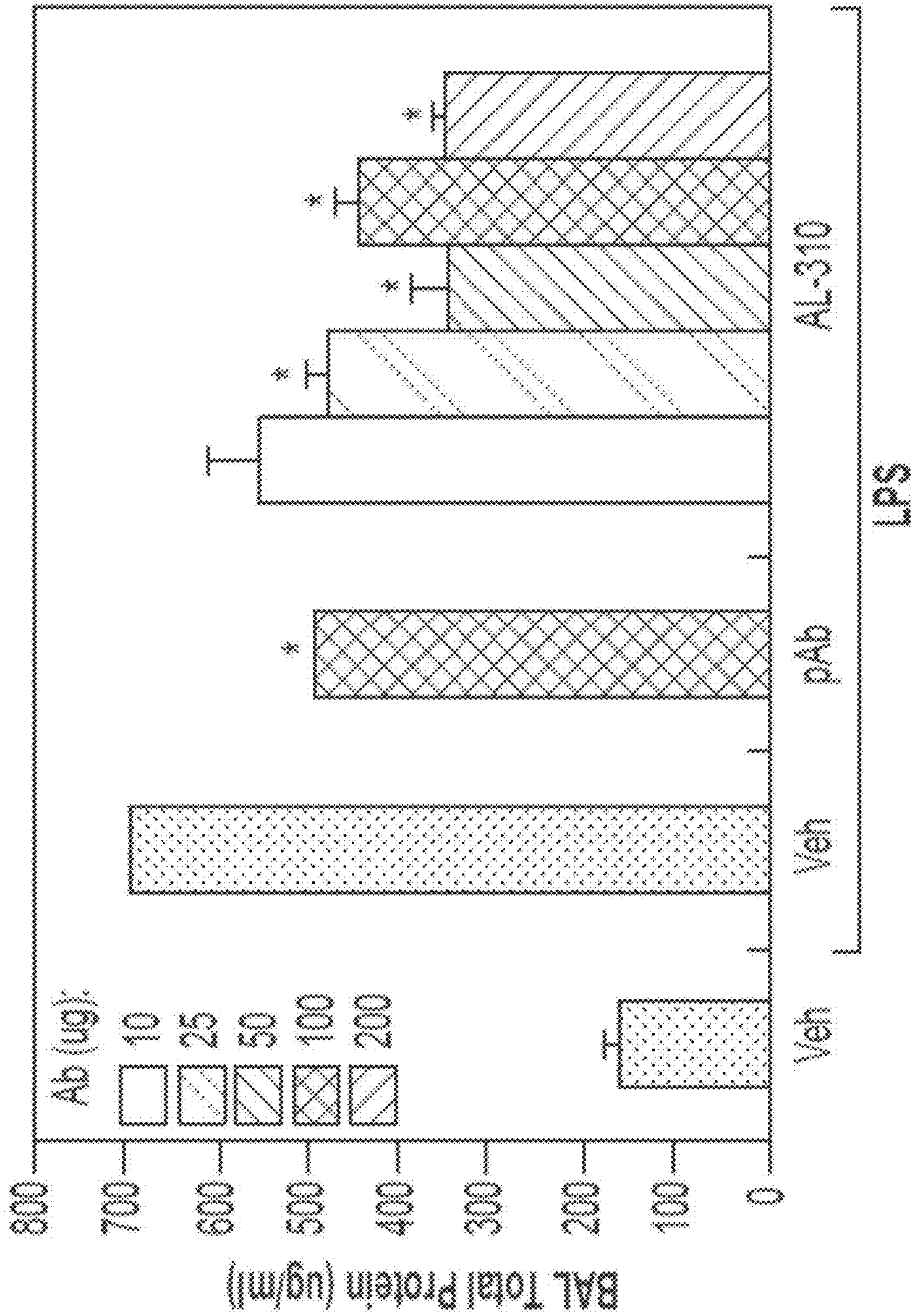


FIG. 6

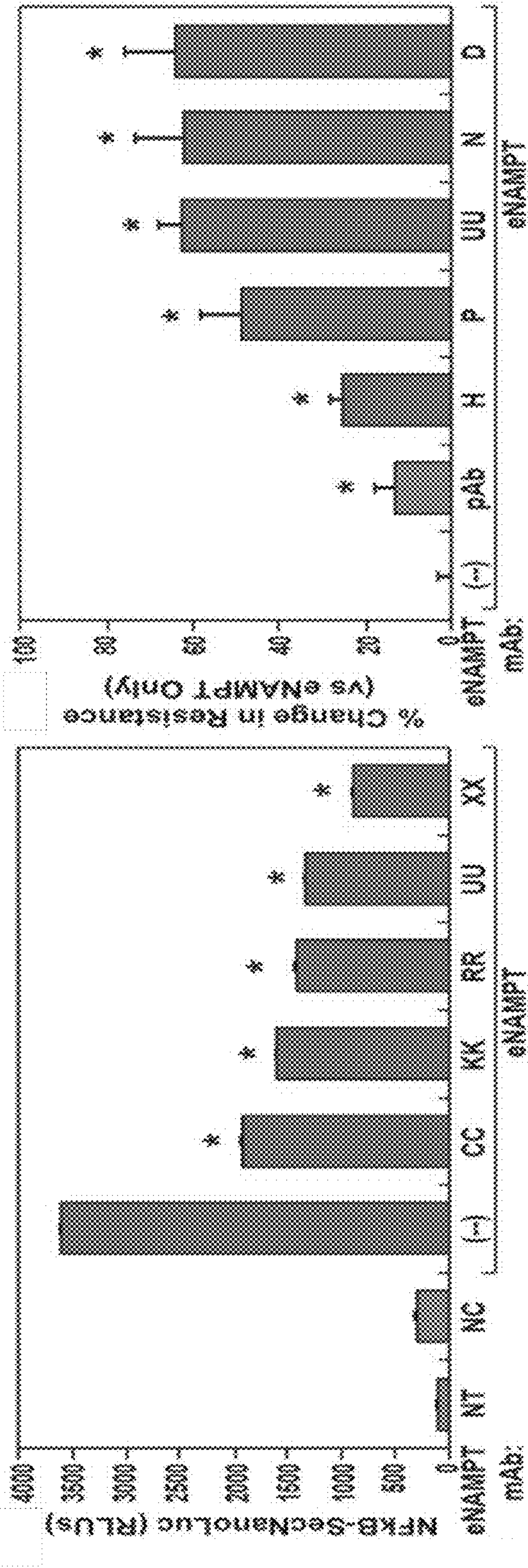


FIG. 7A

FIG. 7B

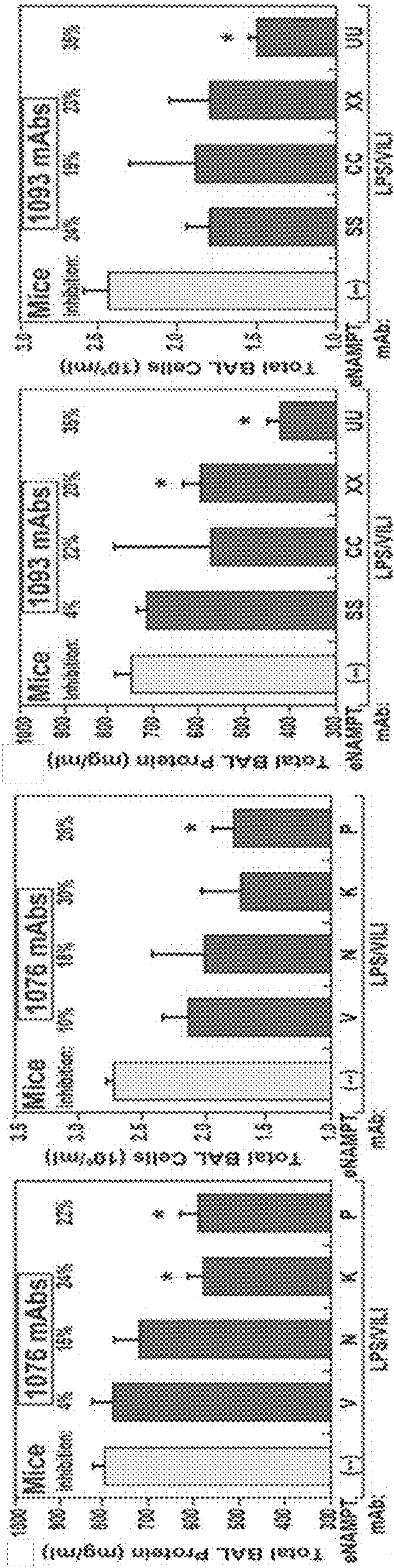


FIG. 8B

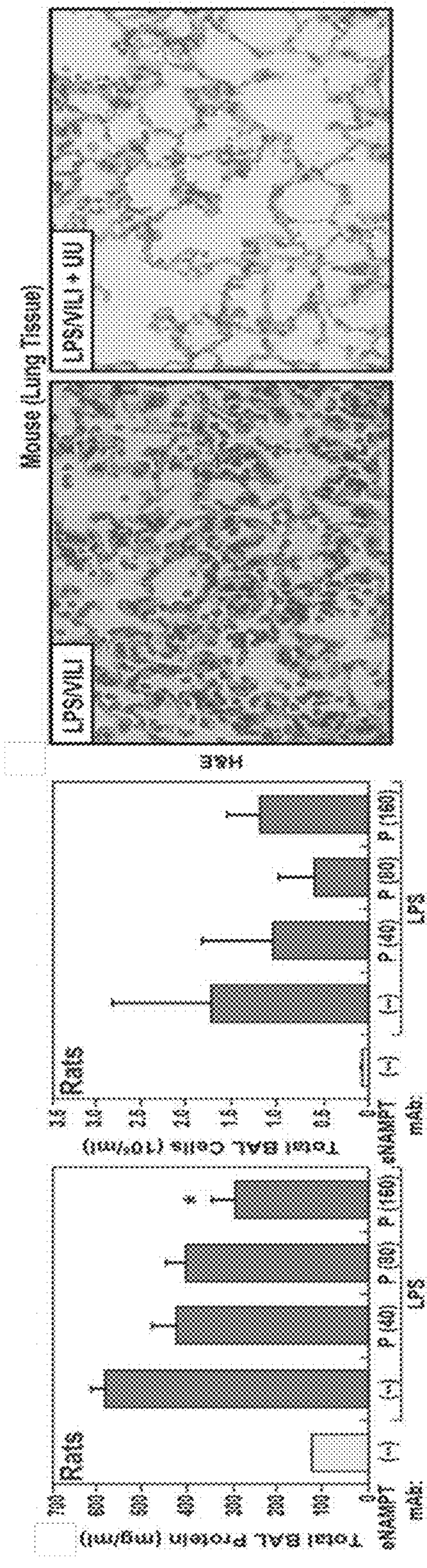
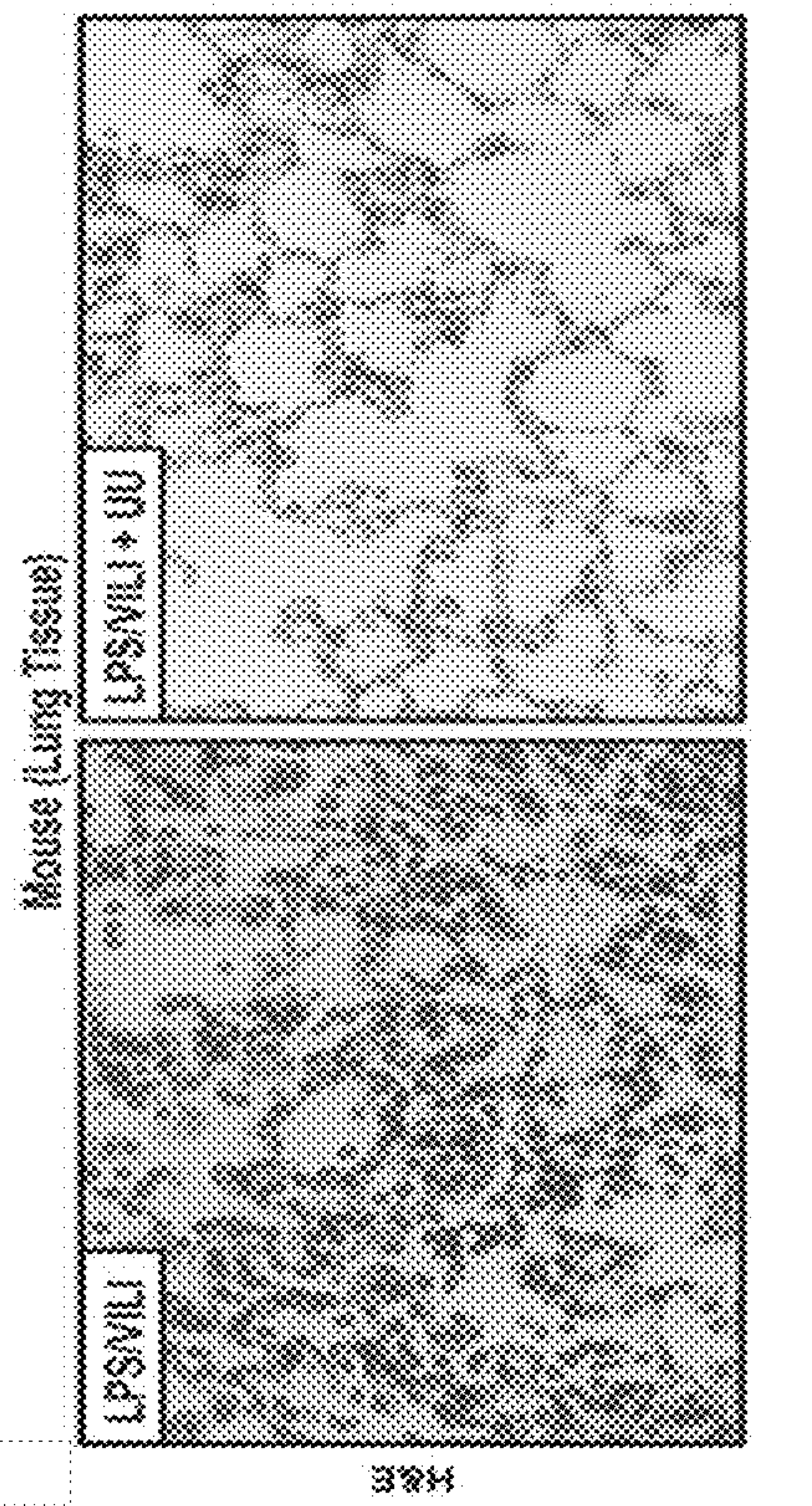


FIG. 8D



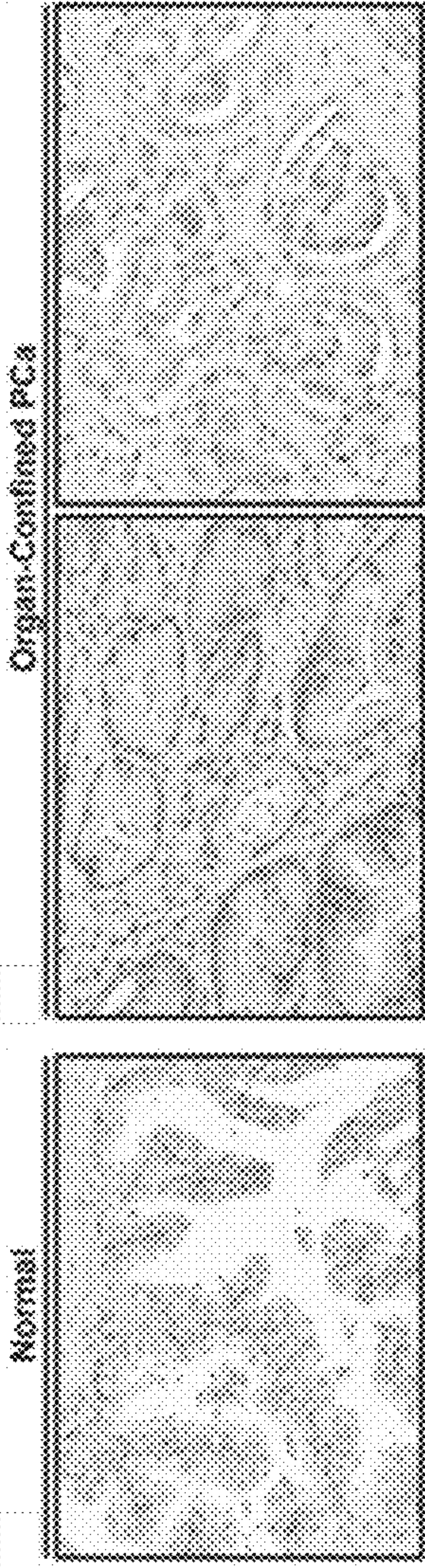


FIG. 9A

FIG. 9B

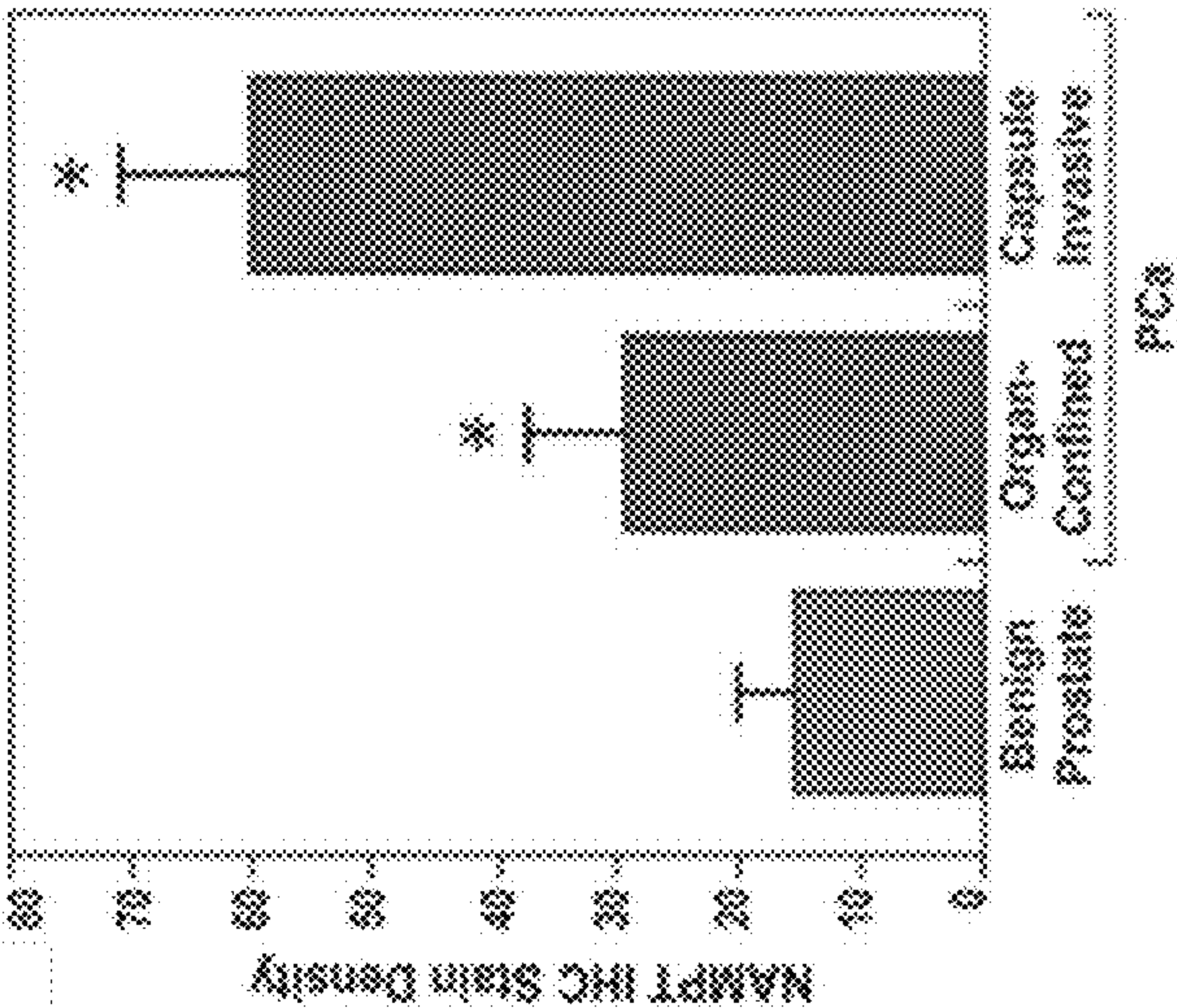
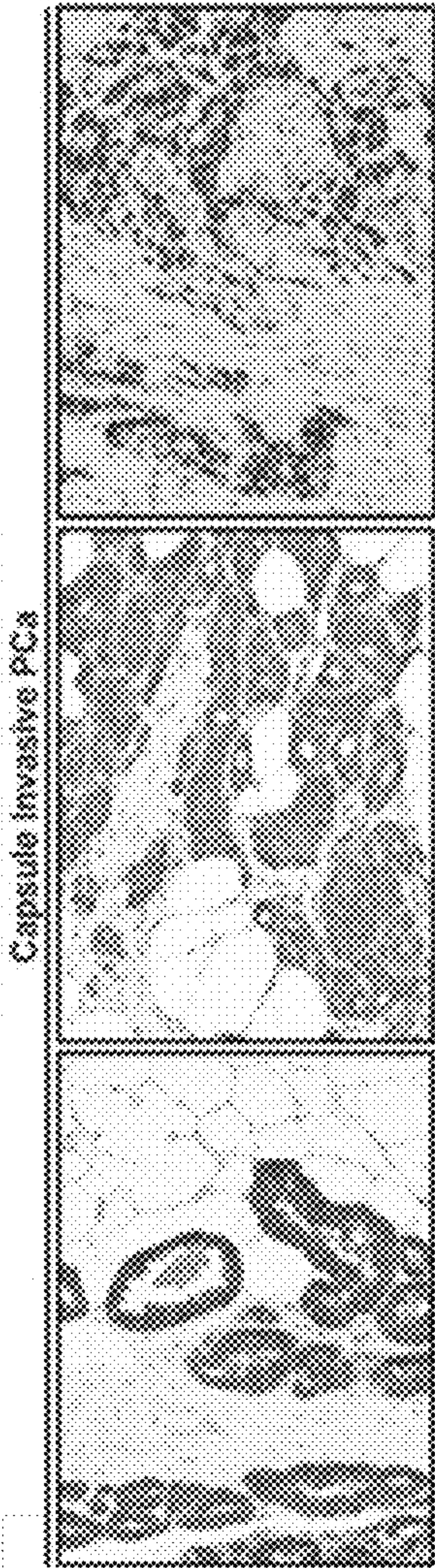


FIG. 9C

FIG. 9D



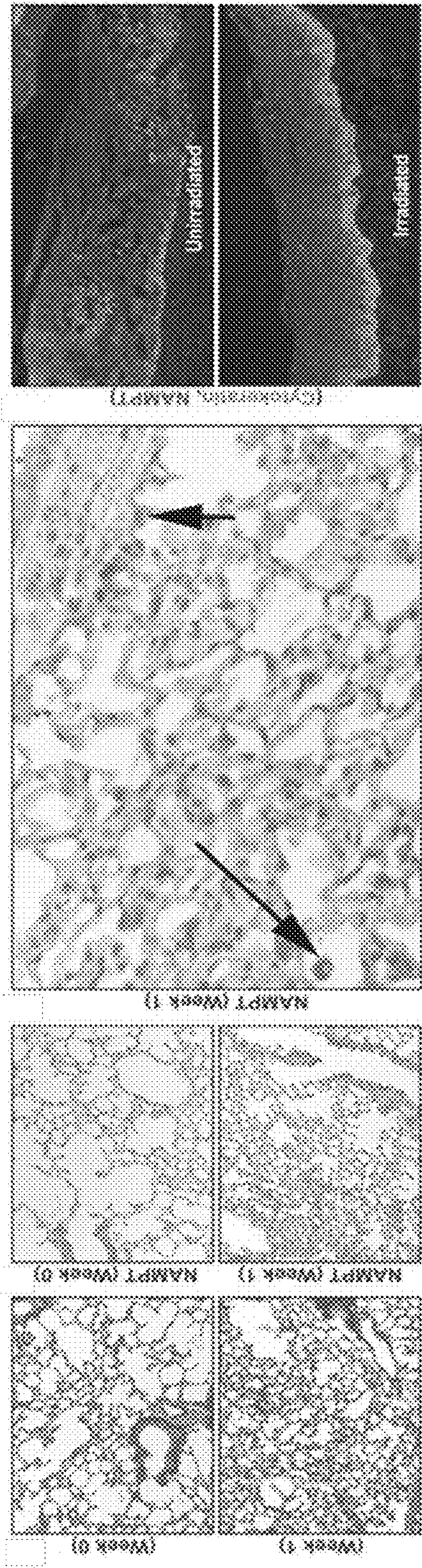


FIG. 10D

FIG. 10C

FIG. 10B

FIG. 10A

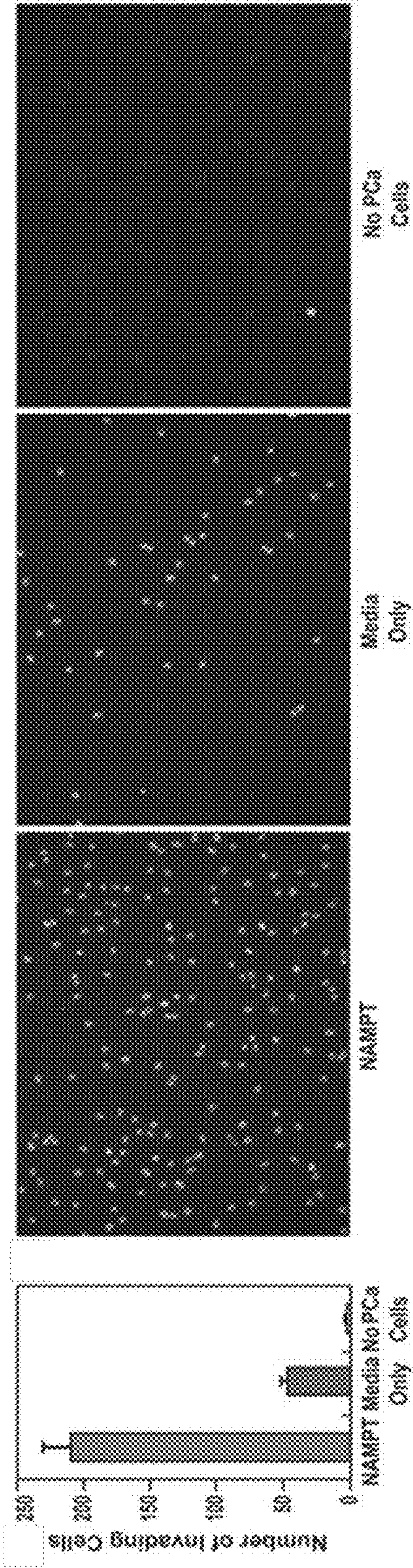


FIG. 11A

FIG. 11B

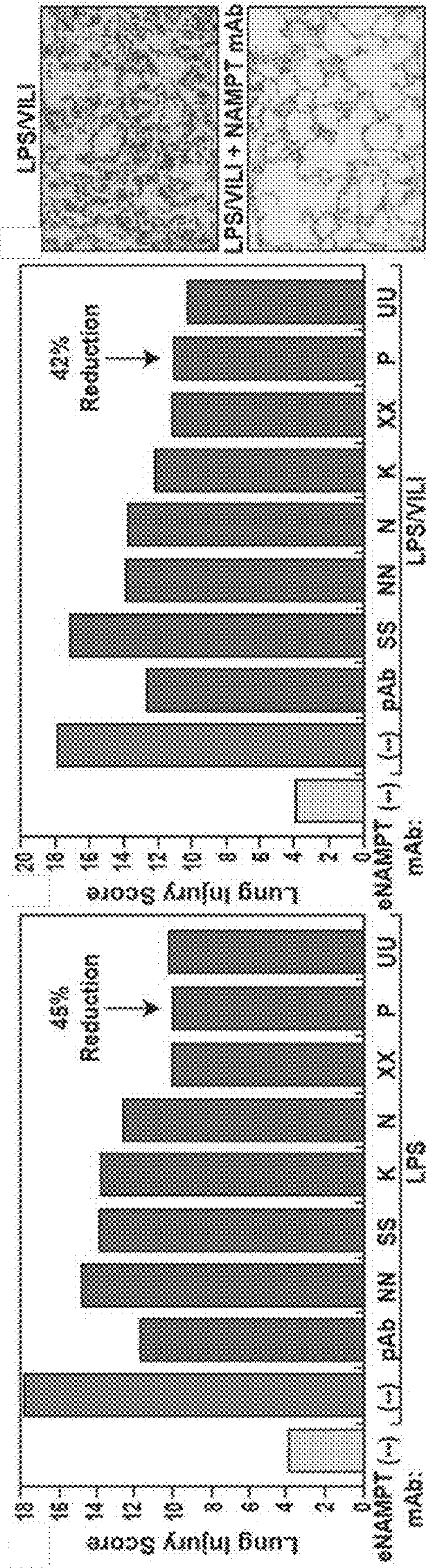


FIG. 12A

FIG. 12B

FIG. 12C

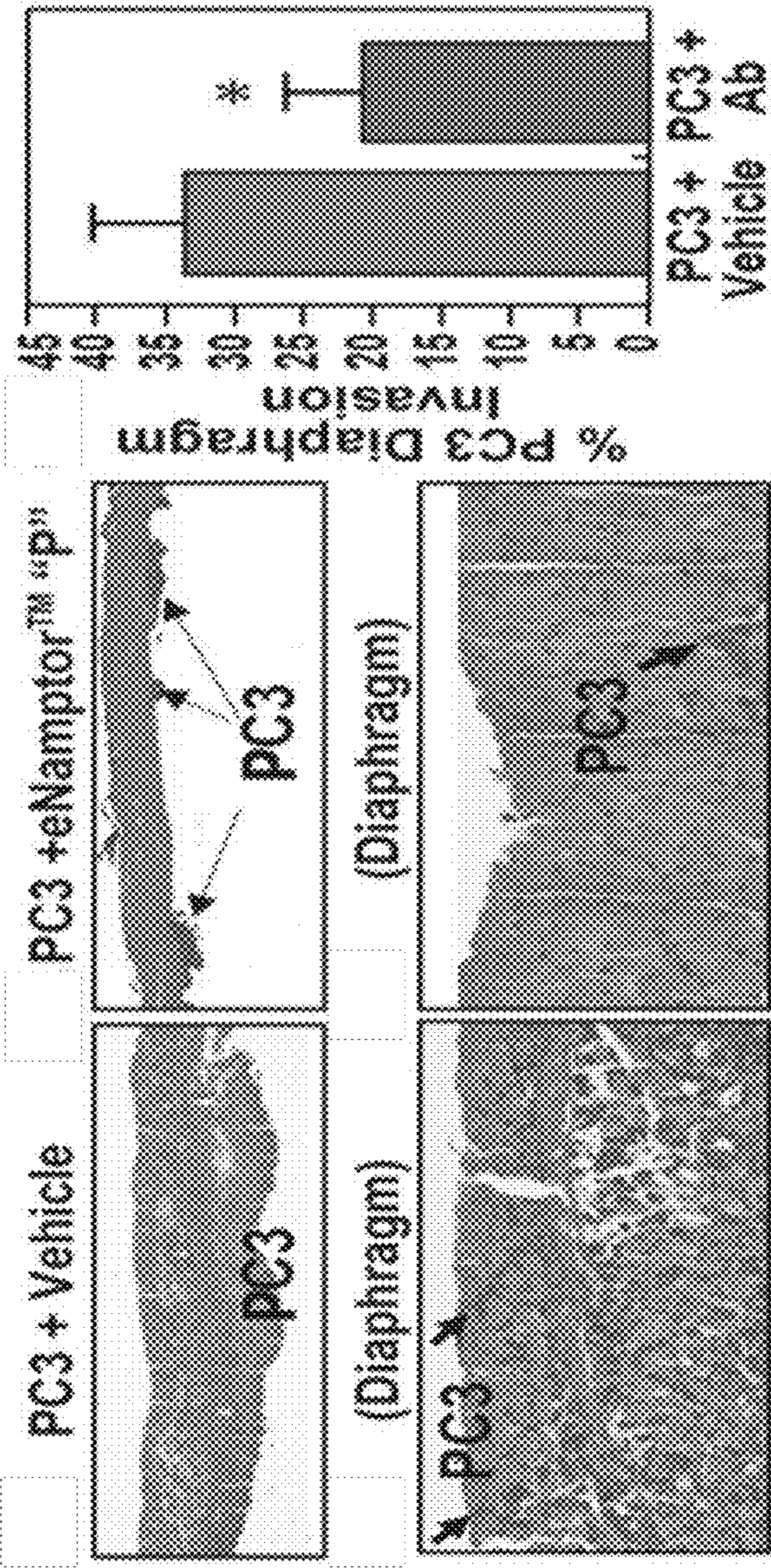
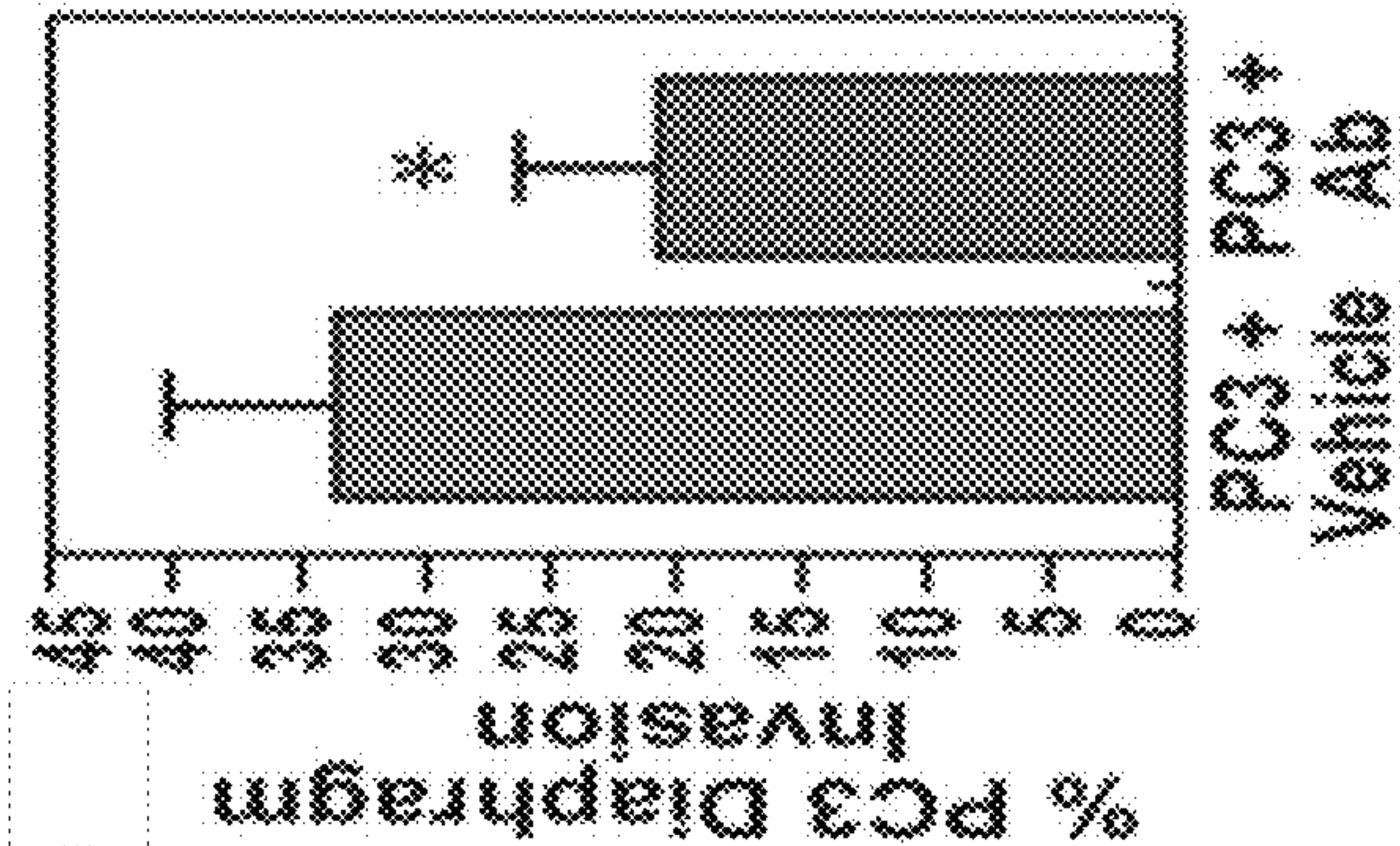


FIG. 13A

FIG. 13B

FIG. 13C



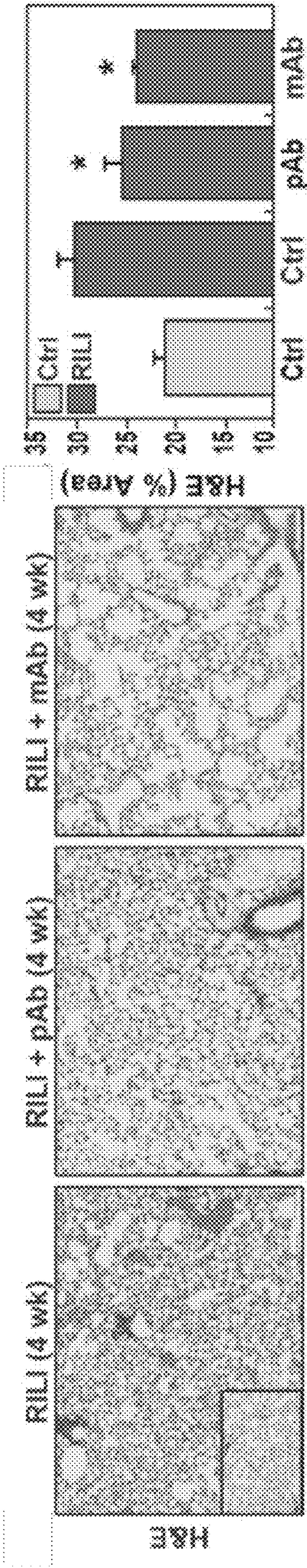


FIG. 14B

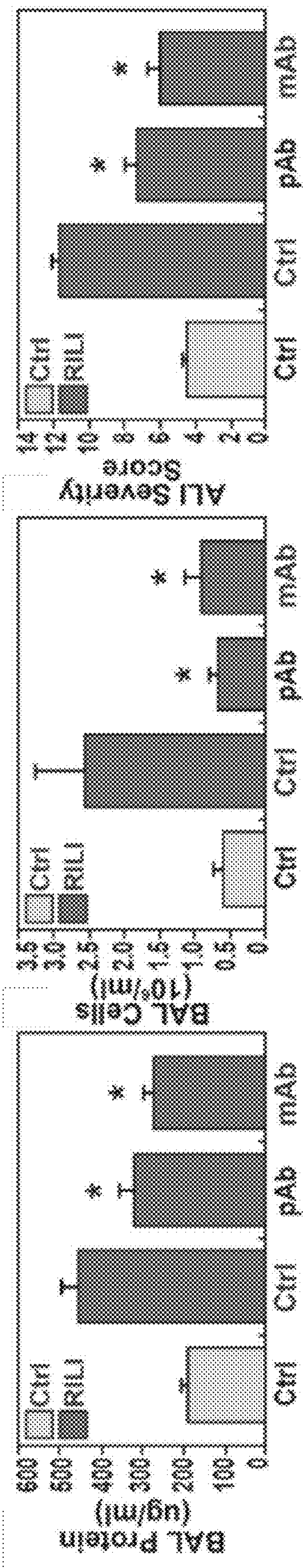


FIG. 14D

FIG. 14E

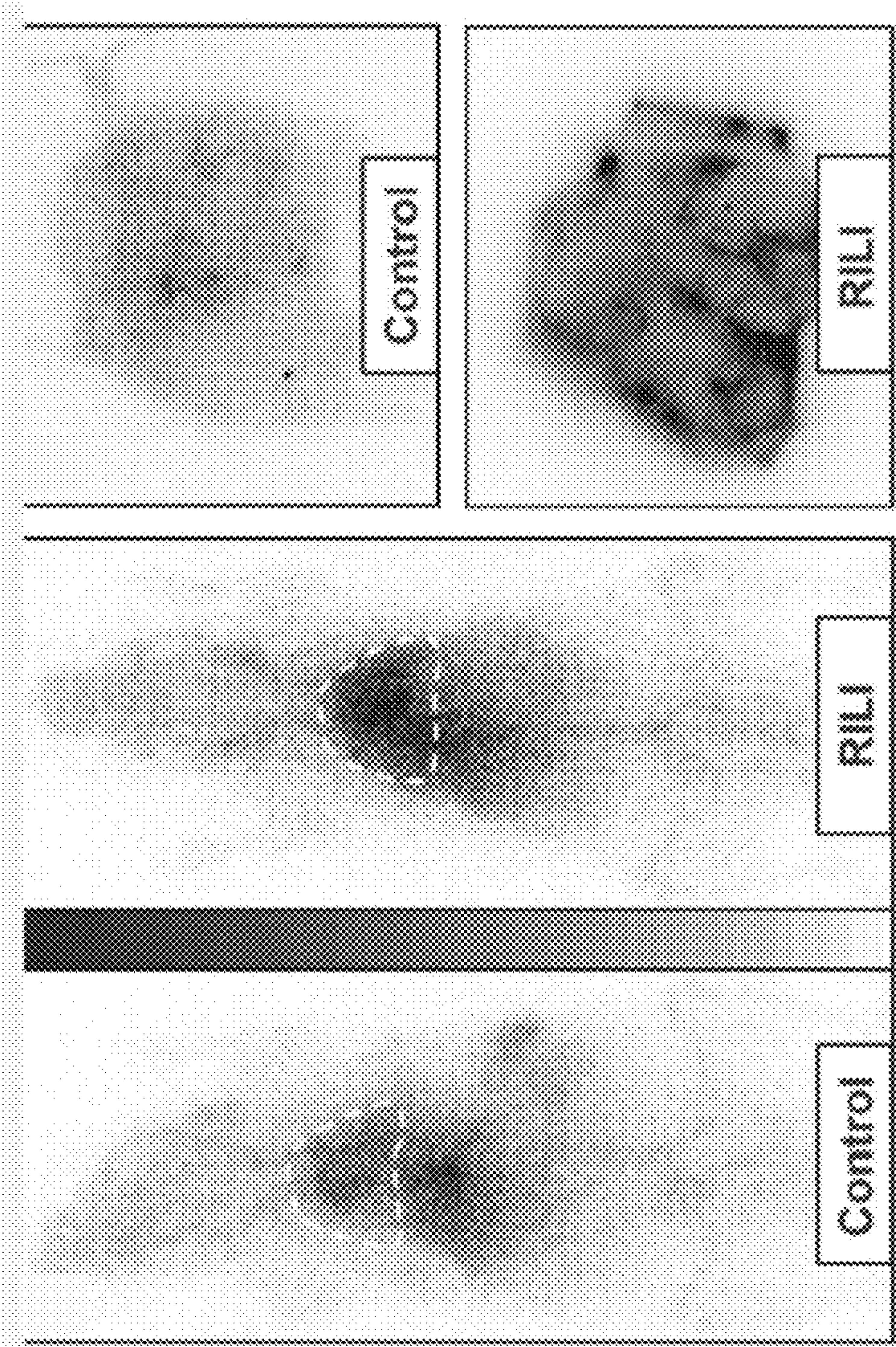


FIG. 15A

FIG. 15B

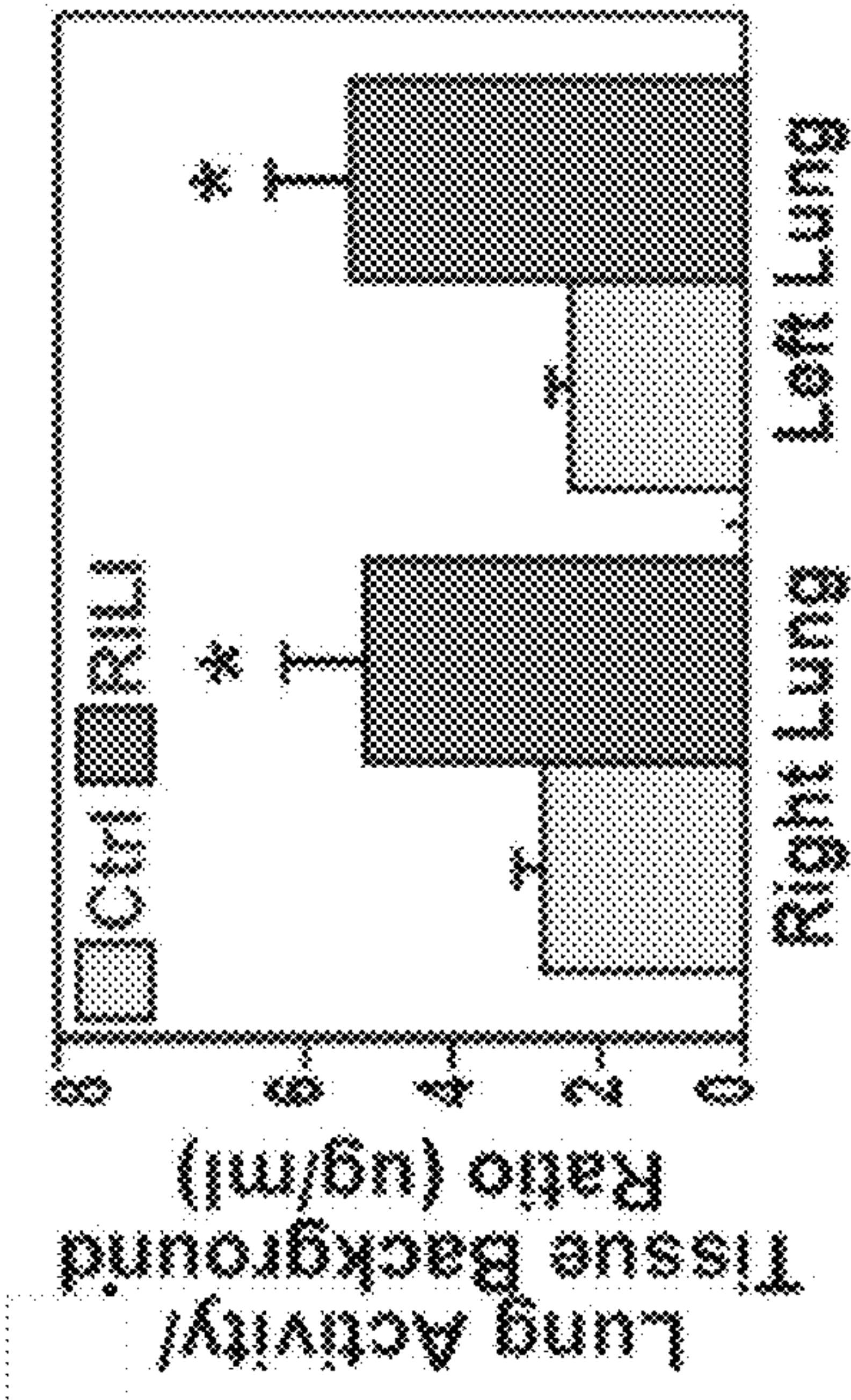


FIG. 15C

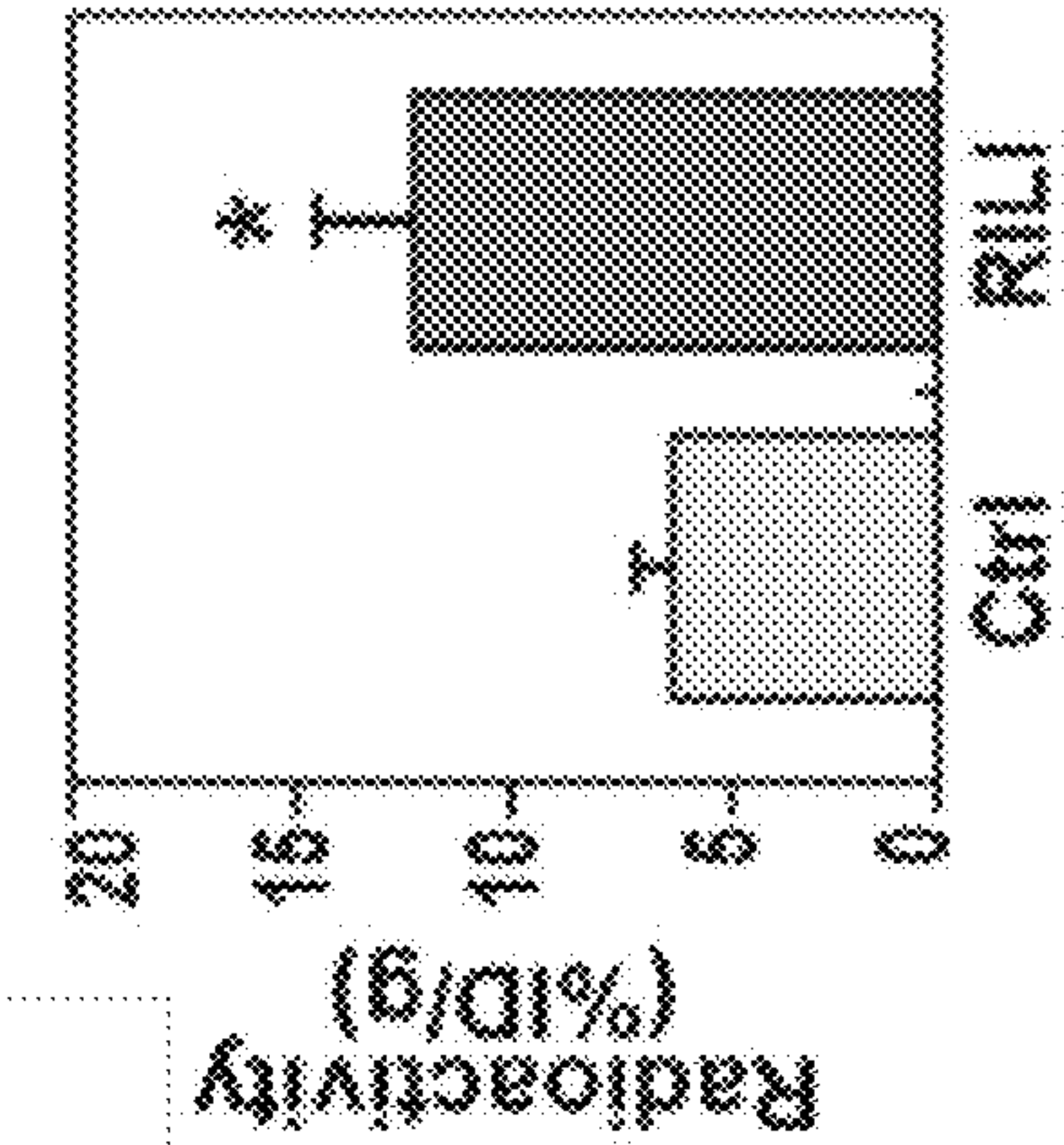
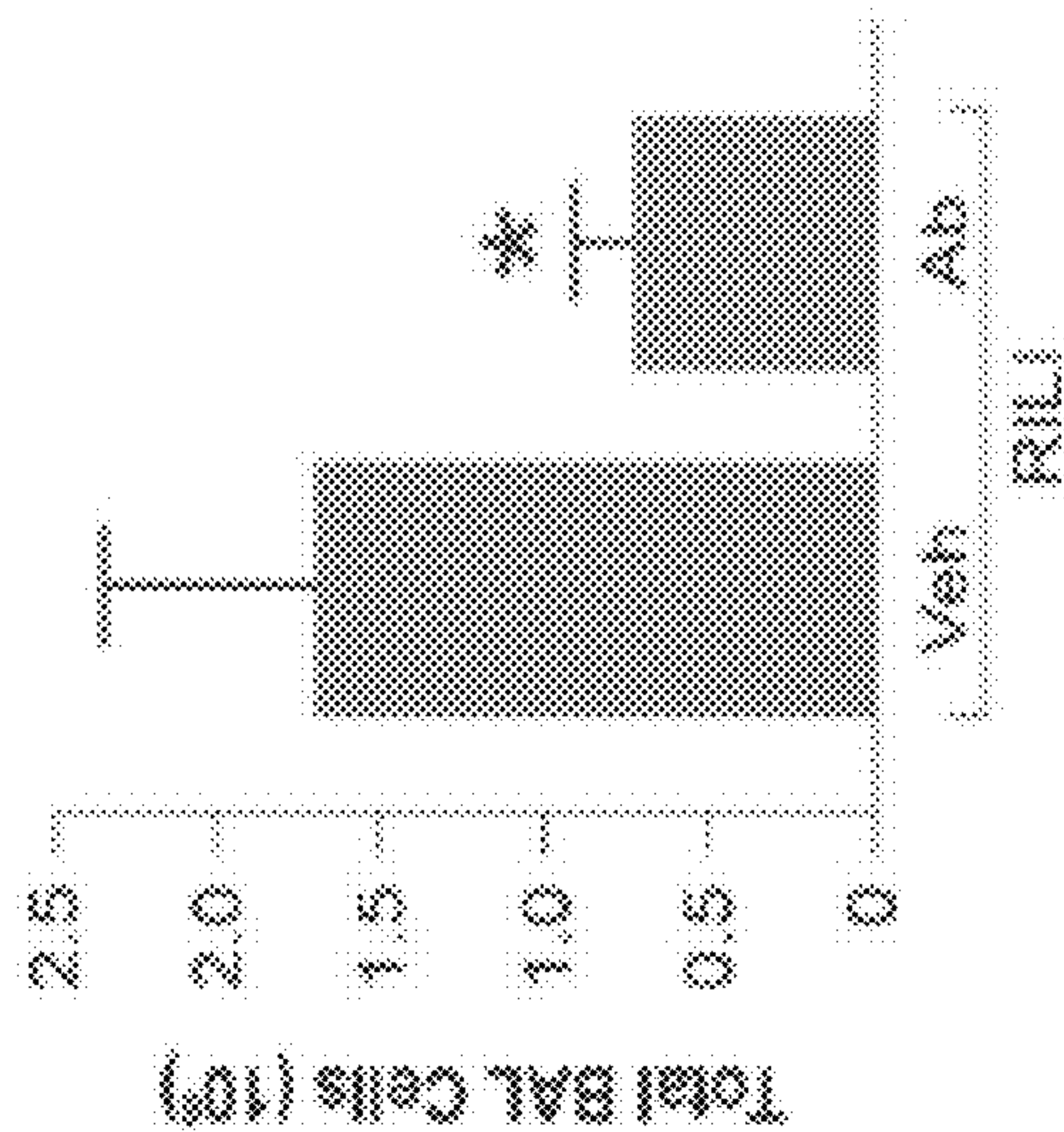
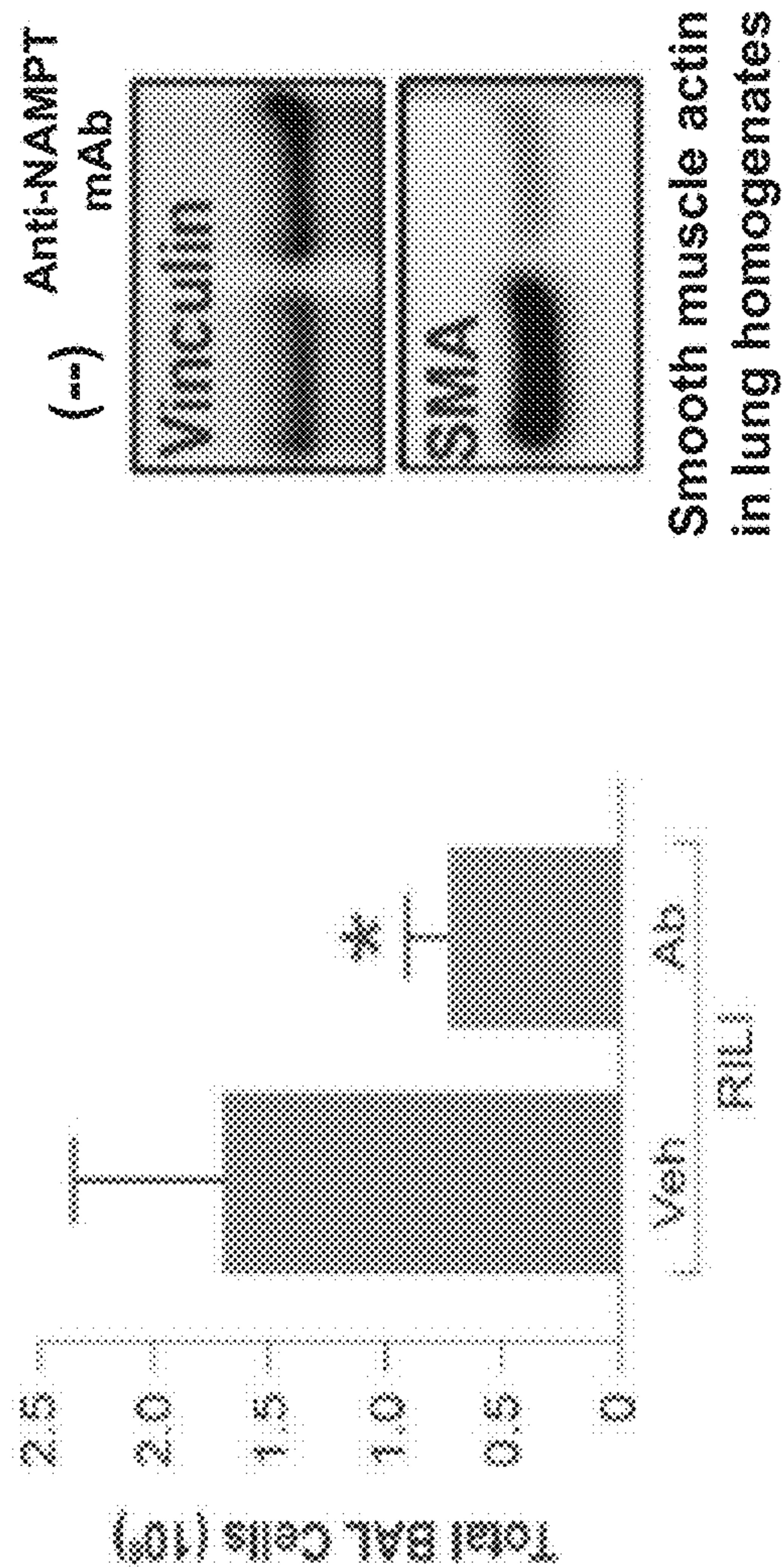
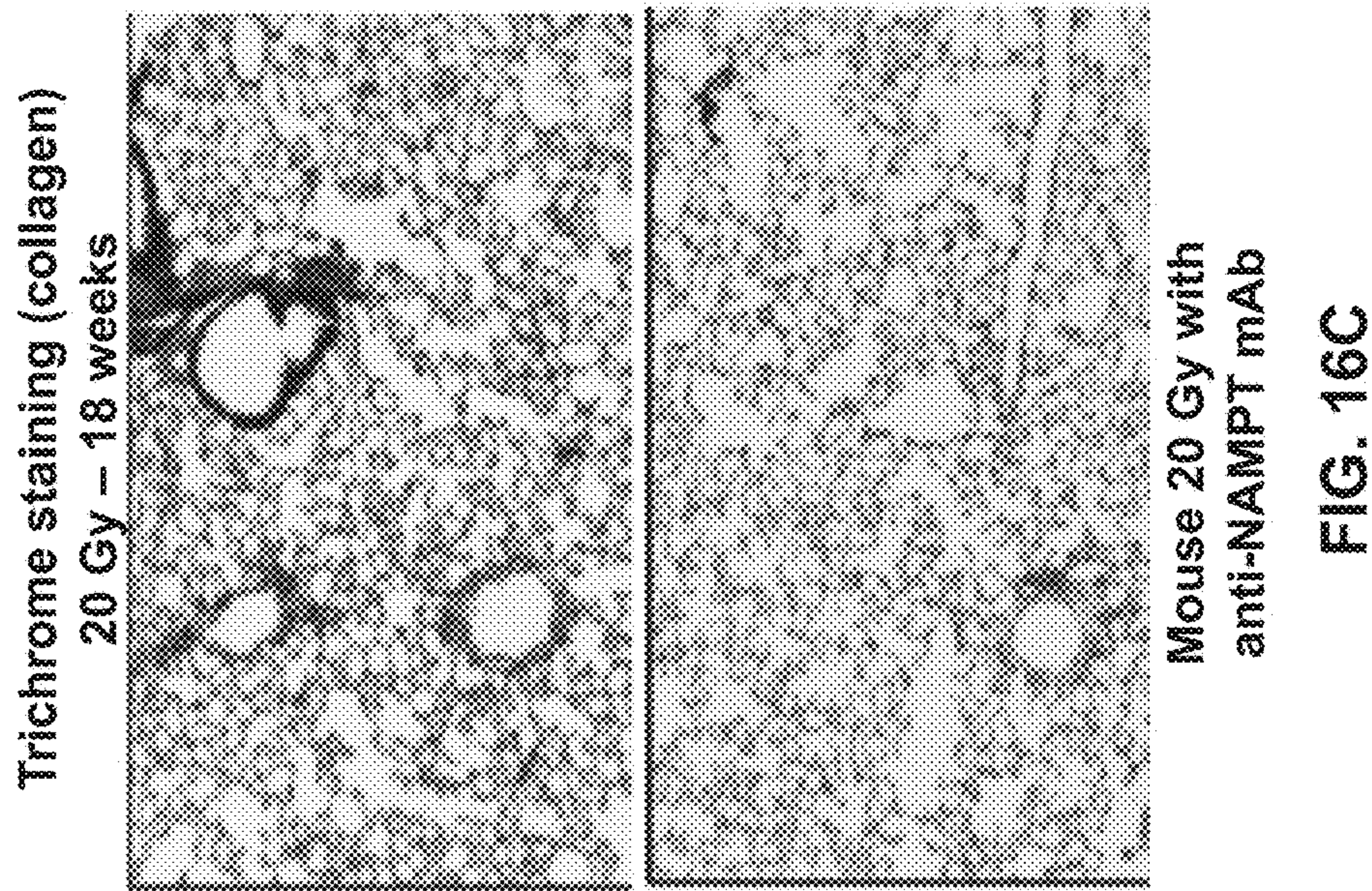


FIG. 15D



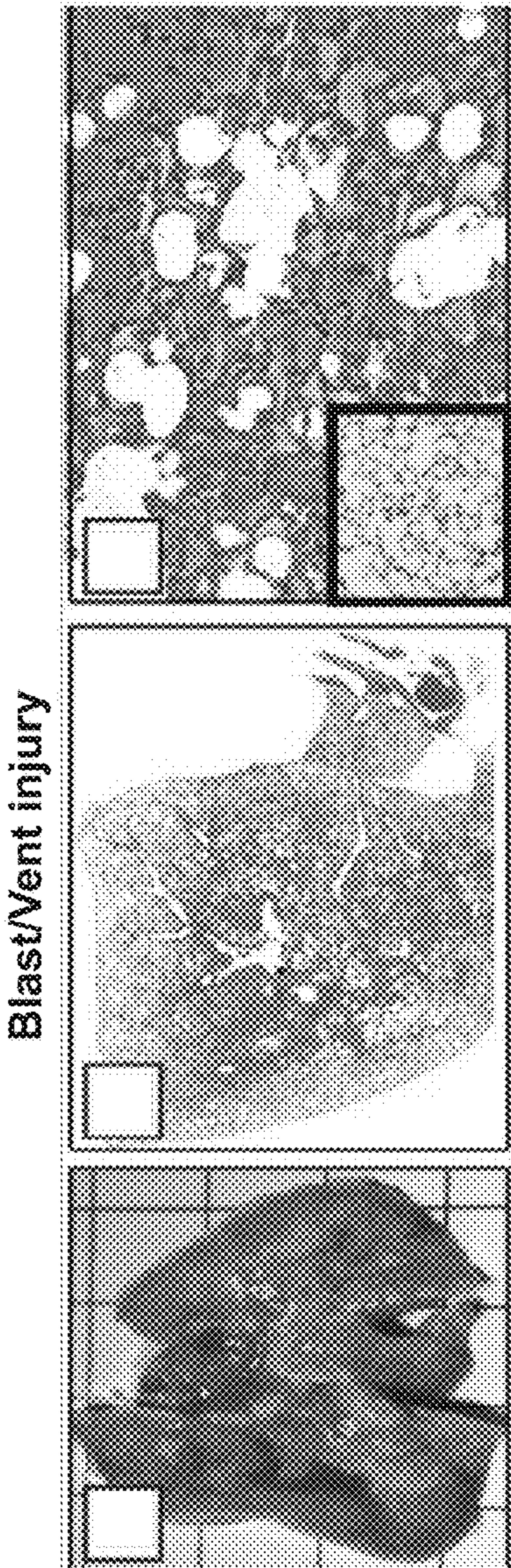


FIG. 17A

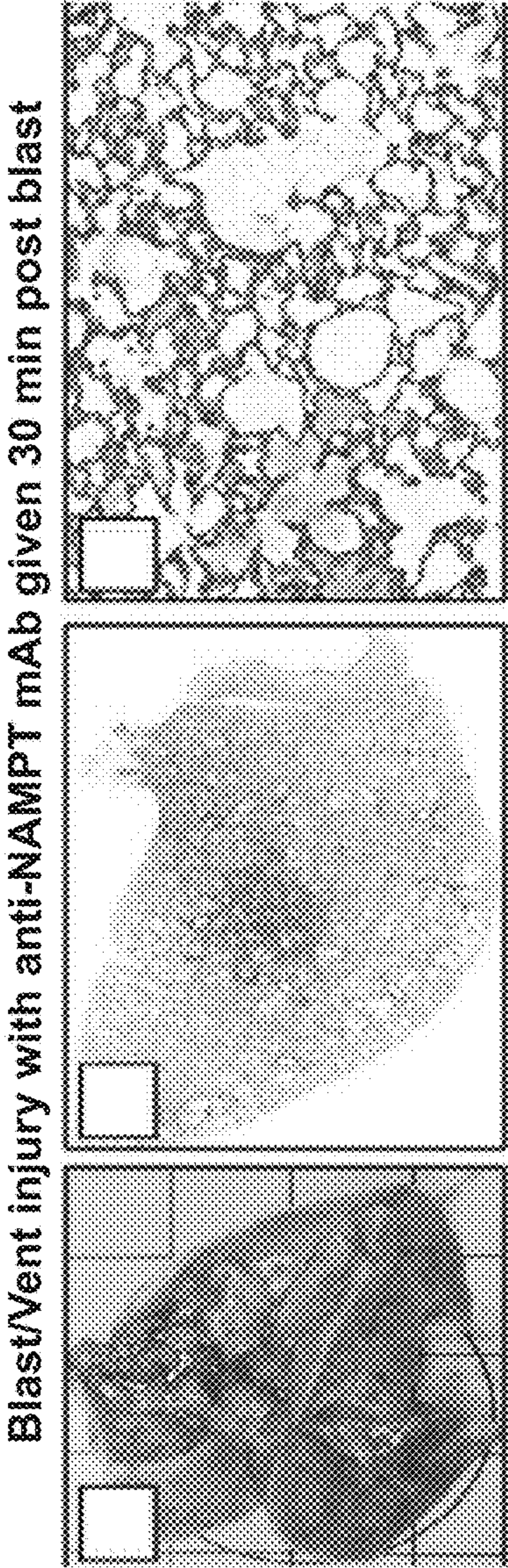


FIG. 17B

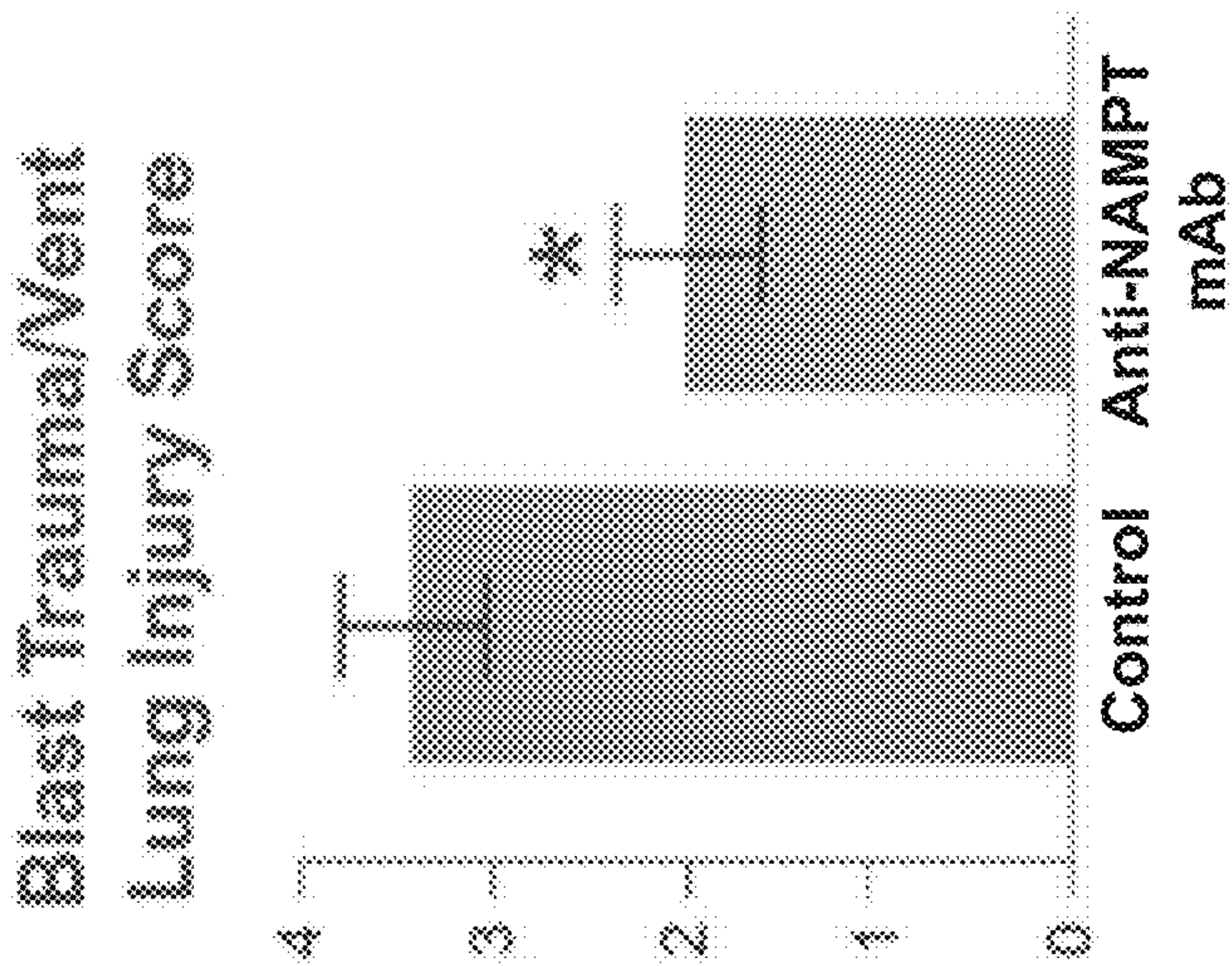


FIG. 17C

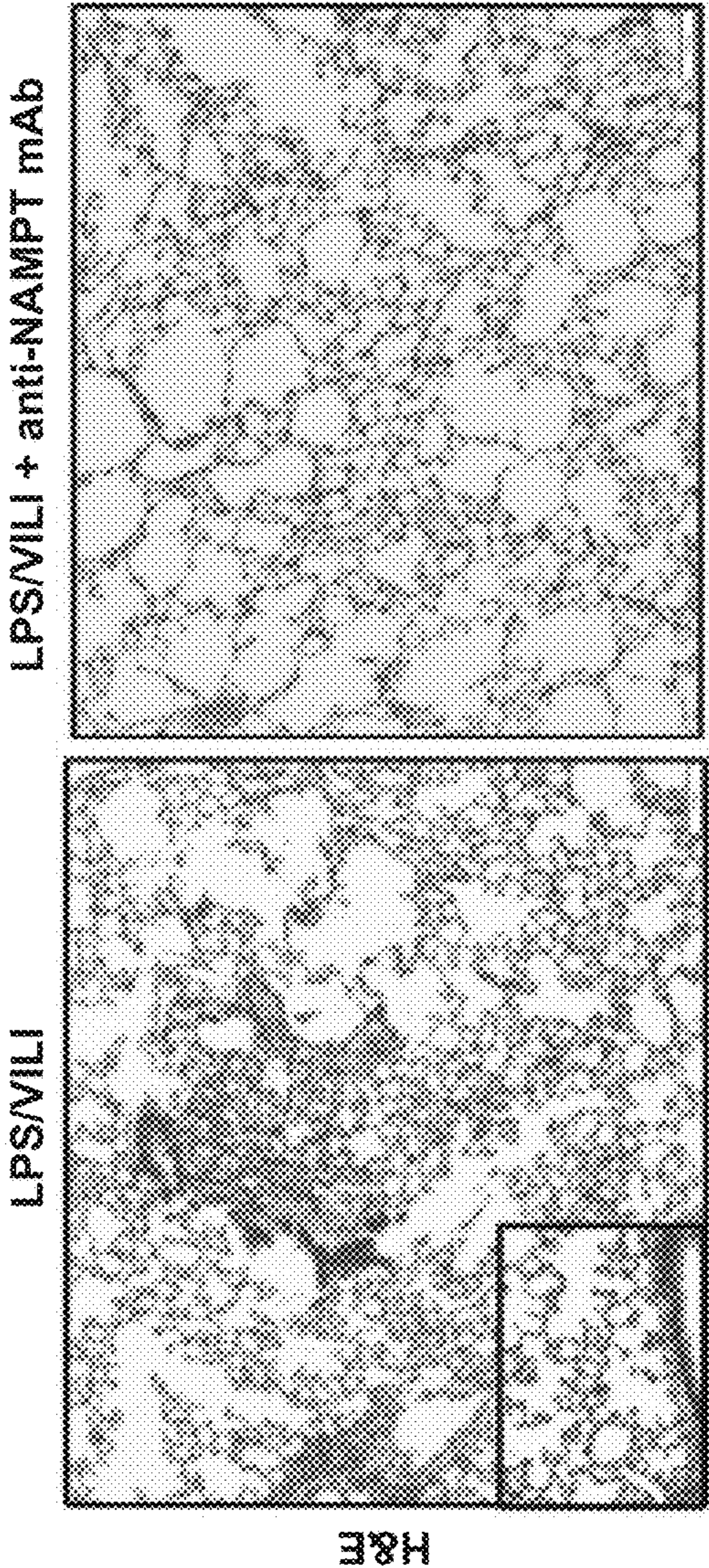


FIG. 18A

FIG. 18B

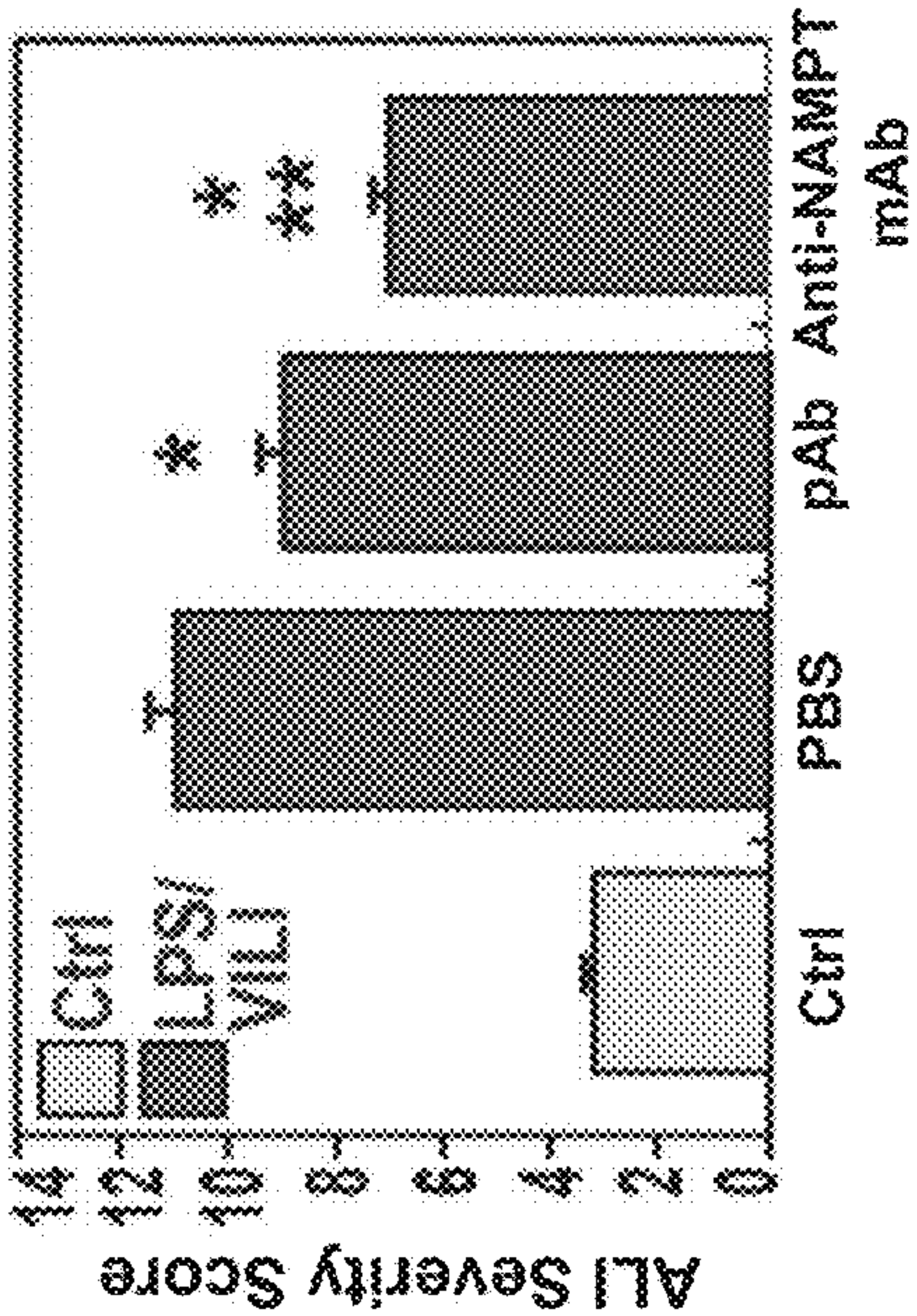


FIG. 18C

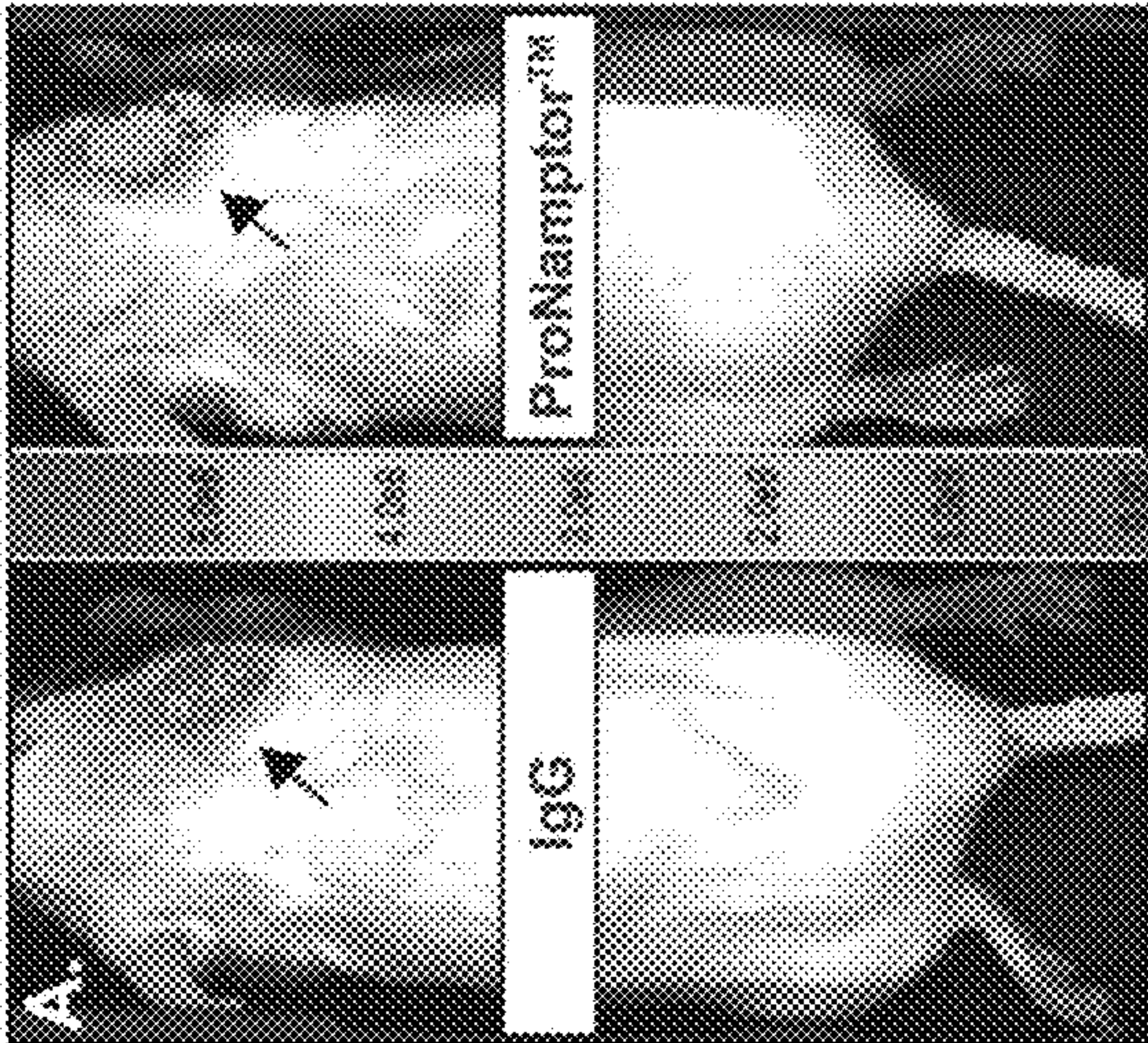


FIG. 19A

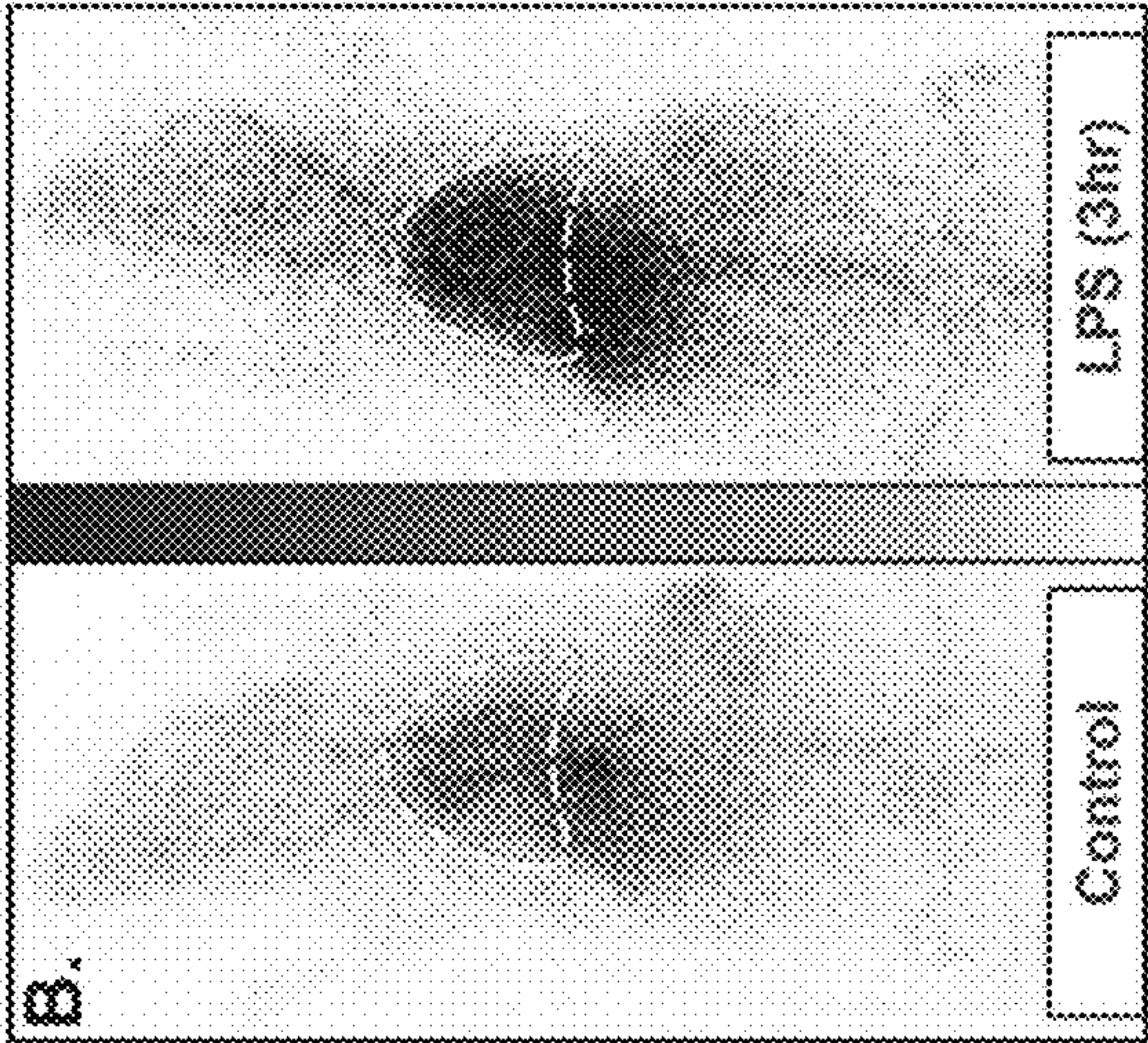


FIG. 19B

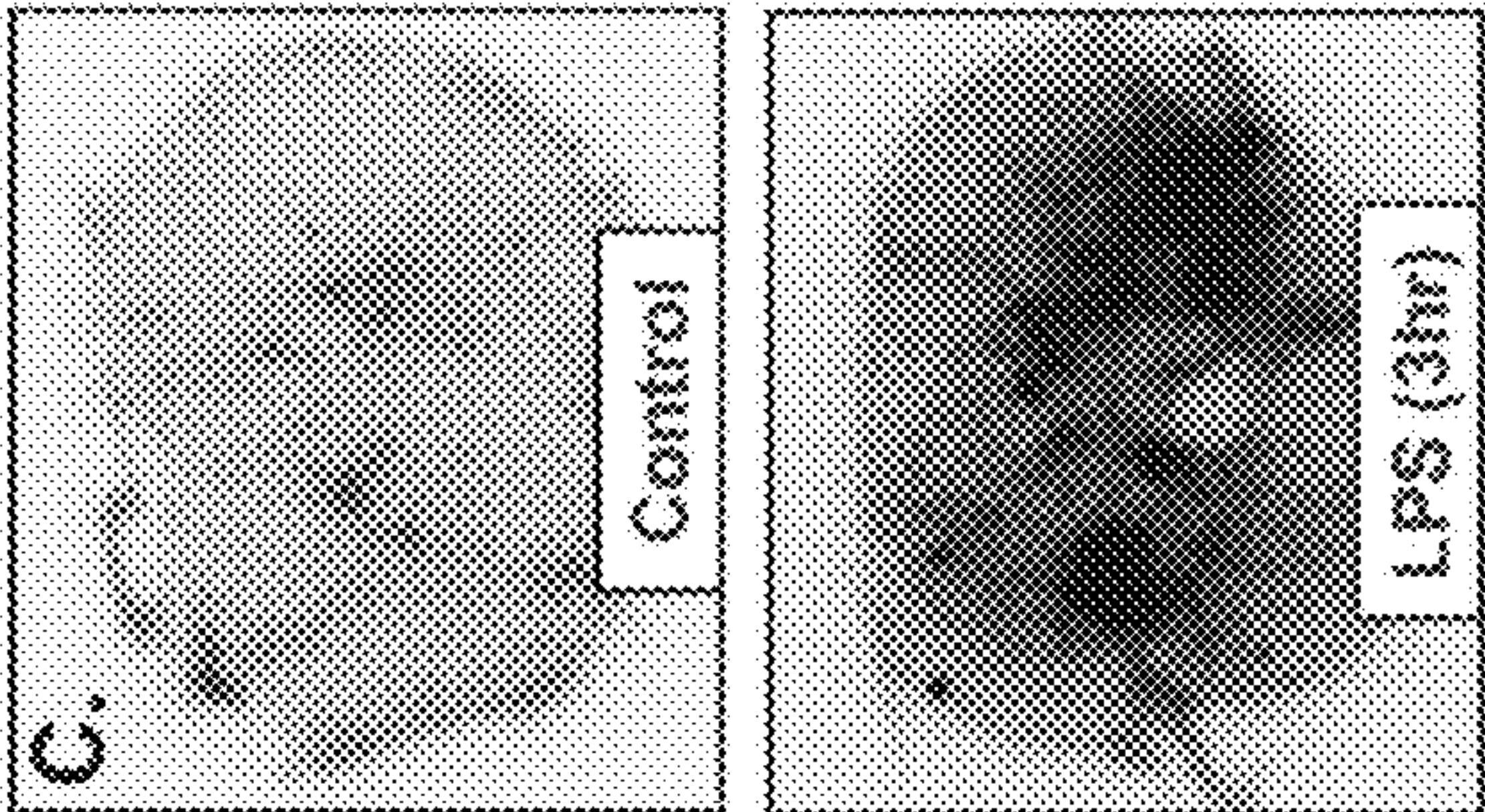


FIG. 19C

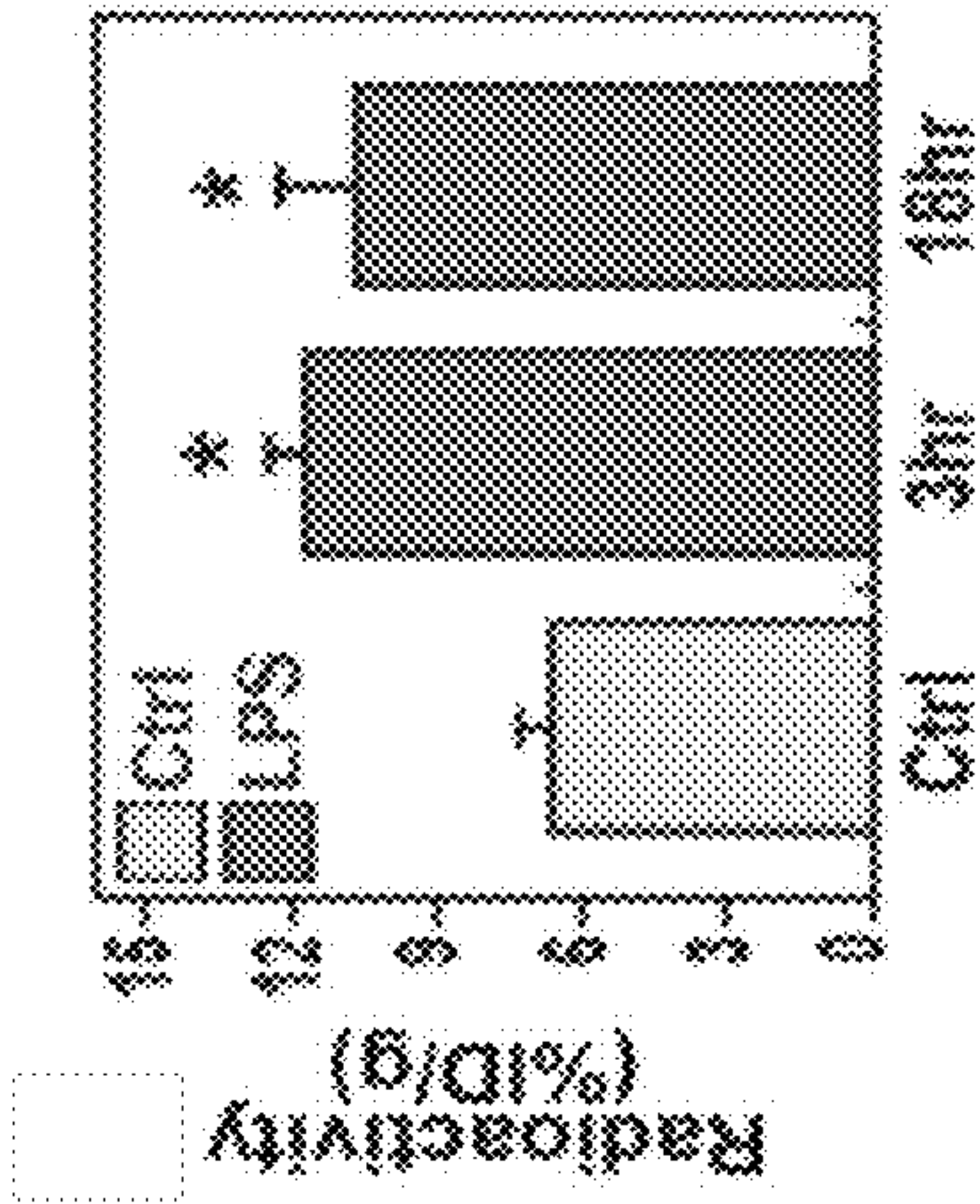


FIG. 19D

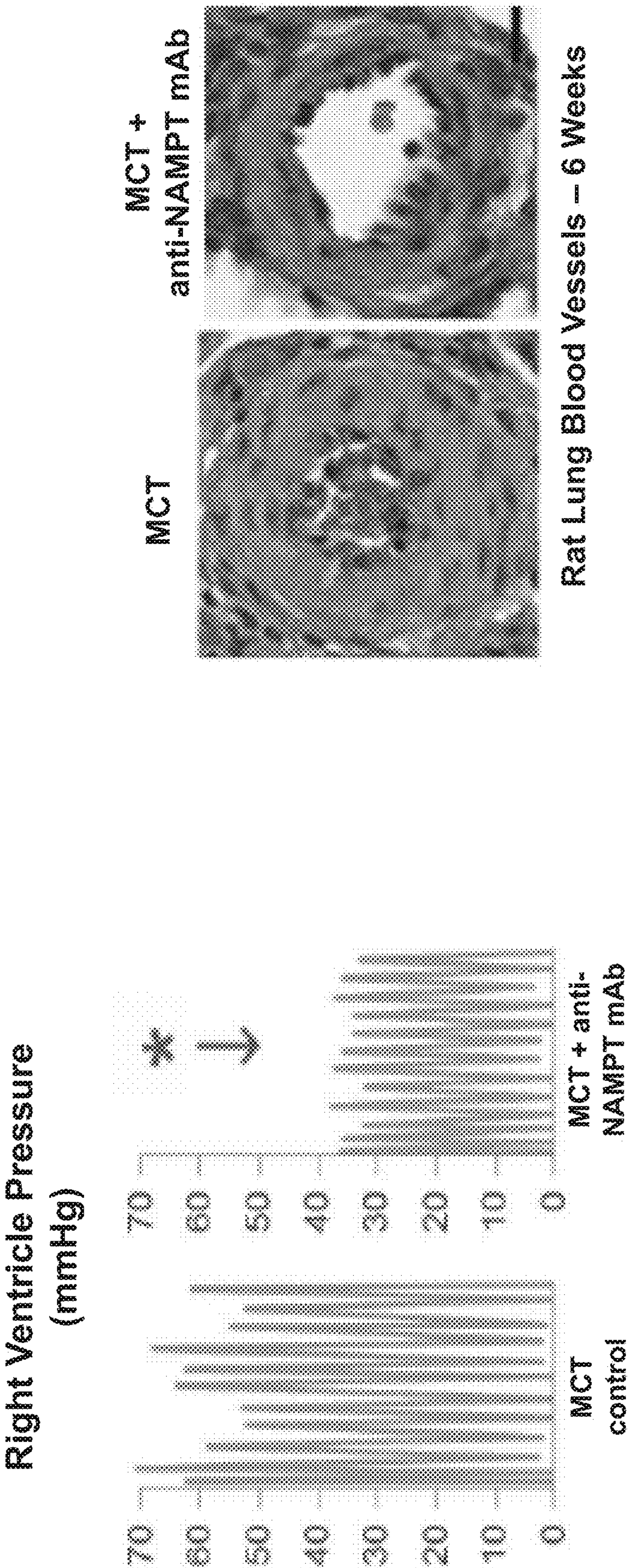


FIG. 20A

FIG. 20B

ANTI-HUMAN NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE (NAMPT) ANTIBODIES

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 17/498,091, filed on Oct. 11, 2021, now issued U.S. Pat. No. 11,466,099, which is a continuation of U.S. application Ser. No. 16/988,383, filed on Aug. 7, 2020, now issued U.S. Pat. No. 11,142,586, which claims priority to U.S. Provisional Application No. 62/883,952, filed on Aug. 7, 2019. The entire contents of the foregoing priority applications are incorporated herein by reference.

FEDERALLY-SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with U.S. government support under grant number R41 HL110707 STTR and R42 HL152888 by National Institutes of Health (NIH). The U.S. government has certain rights in the invention.

SEQUENCE LISTING

[0003] The instant application contains a Sequence Listing which has been submitted electronically in "Sequence Listing XML" format and is hereby incorporated by reference in its entirety. Said "Sequence Listing XML" copy, created on Oct. 10, 2022, is named A105818_1020US.1_SL.xml and is 103 kilobytes in size.

BACKGROUND

[0004] The Nicotinamide phosphoribosyltransferase (NAMPT) gene encodes a protein that catalyzes the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide. The protein belongs to the nicotinic acid phosphoribosyltransferase (NAPRTase) family and is thought to be involved in many important biological processes, including metabolism, stress response and aging.

[0005] Nicotinamide phosphoribosyltransferase (NAMPT) exists as both intracellular NAMPT and extracellular NAMPT (eNAMPT) proteins. eNAMPT is secreted into the blood and functions as a cytokine/enzyme (cytozyme) that activates NF- κ B signaling via ligation of Toll-like receptor 4 (TLR4), further serving as a biomarker for inflammatory lung disorders such as acute respiratory distress syndrome.

SUMMARY OF THE INVENTION

[0006] Provided herein are anti-NAMPT antibodies, including humanized antibodies useful for therapeutic purposes. Currently known therapies for clinical treatment of acute and chronic inflammatory lung disorders (e.g., ARDS, VILI) are merely supportive. Thus, there is an unmet need to in the art for effective prophylactic and therapeutic agents to reduce the morbidity and mortality of inflammatory disorders and observed in patients, particularly in critically ill patients, suffering from these disorders.

[0007] Also provided are methods of treating a subject having Coronavirus disease 2019 (COVID-19) by administering to the subject an effective amount of an isolated

antibody or an antigen-binding fragment thereof that binds to human nicotinamide phosphoribosyltransferase (NAMPT).

[0008] In some embodiments of the above aspect, the antibody or antigen-binding fragment thereof comprises: (i) a heavy chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NOs: 4 or 29; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; and (ii) a light chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6 or 11; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 7, 12, 14, 33, 35 or 37; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8.

[0009] In some embodiments of the aforementioned aspect, the isolated antibody or antigen-binding fragment thereof comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 2, 10, 13, 30, 31, 32, 34 or 36; and/or a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 1, 9, 15, 16 or 28.

[0010] In some embodiments of the above aspect, the subject shows one or more symptoms of COVID-19 and/or is diagnosed with COVID-19.

[0011] In some embodiments of the above aspect, the subject is a human.

[0012] Also provided are isolated antibodies, or an antigen-binding fragments thereof, that specifically binds to human nicotinamide phosphoribosyltransferase (NAMPT), said antibody or antigen-binding fragment thereof comprising: (i) a heavy chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NOs: 4 or 29; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; and (ii) a light chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6 or 11; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 7, 12, 14, 33, 35 or 37; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8.

[0013] In some embodiments of the above aspect, the heavy chain variable region of the isolated antibody, or antigen-binding fragment thereof comprises: (a) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; or (b) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 29, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5.

[0014] In some embodiments, the light chain variable region of the isolated antibody or antigen-binding fragment thereof comprises: (a) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8; (b) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO:

[illegible]

[0015] In some embodiments, the antibody or antigen-binding fragment thereof comprises: (a) a heavy chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; and a light chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8; (b) a heavy chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; and a light chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain having an amino acid sequence as set forth in SEQ

[illegible]

domain having an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; and a light chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 11; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 35; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8; or (j) a heavy chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; and a light chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 11; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 37; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8.

[0016] In some embodiments, the isolated antibody or antigen-binding fragment thereof is humanized.

[0017] In some embodiments, the isolated antibody or antigen-binding fragment thereof comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 2, 10, 13, 30, 31, 32, 34 or 36. In some embodiments, the isolated antibody, or antigen-binding fragment thereof comprises a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 1, 9, 15, 16 or 28.

[0018] In some embodiments, the isolated antibody or the antigen-binding fragment thereof comprises a heavy chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 15, and a light chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 13.

[0019] In some embodiments, the isolated antibody or the antigen-binding fragment thereof comprises a heavy chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 26, and a light chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 18.

[0020] In some embodiments, the isolated antibody or the antigen-binding fragment thereof comprises a heavy chain comprising a variable region as described in Table 17, and a light chain comprising a variable region as described in Table 17.

[0021] In some embodiments, the antibody or the antigen-binding fragment thereof comprises a heavy chain comprising a heavy chain CDR1, CDR2, and CDR3 as described in Table 17, and a light chain comprising a light chain CDR1, CDR2, and CDR3 as described in Table 17.

[0022] Some embodiments comprise an isolated anti-NAMPT antibody which comprises a heavy chain variable region and a light chain variable region of antibody AL-303.

[0023] Some embodiments comprise an isolated anti-NAMPT antibody which comprises a heavy chain variable region and a light chain variable region of antibody AL-310.

[0024] In some embodiments, the isolated antibody or the antigen-binding fragment thereof is an isolated humanized anti-NAMPT antibody comprising a humanized heavy chain variable region derived from murine antibody AL-303 or AL-310, and a humanized light chain variable region derived from murine antibody AL-303 or AL-310.

[0025] In some embodiments, the isolated antibody or the antigen-binding fragment thereof is an isolated anti-

NAMPT antibody that specifically binds to human NAMPT in a homodimeric conformation, wherein the antibody binds an epitope on human NAMPT comprising either: (a) an epitope on human NAMPT comprising at least one amino acid in amino acid residues 17-44 of SEQ ID NO: 60; at least one amino acid in amino acid residues 117-127 of SEQ ID NO: 60; at least one amino acid in amino acid residues 162-170 of SEQ ID NO: 60; at least one amino acid in amino acid residues 242-261 of SEQ ID NO: 60; at least one amino acid in amino acid residues 262-273 of SEQ ID NO: 60; at least one amino acid in amino acid residues 289-305 of SEQ ID NO: 60; at least one amino acid in amino acid residues 332-342 of SEQ ID NO: 60; at least one amino acid in amino acid residues 374-389 of SEQ ID NO: 60; at least one amino acid in amino acid residues 418-425 of SEQ ID NO: 60; at least one amino acid in amino acid residues 453-466 of SEQ ID NO: 60; and at least one amino acid in amino acid residues 408-416 of SEQ ID NO: 60; or (b) an epitope on human NAMPT comprising at least one amino acid in amino acid residues 29-51 of SEQ ID NO: 60; at least one amino acid in amino acid residues 61-72 of SEQ ID NO: 60; at least one amino acid in amino acid residues 156-170 of SEQ ID NO: 60; at least one amino acid in amino acid residues 216-234 of SEQ ID NO: 60; at least one amino acid in amino acid residues 316-331 of SEQ ID NO: 60; at least one amino acid in amino acid residues 332-342 of SEQ ID NO: 60; at least one amino acid in amino acid residues 373-389 of SEQ ID NO: 60; at least one amino acid in amino acid residues 417-431 of SEQ ID NO: 60; at least one amino acid in amino acid residues 454-469 of SEQ ID NO: 60; and at least one amino acid in amino acid residues 470-478 of SEQ ID NO: 60.

[0026] In some embodiments, the isolated antibody or the antigen-binding fragment thereof comprises an Fc domain.

[0027] In some embodiments, the isolated antibody or antigen-binding fragment thereof is a monoclonal antibody.

[0028] In some embodiments, the isolated antibody or antigen-binding fragment thereof is an IgG antibody. In some embodiments, the isolated antibody or antigen-binding fragment thereof is an IgG1 antibody. In some embodiments, the isolated antibody or antigen-binding fragment thereof is an IgG4 antibody.

[0029] Also provided are nucleic acids encoding any of the isolated antibodies or antigen-binding fragments featured herein, a vector comprising the nucleic acid, and/or a host cell comprising the nucleic acid or the vector.

[0030] Also provided are pharmaceutical compositions comprising any of the isolated antibodies or antigen-binding fragments, and a pharmaceutically acceptable carrier.

[0031] Also provided are methods of treating a disorder associated with detrimental NAMPT activity in a subject in need thereof by administering to the subject an effective amount of any of the isolated antibodies or antigen-binding fragments featured herein.

[0032] Also provided are methods of treating a subject having an inflammatory condition, said method comprising administering to the subject an effective amount of an isolated antibody or antigen-binding fragment described herein. In some embodiments, the inflammatory condition is pulmonary fibrosis (IPF), pulmonary hypertension, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), ventilator-induced lung injury (VILI), ARDS/VILI-induced ALI, trauma-induced acute lung injury (TALI) and brain injury, or radiation-induced lung injury

(e.g., radiation-induced lung injury that is caused by radiation associated with cancer therapy).

[0033] Also provided are methods for treating prostate cancer (PCa) in a subject in need thereof, said method comprising administering to the subject an effective amount of any of the isolated antibodies or antigen-binding fragments described herein. In some embodiments, the subject has recurrent PCa. In some embodiments, the subject is at a risk of developing metastatic PCa. In certain embodiments, the PCa is resistant to androgen deprivation therapy (ADT). In some embodiments, the method further includes administering ADT to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] FIG. 1 is a Western blot assay depicting the detection of human and mouse NAMPT by murine anti-NAMPT antibodies AL-303, AL-304, AL-305, AL-309, and AL-310.

[0035] FIG. 2 is a Western blot assay depicting the capacity of murine anti-NAMPT antibodies AL-303, AL-304, AL-305, AL-309, and AL-310mAb, to reduce hNAMPT-induced phosphorylation of NF κ B.

[0036] FIG. 3 is a schematic depiction of experimental protocol for in vivo studies to assess the effect of murine anti-NAMPT antibodies AL-303, AL-304, and AL-305 on NAMPT-induced murine lung injury.

[0037] FIGS. 4A-4B are graphical representations of the effect of murine anti-NAMPT antibodies AL-303, AL-304, and AL-305 on NAMPT-induced murine lung injury. FIG. 4A is a graph showing the effect of the murine anti-NAMPT antibodies on NAMPT-induced bronchoalveolar lavage (BAL) protein levels, and FIG. 4B is a graph showing the effect of the murine anti-NAMPT antibodies on NAMPT-induced BAL-expressing polymorphonuclear neutrophil (PMN) count (n=3-6 mice, *P<0.05).

[0038] FIG. 5 is a schematic depiction of experimental protocol for in vivo studies to assess the effect of murine anti-NAMPT antibody AL-310 on LPS-induced murine lung injury.

[0039] FIG. 6 is a graph showing the effect of murine anti-NAMPT antibody AL-310 on LPS-induced BAL protein levels.

[0040] FIGS. 7A-7B are graphical representations of the effect of humanized 1076 and 1093 anti-hNAMPT antibodies. FIG. 7A is a graphical representation of the effect of humanized 1076 and 1093 anti-hNAMPT antibodies on hNAMPT-induced NF κ B phosphorylation. FIG. 7B is a graphical representation of the effect of humanized 1076 and 1093 anti-hNAMPT antibodies on hNAMPT-induced decline in endothelial cell (EC) barrier integrity.

[0041] FIGS. 8A-8D depict the effect of humanized 1076 and 1093 anti-hNAMPT antibodies on murine and rat models of lung injury. FIG. 8A is a graphical representation of the effect of 1076 anti-hNAMPT antibodies V-1076, N-1076, K-1076, and P-1076 on BAL protein levels (FIG. 8A, left panel) and BAL PMN count (FIG. 8A, right panel) in a mouse model of lung injury.

[0042] FIG. 8B is a graphical representation of the effect of 1093 anti-hNAMPT antibodies SS-1093, CC-1093, XX-1093, and UU-1093 on BAL protein levels (FIG. 8B, left panel) and BAL PMN count (FIG. 8B, right panel) in a mouse model of lung injury. FIG. 8C is a graphical representation of the effect of 1076 anti-hNAMPT antibody P-1076 on BAL protein levels (FIG. 8C, left panel) and BAL PMN count (FIG. 8C, right panel) in a rat model of lung

injury. FIG. 8D depicts H&E stained micrographs showing the effect of 1093 anti-hNAMPT antibody UU-1093 on cell infiltration and edema in a mouse model of lung injury.

[0043] FIGS. 9A-9D show immunohistochemical (IHC) staining for NAMPT in normal, minimally invasive and highly invasive prostate cancer (PCa). FIG. 9A is a micrograph showing extremely low NAMPT expression in normal prostatic gland tissue. FIG. 9B is a micrograph showing significantly increased albeit moderate NAMPT expression in gland-confined prostatic adenocarcinoma. FIG. 9C is a micrograph showing strong NAMPT expression within tumor cells in three separate prostatic adenocarcinomas with smooth muscle capsular penetration and invasion into periprostatic adipose tissue. FIG. 9D is a graph showing cumulative analysis of NAMPT expression in 26 PCa patients with organ-confined (n=12) and capsule invasive disease (n=14).

[0044] FIGS. 10A-10D depict results from analysis of murine and human tissues following acute and subacute radiation. FIG. 10A provides micrographs of H&E staining showing evidence of inflammation and injury of murine lung tissue at 1-week post radiation exposure (FIG. 10A, lower panel), and prior to exposure to a single dose of thoracic radiation (FIG. 10A, upper panel). FIG. 10B provides micrographs of IHC staining showing NAMPT expression in murine lung tissue at 1-week post radiation exposure (FIG. 10B, lower panel), and prior to exposure to radiation (FIG. 10B, upper panel). FIG. 10C is a high magnification image of a micrograph showing NAMPT expression in alveolar macrophages (long arrow) and pneumocytes (short arrow). FIG. 10D depicts micrographs showing NAMPT expression in normal, post-surgical human tonsillar epithelial tissue that were either exposed to 8 Gy radiation for 24 hrs ("Irradiated") (FIG. 10D, lower panel), or not exposed to radiation ("Unirradiated") (FIG. 10D, upper panel).

[0045] FIGS. 11A-11B depict results from in vitro assay of human DU-145 PCa cell migration through human smooth muscle cells. FIG. 11A is a graph showing the number of invading DU-145 PCa cells in absence ("Media Only") or presence ("NAMPT") of NAMPT; medium with no PCa cells ("No PCa Cells") served as negative control. FIG. 11B provides micrographs of wells with PCa cells that were cultured in absence ("Media Only") or presence ("NAMPT") of NAMPT; wells with no PCa cells ("No PCa Cells") served as negative control.

[0046] FIGS. 12A-12C depict results from in vivo testing of 1076 humanized anti-hNAMPT antibodies (N-1076, K-1076, and P-1076) and 1093 humanized anti-hNAMPT antibodies (SS-1093, XX-1093, and UU-1093) on inflammation and injury in murine lung injury models. FIG. 12A is a graph showing the effect of the humanized anti-hNAMPT antibodies on lung injury score in the LPS-induced "one hit" lung injury model. FIG. 12B is a graph showing the effect of the humanized anti-hNAMPT antibodies on lung injury score in the LPS/VILI-induced "two hit" lung injury model. FIG. 12C provides micrographs showing the histological indices of the effect of humanized anti-hNAMPT antibody P-1076 on lung injury in the LPS-induced "one hit" lung injury model (FIG. 12C, upper panel) and LPS/VILI-induced "two hit" lung injury model (FIG. 12C, lower panel).

[0047] FIGS. 13A-13C depict results from in vivo assay of PCa cell invasiveness through diaphragmatic smooth muscle. FIG. 13A is a micrograph showing severe studding

of the peritoneum with invasion through the smooth muscle layer in SCID mice, 6 weeks after intraperitoneal (IP) injection of PC3, a highly metastatic human PCa cell; an enlarged image of the micrograph is provided in FIG. 13A, lower panel. FIG. 13B is a micrograph showing inhibition of PC3 cell invasion in PC3-injected mice that received a humanized anti-hNAMPT antibody, P-1076; an enlarged image of the micrograph is provided in FIG. 13B, lower panel. FIG. 13C is a graph showing the percent of PC3 cells invading the diaphragm in mice that were treated with the anti-hNAMPT antibody P-1076, or vehicle alone.

[0048] FIGS. 14A-14E depict the effects of NAMPT-neutralizing antibodies on lung inflammation (assessed by H&E staining), amount of BAL protein and count of BAL-expressing cells, as evaluated in a murine model of RILI. FIG. 14A provides representative micrographs showing H&E staining in lung tissues of non-irradiated control mice (inset of FIG. 14A, left panel) or irradiated RILI mice that were injected with vehicle control (FIG. 14A, left panel), an anti-NAMPT polyclonal antibody (pAb) (FIG. 14A, middle panel), or an anti-NAMPT monoclonal antibody (mAb) (FIG. 14A, right panel) post radiation exposure. FIG. 14B is a graphical depiction of H&E staining (% area) in lung tissue of non-irradiated control mice or irradiated RILI mice that were injected with vehicle control, anti-NAMPT pAb, or anti-NAMPT mAb. FIG. 14C is a graphical representation of BAL protein levels ($\mu\text{g/ml}$) in lung tissues of non-irradiated control mice or irradiated RILI mice that were injected with vehicle control, anti-NAMPT pAb, or anti-NAMPT mAb. FIG. 14D is a graphical representation of number of BAL-expressing cells in lung tissues of non-irradiated control mice or irradiated RILI mice that were injected with vehicle control, anti-NAMPT pAb, or anti-NAMPT mAb. FIG. 14E is a graphical representation of ALI severity score of non-irradiated control mice or irradiated RILI mice that were injected with vehicle control, anti-NAMPT pAb, or anti-NAMPT mAb. * indicates $p < 0.05$

[0049] FIGS. 15A-15D depict detection of NAMPT expression by ^{99m}Tc -labeled anti-NAMPT mAb probe. FIG. 15A provides representative autoradiograph images depicting detection of NAMPT expression by the ^{99m}Tc -labeled anti-NAMPT mAb probe in a non-irradiated control mouse (FIG. 15A, left panel) or in an irradiated (RILI) mouse exposed to 8Gy partial body irradiation (PBI) (FIG. 15A, right panel). FIG. 15B provides representative autoradiograph images depicting detection of NAMPT expression by the ^{99m}Tc -labeled anti-NAMPT mAb probe in a non-irradiated control mouse (FIG. 15B, top panel) or in an irradiated (RILI) mouse (FIG. 15B, bottom panel). FIG. 15C is a graphical representation of ratio of lung activity over tissue background from left and right lungs of non-irradiated control mice or irradiated (RILI) mice. FIG. 15D is a graphical representation of radioactivity (% ID/g) in lung tissues of non-irradiated control mice or irradiated (RILI) mice. * indicates $p < 0.05$

[0050] FIGS. 16A-16C depict the effects of a humanized anti-NAMPT mAb on BAL cell count, collagen deposition, and expression of lung tissue smooth muscle actin (SMA), as evaluated in a murine model of RILI 18 weeks after 20Gy radiation exposure. FIG. 16A is a graph depicting number of BAL-expressing cells in lung tissues of irradiated RILI mice that were intraperitoneally injected with anti-NAMPT mAb or vehicle control. FIG. 16B provides representative images from western blot analyses showing expression of SMA in

lung tissue homogenate of irradiated RILI mice that were intraperitoneally injected with anti-NAMPT mAb or vehicle control. FIG. 16C provides representative micrographs showing collagen deposition, as detected by Trichrome staining, in lung tissue of irradiated RILI mice that were intraperitoneally injected with anti-NAMPT mAb or vehicle control. * indicates $p < 0.05$.

[0051] FIGS. 17A-17C depict the effects of a humanized anti-NAMPT mAb on inflammatory cell infiltration, edema and lung injury score, as evaluated in a rat model of trauma (blast)/ventilation-induced lung injury (VILI). FIG. 17A provides representative images and micrographs showing lung or lung tissue section of trauma/VILI challenged rats that were injected with vehicle control. The left panel of FIG. 17A provides representative image of lung from trauma/VILI challenged rats injected with vehicle control. The middle and right panels of FIG. 17A provides representative micrographs showing inflammatory cell infiltration and edema, as assessed by H&E staining, in trauma/VILI challenged rats injected with vehicle control. The inset of the rightmost panel of FIG. 17A provides representative micrograph showing H&E staining in lung tissue of rats not challenged with trauma/VILI. FIG. 17B provides representative images and micrographs showing lung or lung tissue section of trauma/VILI challenged rats that were injected with anti-NAMPT mAb. The left panel of FIG. 17B provides representative image of lung from trauma/VILI challenged rats injected with anti-NAMPT mAb. The middle and right panels of FIG. 17B provides representative micrographs showing inflammatory cell infiltration and edema, as assessed by H&E staining, in trauma/VILI challenged rat injected with anti-NAMPT mAb. FIG. 17C is a graph depicting lung injury score of trauma/VILI challenged rats that were injected with either anti-NAMPT mAb or vehicle control.

[0052] FIGS. 18A-18C depict the effects of NAMPT-neutralizing antibodies on inflammatory cell infiltration, edema and lung injury score, as evaluated in a murine LPS/VILI lung injury model. FIG. 18A provides a representative micrograph showing inflammatory cell infiltration and edema, as assessed by H&E staining, in LPS/VILI challenged mouse injected with vehicle control. The inset of FIG. 18A provides representative a micrograph showing H&E staining in lung tissue from mouse not challenged with LPS/VILI. FIG. 18B provides a representative micrograph showing inflammatory cell infiltration and edema, as assessed by H&E staining, in LPS/VILI challenged mouse injected with anti-NAMPT mAb. FIG. 18C is a graph depicting ALI severity score as assessed in LPS/VILI challenged mice that were injected with anti-NAMPT mAb, anti-NAMPT pAb or vehicle control (PBS). The graph in FIG. 18C also depicts ALI severity score of control mice that were not challenged with LPS/VILI. * indicates $p < 0.05$; *** indicates $p < 0.001$.

[0053] FIGS. 19A-19D depict detection of NAMPT expression by ^{99m}Tc -labeled anti-NAMPT mAb probe. FIG. 19A provides representative autoradiograph images depicting detection of NAMPT expression by the ^{99m}Tc -labeled anti-NAMPT mAb probe (PRONAMPTOR) (FIG. 19A, right panel) or a radiolabeled IgG control Ab (FIG. 19A, left panel) in mice that were exposed to 20Gy total lung irradiation (WTLI). FIG. 19B provides representative autoradiograph images depicting detection of NAMPT expression by the ^{99m}Tc -labeled anti-NAMPT mAb probe in LPS

challenged mouse 3 hours after LPS challenge (FIG. 19B, right panel) or in a non-challenged control mouse (FIG. 19B, left panel). FIG. 19C provides representative autoradiograph images depicting detection of NAMPT expression by the ^{99m}Tc -labeled anti-NAMPT mAb probe in lung of LPS challenged mouse 3 hours after LPS challenge (FIG. 19C, bottom panel) or in lung of a non-challenged control mouse (FIG. 18C, top panel). FIG. 19D is a graphical representation of uptake of the radiolabeled anti-NAMPT mAb probe, as assessed by radioactivity (% ID/g), in lung tissues of LPS challenged mouse at 3 hours and 18 hours post LPS challenge or in lung tissues of non-challenged control mice. * indicates $p < 0.05$.

[0054] FIGS. 20A-20B depict effects of a humanized anti-NAMPT mAb on right ventricular systolic pressure (RVSP) and pulmonary artery thickness, as evaluated in a rat monocrotaline (MCT) model of PAH. FIG. 20A is a graphical representation of RVSP in MCT-challenged rats that were injected with either anti-NAMPT mAb or vehicle control (control MCT mice). FIG. 20B provides representative micrographs showing pulmonary artery thickness, as assessed by H&E staining, in MCT-challenged rats that were injected with either anti-NAMPT mAb (FIG. 20B, right panel) or vehicle control (FIG. 20B, left panel). * indicates $p < 0.05$.

DETAILED DESCRIPTION OF THE INVENTION

[0055] The invention may be embodied in many different forms. Disclosed herein are non-limiting, illustrative embodiments of the invention that exemplify the principles thereof. Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. For the purposes of the instant disclosure all identifying sequence accession numbers may be found in the NCBI Reference Sequence (REF SEQ) database and/or the NCBI GenBank® archival sequence database unless otherwise noted.

[0056] Various aspects of the invention relate to anti-NAMPT antibodies and antibody fragments, and pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such antibodies and fragments. Methods of using the antibodies described herein to detect human NAMPT, to inhibit human NAMPT activity (in vitro or in vivo), and to treat NAMPT-related disease, including, but not limited to, pulmonary fibrosis (IPF), pulmonary hypertension, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), ventilator-induced lung injury (VILI), ARDS/VILI-induced ALI, trauma-induced acute lung injury (TALI) and brain injury, radiation-induced lung injury, and cancer (e.g., prostate cancer (PCa)), which are also encompassed by the invention.

Definitions

[0057] In order that the invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

[0058] The term “NAMPT” or “eNAMPT”, used interchangeably herein, refers to the secreted form of nicotina-

mid phosphoribosyltransferase unless specifically mentioned to relate to a non-secreted form (e.g., intracellular NAMPT or NAMPT nucleic acids). The amino acid sequence of secreted human NAMPT (also referred to as human eNAMPT) is provided below as SEQ ID NO: 60 (see also NCBI Gene Ref. No. NC_000007.14 and Protein Ref. No. NP_005737.1).

(SEQ ID NO: 60)

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MNPAAEAEFN ILLATDSYKV THYKQYPPNT SKVYSYFECR
EKKTENSKLR KVKYEETVIFY GLQYILNKYL KGKVVTKEDI
QEAKDVYKEH FQDDVFNEKG WNYILEKYDG HLPDIEIKAVP
EGFVIPRGNV LFTVENTDPE CYWLTNWIET ILVQSWYPIT
VATNSREQKK ILAKYLLETS GNLDGLETKL HDFGYRGVSS
QETAGIGASA HLVNFKGTDI VAGLALIKKY YGTDKDPVPGY
SVPAAEHSTI TAWGKDHEKD AFEHIVTQFS SVPVSVVSIDS
YDIYNACEKI WGEDLRHLIV SRSTQAPLII RPDGSGNPLDT
VLKVLLEILGK KFPVTENSKG YKLLPPYLRV IQGDGVDINT
LQEIIVEGMKQ KMWSIENIAF GSGGGLLQKL TRDLLNCSFK
CSYVVTNGLG INVFKDPVAD PNKRSKKGRL SLHRTAGNF
VTLEEGKGDL EEEYQDILLHT VFKNGKVTKS YSFDEIRKNA
QLNIELEAAHH

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NAMPT is also referred to as pre-B cell colony enhancing factor (PBEF) or visfatin.

[0059] The terms “NAMPT antibody” or “anti-NAMPT antibody”, used interchangeably herein, refer to an antibody that specifically binds to the secreted form of NAMPT (also referred to herein as eNAMPT). An antibody “which binds” an antigen of interest, i.e., NAMPT, is one capable of binding that antigen with sufficient affinity such that the antibody is useful in targeting a cell expressing the antigen. In a preferred embodiment, the antibody specifically binds to human NAMPT (hNAMPT), particularly extracellular human NAMPT (human eNAMPT). Examples of anti-eNAMPT antibodies are disclosed in the examples and in the Sequence Table provided below.

[0060] “Biological activity of NAMPT” as used herein, refers to all inherent biological properties of NAMPT, including, but not limited to, binding to TLR4.

[0061] The term “specifically binds,” or “binds specifically to”, or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen, e.g., NAMPT, that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about 1×10^{-8} M or less (e.g., a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like.

[0062] The term “antibody” broadly refers to an immunoglobulin (Ig) molecule, generally comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment, mutant, variant, or derivative thereof, that retains the essential target binding features of an Ig molecule. Such mutant, variant, or deriva-

tive antibody formats are known in the art. Non-limiting embodiments of which are discussed below.

[0063] In a full-length antibody, each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region.

[0064] Both the light and heavy chains are divided into regions of structural and functional homology. The terms “constant” and “variable” are used functionally. In this regard, it will be appreciated that the variable domains of both the variable light (VL) and variable heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention the numbering of the constant region domains increases as they become more distal from the antigen binding site or amino-terminus of the antibody. The N-terminal portion is a variable region and at the C-terminal portion is a constant region; the CH3 (or CH4 in the case of IgM) and CL domains actually comprise the carboxy-terminus of the heavy and light chain, respectively.

[0065] The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Immunoglobulin molecules can be of any class (e.g., IgG, IgE, IgM, IgD, IgA and IgY) and isotype (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. Light chains are classified as either kappa or lambda (κ , λ).

[0066] The “complementarity determining regions” or “CDRs” present in an antibody antigen-binding domain are each short, non-contiguous sequences of amino acids that are specifically positioned to form the binding domain as the antibody assumes its three dimensional configuration in an aqueous environment. The remainder of the amino acids in the binding domain of an antibody, referred to as “framework” or “FW” regions, show less inter-molecular variability. The binding domain formed by the positioned CDRs defines a surface complementary to the epitope on the immunoreactive antigen. This complementary surface promotes the non-covalent binding of the antibody to its cognate epitope. The amino acids that make up the CDRs and the framework regions, respectively, can be readily identified for any given heavy or light chain variable region by one of ordinary skill in the art, since they have been defined in various different ways as described below. Exemplary CDRs are provided herein. However, CDRs can also be defined according to Kabat, Chothia, Martin, PyIgClassify, or IMGT. Exemplary CDR definitions are described in Chiu et al, “Antibody Structure and Function: The Basis for Engineering Therapeutics,” *Antibodies*, 8(55): 1-80 (2019), which is incorporated herein by reference in its entirety.

[0067] For heavy chain constant region amino acid positions discussed in the invention, numbering is according to the EU index first described in Edelman et al., 1969, *Proc.*

Natl. Acad. Sci. USA 63(1): 78-85 describing the amino acid sequence of the myeloma protein Eu, which reportedly was the first human IgG1 sequenced. The EU index of Edelman is also set forth in Kabat et al., 1991 (supra.). Thus, the terms “EU index as set forth in Kabat” or “EU index of Kabat” or “EU index” or “EU numbering” in the context of the heavy chain refers to the residue numbering system based on the human IgG1 Eu antibody of Edelman et al. as set forth in Kabat et al., 1991 (supra.) The numbering system used for the light chain constant region amino acid sequence is similarly set forth in Kabat et al., (supra.) An exemplary kappa light chain constant region amino acid sequence compatible with the present disclosure is set forth immediately below:

(SEQ ID NO: 59)

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK
SFNRGEC

Similarly, an exemplary IgG1 heavy chain constant region amino acid sequence compatible with the present invention is set forth immediately below:

(SEQ ID NO: 58)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGLV
HTFPAVLQSSGLYSLSSVTVTTPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYCKKVSNNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL
LVKGFFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW
QQGNVVFSCSVMEALHNHYTQKSLSLSPGK

[0068] The term “antigen binding portion” or “binding fragment” of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hNAMPT). It has been shown that the antigen binding function of an antibody can be performed by fragments of a full-length antibody. Such antibody embodiments may also be bispecific, dual specific, or multi-specific formats; specifically binding to two or more different antigens. Examples of binding fragments encompassed within the term “antigen binding portion” of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) *Nature* 341:544-546, Winter et al., PCT publication WO 90/05144 A1 herein incorporated by reference), which comprises a single variable domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules

(known as single chain Fv (scFv); see e.g., Bird et al. (1988) *Science* 242:423-426; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term “antigen binding portion” of an antibody. In certain embodiments of the invention, scFv molecules may be incorporated into a fusion protein. Other forms of single chain antibodies, such as diabodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak, R. J., et al. (1994) *Structure* 2:1121-1123). Such antibody binding portions are known in the art (Kontermann and Dubel eds., *Antibody Engineering* (2001) Springer-Verlag, New York. 790 pp. (ISBN 3-540-41354-5).

[0069] A “fully human” antibody comprises an antibody variable domain that has a sequence derived from a human immunoglobulin (e.g., obtained from a human immunoglobulin coding sequence). The term “human antibody” includes, for example, antibodies having variable and constant regions (if present) derived from human germline immunoglobulin sequences. The term “human” as applied herein to an antibody or to a fragment such as a variable domain does not encompass an antibody from another species, e.g., mouse, that has been “humanized” through grafting of human constant region sequences onto an antibody polypeptide (i.e., replacing non-human constant regions with human constant regions) or through grafting of human V region framework sequences onto an immunoglobulin variable domain from a non-human mammal (i.e., replacing non-human framework regions of a V domain with human framework regions). Methods of humanizing immunoglobulin variable regions through rational modification of complementarity determining residues have been described (US 2006/0258852).

[0070] The term “humanized antibody” designates antibodies from a non-human species having one or more complementarity determining regions (CDRs) from said non-human species and a framework region from a human immunoglobulin molecule. Humanized antibodies may optionally further comprise one or more framework residues derived from the non-human species from which the CDRs were derived. Such framework sequences can be obtained from public DNA database covering germline antibody gene sequences or from published references. For example, germline DNA sequences of human heavy and light chain variable region genes can be found in “VBase” human germline sequence database (available on the world wide web (www) at mrcpe.com.ac.uk/vbase), as well as can be found in Kabat, E A, et al, 1991 *Sequences of Proteins of Immunological Interest*, 5th Ed. To avoid the decrease in the activity during immunogenicity reduction, the variable region frame sequence of the human antibody is subjected to a minimum back mutation to maintain the activity.

[0071] The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including without limitation IgG1, IgG2, IgG3 and IgG4. The humanized antibody may comprise sequences from more than one class or isotype, and

particular constant domains may be selected to optimize desired effector functions using techniques well-known in the art.

[0072] The term “multispecific” antibody refers to an antibody that has binding domains for two or more different epitopes within a single antibody molecule. Other binding molecules in addition to the canonical antibody structure can be constructed with two binding specificities. Epitope binding by bispecific or multispecific antibodies can be simultaneous or sequential. Triomas and hybrid hybridomas are two examples of cell lines that can secrete bispecific antibodies. Bispecific antibodies can also be constructed by recombinant means. (Strohlein and Heiss, *Future Oncol.* 6:1387-94 (2010); Mabry and Snavely, *IDrugs*. 13:543-9 (2010)). A bispecific antibody can also be a diabody.

[0073] The term “labeled antibody” as used herein, refers to an antibody, or an antigen binding portion thereof, with a label incorporated that provides for the identification of the binding protein, e.g., an antibody. Preferably, the label is a detectable marker, e.g., incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^3H , ^{14}C , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I , ^{177}Lu , ^{166}Ho , or ^{153}Sm); fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, luciferase, alkaline phosphatase); chemiluminescent markers; biotinyl groups; predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags); and magnetic agents, such as gadolinium chelates.

[0074] A “conservative amino acid substitution” is one in which one amino acid is replaced with another amino acid having a similar side chain. Families of amino acids having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). For example, substitution of a phenylalanine for a tyrosine is a conservative substitution. In certain embodiments, conservative substitutions in the sequences of the polypeptides and antibodies of the present disclosure do not abrogate the binding of the polypeptide or antibody containing the amino acid sequence to the antigen to which the binding molecule binds. Methods of identifying nucleotide and amino acid conservative substitutions which do not eliminate antigen-binding are well-known in the art (see, e.g., Brummell et al., *Biochem.* 32: 1180-1187 (1993); Kobayashi et al., *Protein Eng.* 12(10):879-884 (1999); and Burks et al., *Proc. Natl. Acad. Sci. USA* 94:412-417 (1997)).

[0075] The term “polynucleotide” is intended to encompass a singular nucleic acid as well as plurality of nucleic acids, and refers to an isolated nucleic acid molecule or construct, e.g., messenger RNA (mRNA), cDNA, or plasmid DNA (pDNA). A polynucleotide can comprise a conven-

tional phosphodiester bond or a non-conventional bond (e.g., an amide bond, such as found in peptide nucleic acids (PNA)). The terms “nucleic acid” or “nucleic acid sequence” refer to any one or more nucleic acid segments, e.g., DNA or RNA fragments, present in a polynucleotide.

[0076] By an “isolated” nucleic acid or polynucleotide is intended any form of the nucleic acid or polynucleotide that is separated from its native environment. For example, gel-purified polynucleotide, or a recombinant polynucleotide encoding a polypeptide contained in a vector would be considered to be “isolated.” Also, a polynucleotide segment, e.g., a PCR product, which has been engineered to have restriction sites for cloning is considered to be “isolated.” Further examples of an isolated polynucleotide include recombinant polynucleotides maintained in heterologous host cells or purified (partially or substantially) polynucleotides in a non-native solution such as a buffer or saline. Isolated RNA molecules include in vivo or in vitro RNA transcripts of polynucleotides, where the transcript is not one that would be found in nature. Isolated polynucleotides or nucleic acids further include such molecules produced synthetically. In addition, polynucleotide or a nucleic acid can be or can include a regulatory element such as a promoter, ribosome binding site, or a transcription terminator.

[0077] The term “expression” as used herein refers to a process by which a gene produces a biochemical, for example, a polypeptide. The process includes any manifestation of the functional presence of the gene within the cell including, without limitation, gene knockdown as well as both transient expression and stable expression. It includes without limitation transcription of the gene into messenger RNA (mRNA), and the translation of such mRNA into polypeptide(s). If the final desired product is a biochemical, expression includes the creation of that biochemical and any precursors. Expression of a gene produces a “gene product.” As used herein, a gene product can be either a nucleic acid, e.g., a messenger RNA produced by transcription of a gene, or a polypeptide which is translated from a transcript. Gene products described herein further include nucleic acids with post transcriptional modifications, e.g., polyadenylation, or polypeptides with post translational modifications, e.g., methylation, glycosylation, the addition of lipids, association with other protein subunits, proteolytic cleavage, and the like.

[0078] As used herein, a “neutralizing antibody”, (e.g., an “antibody that inhibits NAMPT activity”), is intended to include to an antibody whose binding to NAMPT results in inhibition of the biological activity of NAMPT. A neutralizing antibody will substantially inhibit binding of NAMPT to its ligand or substrate when an excess of antibody reduces the quantity of binding partner bound to the determinant by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more as measured, for example, by target molecule activity or in an in vitro competitive binding assay. It will be appreciated that the modified activity may be measured directly using art recognized techniques or may be measured by the impact the altered activity has downstream. This inhibition of the biological activity of NAMPT, or its ligands, can be assessed by measuring one or more indicators of NAMPT biological activity, such as quantities of extracellular NAMPT (either in vitro or in vivo), NAMPT-induced cellular activation (e.g., NFκB phosphorylation) and NAMPT binding to NAMPT ligands. These

indicators of NAMPT biological activity can be assessed by one or more of several standard in vitro or in vivo assays known in the art (see Examples). For example, in some embodiments, the ability of an antibody to inhibit NAMPT activity is assessed by inhibition of NAMPT-induced activation of endothelial cells. As an additional or alternative parameter of NAMPT activity, the ability of an antibody to inhibit NAMPT-induced transcription activities via NFκB as a measure of NAMPT-induced cellular activation, can be assessed.

[0079] Terms such as “treating” or “treatment” or “to treat” or “alleviating” or “to alleviate” refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt or slow the progression of an existing diagnosed pathologic condition or disorder. Such treatment can include, but does not require, a total elimination of all symptoms or a cure of the disease. Terms such as “prevent,” “prevention,” “avoid,” “deterrence” and the like refer to prophylactic or preventative measures that prevent the development of an undiagnosed targeted pathologic condition or disorder. Thus, “those in need of treatment” can include those already with the disorder; those prone to have the disorder; those at risk of developing the disorder; and those in whom the disorder is to be prevented.

[0080] By “subject” or “individual” or “animal” or “patient” or “mammal,” is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. Mammalian subjects include humans, domestic animals, farm animals, and zoo, sports, or pet animals such as dogs, cats, guinea pigs, rabbits, rats, mice, horses, swine, cows, bears, and so on.

[0081] As used herein, phrases such as “a subject that would benefit from therapy” and “an animal in need of treatment” includes subjects, such as mammalian subjects, that would benefit from administration of an anti-NAMPT antibody (e.g., a humanized anti-NAMPT antibody). Such antibodies, can be used, e.g., for a diagnostic procedure and/or for treatment or prevention of a disease, e.g., inflammatory lung disorder or cancer (e.g., prostate cancer).

[0082] The terms “effective amount” and “therapeutically effective amount” are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result. Such results may include, but are not limited to, the inhibition of NAMPT expression or activity, or the expression or activity of signaling molecules which are downstream of NAMPT as determined by any means suitable in the art. For example, NAMPT activity includes but is not limited to cytokine activity, nicotinamide phosphoribosyltransferase activity, chemotactic factor, NF-κB signaling activity, redox signaling activity, and/or a role in mitochondrial function and apoptosis. It is emphasized that a therapeutically effective amount will not always be effective in treating a condition, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art. For convenience only, exemplary dosages, drug delivery amounts, therapeutically effective amounts and therapeutic levels are provided herein with reference to adult human subjects. Those skilled in the art can adjust such amounts in accordance with standard practices as needed to treat a specific subject and/or condition.

Anti-NAMPT Antibodies

[0083] As provided herein, the present disclosure relates to anti-nicotinamide phosphoribosyltransferase (NAMPT) antibodies, or antigen binding fragments thereof, including compositions, methods, and articles of manufacture (e.g., kits, systems) comprising the same for prophylactic and therapeutic uses in patients suffering from NAMPT-associated local and systemic inflammatory disorders. Also described are nucleic acids including polynucleotide sequences that encode such antibodies. In particular embodiments, the monoclonal antibodies provided herein bind to extracellular NAMPT (eNAMPT), and prevent Toll-like receptor 4 (TLR4) activation, thereby reducing or blocking one or more downstream signal transduction pathways and the consequent systemic and lung inflammation in specific respiratory disorders.

[0084] The NAMPT gene product is the rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD⁺) salvage pathway that converts nicotinamide to nicotinamide mononucleotide in mammals to enable NAD⁺ biosynthesis. The mature form of the extracellular NAMPT protein is a homodimer of approximately 120 kDa (Takahashi, et al., *J. Biochem.* 147: 95-107 (2010)). It has been established that mutations which reduce or inhibit the function of the NAMPT enzyme can reduce the pathophysiological processes that give rise to disorders such as leukemia and pulmonary arterial hypertension (PAH).

[0085] The human NAMPT gene (NAMPT) is located at chromosome 7, (segment 7q22.3; base pairs 106,248,285 to 106,286,326). Nucleic acid sequences for the human NAMPT gene product are known in the art. See, for example, NCBI Reference Sequence: NM_005746.2, *Homo sapiens* nicotinamide phosphoribosyltransferase (NAMPT), mRNA (see also Samal, et al., *Mol. Cell. Biol.* 14 (2), 1431-1437 (1994)). Amino acid sequences of the human NAMPT enzyme are known in the art. See, for example, GenBank® Accession No. NP_005737.1. NAMPT has been shown to increase the production of IL-6, TNF- α , and IL-1 β in CD14⁺ monocytes, macrophages, and dendritic cells, enhance the effectiveness of T cells, and be involved in the development of both B and T lymphocytes (Sun, et al., *Cytokine & Growth Factor Reviews* 24(5):433-442 (2013)). A NAMPT enzyme crystal structure is described in detail in Kim, et al. *J. Mol. Biol.*; 362:66-77 (2006).

[0086] The receptor for NAMPT is the Toll-like receptor 4 (TLR4), a protein that in humans is encoded by the TLR4 gene. TLR4 is a transmembrane protein and a member of the toll-like receptor family, which belongs to the pattern recognition receptor (PRR) family. Its activation leads to an intracellular NF- κ B signaling pathway and inflammatory cytokine production which is responsible for activating the innate immune system. It is most well-known for recognizing lipopolysaccharide (LPS), a component present in many Gram-negative bacteria (e.g. *Neisseria* spp.) and select Gram-positive bacteria. Its ligands also include several viral proteins, polysaccharide, and a variety of endogenous proteins such as low-density lipoprotein, beta-defensins, and heat shock protein. The human TLR4 gene (TLR4) is located at chromosome 9, (segment 9q32-q33) (Georgel, et al., *PLoS ONE* 4(11): e7803 (2009)). Nucleic acid sequences for the human TLR4 gene product are known in the art. See, for example, NCBI Reference Sequence: AAY82268.1, *Homo sapiens* toll-like receptor 4 (TLR4), mRNA. Amino acid

sequences of the human TLR4 are known in the art. See, for example, GenBank® Accession No. AAY82268.

[0087] In certain aspects, the present disclosure provides a humanized 1076 anti-hNAMPT antibody or antigen-binding fragment thereof. Examples of anti-NAMPT antibodies are provided below.

[0088] Anti-NAMPT antibody D-1076: D-1076 has (i) a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 1, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5; and (ii) a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 2, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8.

[0089] Anti-NAMPT antibody G-1076: G-1076 has (i) a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 9, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5; and (ii) a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 10, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 12, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8.

[0090] Anti-NAMPT antibody K-1076: K-1076 has (i) a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 9, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5; and (ii) a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 13, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 14, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8.

[0091] Anti-NAMPT antibody N-1076: N-1076 has (i) a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 15, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5; and (ii) a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 2, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8;

[0092] Anti-NAMPT antibody P-1076: P-1076 has (i) a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 15, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid

containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21; and (ii) a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 47, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

[0132] Anti-NAMPT antibody UU-1093-mod18: UU-1093-mod18 has (i) a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 26, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21; and (ii) a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 48, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 49, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 50, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

[0133] Anti-NAMPT antibody UU-1093-mod19: UU-1093-mod19 has (i) a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 26, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21; and (ii) a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 51, containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 52, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 53.

[0134] In some embodiments, the invention includes an anti-NAMPT antibody that binds to human NAMPT in the NAMPT homodimeric conformation to a discontinuous epitope on human NAMPT. In some embodiments, the antibody, or antigen-binding portion thereof, binds to an epitope on human NAMPT comprising at least one amino acid in amino acid residues 17-44 of SEQ ID NO: 60; at least one amino acid in amino acid residues 117-127 of SEQ ID NO: 60; at least one amino acid in amino acid residues 162-170 of SEQ ID NO: 60; at least one amino acid in amino acid residues 242-261 of SEQ ID NO: 60; at least one amino acid in amino acid residues 262-273 of SEQ ID NO: 60; at least one amino acid in amino acid residues 289-305 of SEQ ID NO: 60; at least one amino acid in amino acid residues 332-342 of SEQ ID NO: 60; at least one amino acid in amino acid residues 374-389 of SEQ ID NO: 60; at least one amino acid in amino acid residues 418-425 of SEQ ID NO: 60; at least one amino acid in amino acid residues 453-466 of SEQ ID NO: 60; and/or at least one amino acid in amino acid residues 408-416 of SEQ ID NO: 60. In some embodiments, the antibody, or antigen-binding portion thereof, binds to an epitope on human NAMPT comprising at least one amino acid in amino acid residues 29-51 of SEQ ID NO: 60; at least one amino acid in amino acid residues 61-72 of SEQ ID NO: 60; at least one amino acid in amino acid residues 156-170 of SEQ ID NO: 60; at least one amino acid in amino acid

residues 216-234 of SEQ ID NO: 60; at least one amino acid in amino acid residues 316-331 of SEQ ID NO: 60; at least one amino acid in amino acid residues 332-342 of SEQ ID NO: 60; at least one amino acid in amino acid residues 373-389 of SEQ ID NO: 60; at least one amino acid in amino acid residues 417-431 of SEQ ID NO: 60; at least one amino acid in amino acid residues 454-469 of SEQ ID NO: 60; and/or at least one amino acid in amino acid residues 470-478 of SEQ ID NO: 60.

[0135] In certain aspects, the provided antibody or fragment thereof can have a binding affinity (K_D) for human NAMPT expressed on human cells of about 3 nM to approximately 20 nM as measured by surface plasmon resonance.

[0136] In certain embodiments, an antibody, or antigen binding fragment thereof, described herein binds NAMPT, e.g., human NAMPT, with an off rate (k_{off}) of less than or equal to, e.g., $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$, 10^{-3} sec^{-1} , $5 \times 10^{-4} \text{ sec}^{-1}$, 10^{-4} sec^{-1} , $5 \times 10^{-5} \text{ sec}^{-1}$, or 10^{-5} sec^{-1} , $5 \times 10^{-6} \text{ sec}^{-1}$, 10^{-6} sec^{-1} , $5 \times 10^{-7} \text{ sec}^{-1}$ or 10^{-7} sec^{-1} .

[0137] In certain embodiments, an antibody, or antigen binding fragment thereof, described herein binds NAMPT, e.g., human NAMPT, with an on rate (k_{on}) of greater than or equal to, e.g., $10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $10^4 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, $10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $10^6 \text{ M}^{-1} \text{ sec}^{-1}$, or $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ or $10^7 \text{ M}^{-1} \text{ sec}^{-1}$.

[0138] In certain embodiments, an antibody, or antigen binding fragment thereof, described herein binds NAMPT, e.g., human NAMPT, with a dissociation constant or K_D equal to or greater than, e.g., $5 \times 10^{-7} \text{ M}$, 10^{-7} M , $5 \times 10^{-8} \text{ M}$, 10^{-8} M , $5 \times 10^{-9} \text{ M}$, 10^{-9} M , $5 \times 10^{-10} \text{ M}$, 10^{-10} M , $5 \times 10^{-11} \text{ M}$, 10^{-11} M , $5 \times 10^{-12} \text{ M}$, 10^{-12} M , or $5 \times 10^{-13} \text{ M}$. Binding affinity may be determined using various techniques known in the art, for example, surface plasmon resonance (SPR), bio-layer interferometry, dual polarization interferometry, static light scattering, dynamic light scattering, isothermal titration calorimetry, ELISA, analytical ultracentrifugation, and flow cytometry.

[0139] In certain aspects, an anti-NAMPT antibody or antigen-binding fragment thereof as provided herein can further include a heterologous agent, e.g., a stabilizing agent, an immune response modifier, or a detectable agent. In certain aspects the heterologous agent comprises one or more additional polypeptide sequences fused to the polypeptide subunit via a peptide bond, such as a signal sequence (e.g., a secretory signal sequence), a linker sequence, an amino acid tag or label, or a peptide or polypeptide sequence that facilitates purification. In certain aspects, the heterologous polypeptide can be fused to the N-terminus or the C-terminus of either a heavy chain or light chain antibody subunit, or fragment thereof, as long as the functional characteristics of the domains are maintained.

[0140] In certain aspects, the heterologous agent can be chemically conjugated to an anti-NAMPT antibody or antigen-binding fragment thereof as provided herein. Exemplary heterologous agents that can be chemically conjugated to the polypeptide subunit include, without limitation, linkers, drugs, toxins, imaging agents, radioactive compounds, organic and inorganic polymers, and any other compositions which can provide a desired activity that is not provided by the polypeptide subunit itself. Specific agents include, without limitation, polyethylene glycol (PEG), a cytotoxic agent, a radionuclide, an imaging agent, biotin.

[0141] In some embodiments, an anti-NAMPT antibody, or fragment, is labeled with a radiolabel for use in in vitro or in vivo detection. Examples of radioactive isotopes which may be used to label the antibodies disclosed herein include, but are not limited to At^{211} , I^{131} , I^{125} , Y^{90} , Re^{186} , Re^{188} , Sm^{153} , Bi^{212} , P^{32} , Pb^{212} or radioactive isotopes of Lu. In some embodiments, the invention includes an anti-NAMPT antibody as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At^{211} , I^{131} , I^{125} , Y^{90} , Re^{186} , Re^{188} , Sm^{153} , Bi^{212} , P^{32} , Pb^{212} and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc99m or I123 , or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, MRI), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[0142] In certain embodiments, any of the anti-NAMPT antibodies provided herein is useful for detecting the presence of NAMPT in a biological sample. The term “detecting” as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue, such as cerebrospinal fluid, a cell or tissue of the lung, or blood.

[0143] In some embodiments, an anti-NAMPT antibody for use in a method of diagnosis or detection is provided. In a further aspect, a method of detecting the presence of NAMPT in a biological sample is provided. In certain embodiments, the method comprises contacting the biological sample with an anti-NAMPT antibody as described herein under conditions permissive for binding of the anti-NAMPT antibody to NAMPT, and detecting whether a complex is formed between the anti-NAMPT antibody and NAMPT. Such method may be an in vitro or in vivo method. Further, the complex formed between the anti-NAMPT antibody and NAMPT in a test biological sample can be compared to the complex formed in a control biological sample (e.g., a biological sample from a healthy subject or subjects). The amount of the complex formed between the anti-NAMPT antibody and NAMPT in a test biological sample can also be quantified and compared to the amount of the complex formed in a control biological sample (e.g., a biological sample from a healthy subject or subjects) or to the average amount of the complex known to be formed in healthy subjects.

[0144] Anti-NAMPT antibodies and fragments disclosed herein can also be used as reagents for detection of human NAMPT, and, in some embodiments, murine NAMPT. For example, anti-NAMPT antibodies described herein may be used in ELISA assays. Detection of the presence of NAMPT may be accomplished in a number of ways using the antibodies and fragments disclosed herein, such as by Western blotting (with or without immunoprecipitation), immunoprecipitation, fluorescence activated cell sorting (FACS), flow cytometry, and ELISA procedures for assaying a wide variety of tissues and samples, including plasma or serum. A wide range of immunoassay techniques using such an assay format are available which can include the antibodies disclosed herein, see, e.g., U.S. Pat. Nos. 4,016,043, 4,424,279, and 4,018,653. These include both single-site and two-site or “sandwich” assays of the non-competitive types, as well as

in the traditional competitive binding assays. These assays also include direct binding of a labeled anti-NAMPT antibody to a target biomarker.

[0145] Sandwich assays are among the most useful and commonly used assays. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabeled antibody is immobilized on a solid substrate, and the sample to be tested brought into contact with the bound molecule. After incubation for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labeled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labeled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of biomarker.

[0146] For recombinant production of an anti-NAMPT antibody, nucleic acid encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0147] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0148] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been “humanized,” resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0149] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spo-doptera frugiperda* cells.

[0150] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen*

Virol. 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., Annals N.Y. Acad. Sci. 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, Methods in Molecular Biology, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003).

Anti-NAMPT Antibody Pharmaceutical Compositions and Therapeutic Uses

[0151] Also provided are methods of treating a condition associated with inflammation. Some embodiments comprise reducing inflammation, injury, the amount of proteins in BAL fluid, and/or BAL PMNs in a dose-dependent manner via administration of an anti-NAMPT antibody or antigen-binding fragment thereof. Some embodiments comprise reducing eNAMPT-, lipopolysaccharide-, and/or ventilator-induced lung injury. Conditions treatable with an anti-NAMPT antibody, or binding fragment thereof, include without limitation inflammatory conditions, such as pulmonary fibrosis (IPF), pulmonary hypertension, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), ventilator-induced lung injury (VILI), ARDS/VILI-induced ALI, trauma-induced acute lung injury (TALI), brain injury (including traumatic brain injury), or radiation-induced lung injury (RILI); prostate cancer; lung cancer; cancer associated with inflammation; expectant mothers with chorioamnionitis (e.g., subjects at risk for premature births and maternal/neonatal complications); non-alcoholic steatohepatitis (NASH); hepatic fibrosis; cardiac ischemia; and cardiac fibrosis.

[0152] Also provided are compositions (e.g., a pharmaceutical composition) comprising an anti-NAMPT antibody or an antigen binding fragment thereof, optionally further comprising one or more carriers, diluents, excipients, or other additives. Some embodiments comprise compositions (e.g., a pharmaceutical composition) comprising a polynucleotide or vector, optionally further comprising one or more carriers, diluents, excipients, or other additives.

[0153] Also provided are methods of preparing and administering an anti-NAMPT antibody or an antigen-binding fragment thereof to a subject in need thereof, e.g., to attenuate and/or treat the symptoms, morbidity, or mortality associated with NAMPT-associated acute and chronic inflammatory disorders (e.g., ARDS, VILI, and trauma-induced inflammatory lung injury), are well known to or can be readily determined by those skilled in the art. The anti-NAMPT antibody or an antigen-binding fragment thereof can be administered to the subject, for example, intravenously, intraarterially, intraperitoneally, intrapleurally, intratracheally, topically, subcutaneously, mucosally, intrapericardially, orally, locally, by inhalation, by injection, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, via a catheter, via aerosol, via

nebulizer, and/or via a lavage. In some embodiments, the composition comprising an anti-NAMPT antibody or an antigen-binding fragment thereof is administered directly to a tissue or organ that is inflamed or shows signs of inflammation. Usually, a suitable pharmaceutical composition can comprise, without limitation, a buffer (e.g. acetate, phosphate or citrate buffer), a surfactant (e.g. polysorbate), a stabilizer agent (e.g. human albumin), etc.

[0154] Certain pharmaceutical compositions provided herein can be orally administered in an acceptable dosage form including, e.g., capsules, tablets, aqueous suspensions or solutions. Certain pharmaceutical compositions also can be administered by nasal aerosol or inhalation. Such compositions can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other conventional solubilizing or dispersing agents.

[0155] The amount of an anti-NAMPT antibody or an antigen-binding fragment thereof that can be combined with carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration. The composition can be administered as a single dose, multiple doses or over an established period of time in an infusion. Dosage regimens also can be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). By way of example, an antibody may be intravenously administered/administrable to a patient in an amount from approximately 0.1 mg/kg to about 20 mg/kg at a frequency from approximately weekly to monthly.

[0156] In some embodiments, the intended goal is to prevent or treat an inflammatory condition or disease, which means an effective amount is that amount expected to achieve some prevention or treatment of the inflammatory condition or disease. In some embodiments it refers to preventing or alleviating symptoms and/or cellular processes associated with a particular disease or condition, including but not limited to VILI, ALI or ARDS; such symptoms may be vascular permeability or elevated BAL protein secretion). An inflammatory disease or condition refers to a disease or condition that is characterized by inflammation. The inflammation may affect any of the following tissues or organs: heart, lung, kidney, liver, bone marrow, pancreas, brain, skin, bone, vein, artery, cornea, ear, eye, nasopharyngeal tissue, stomach, joints, cartilage, vascular tissue or cells, blood, small intestine, large intestine, larynx, brain, spinal cord, smooth muscle, nerves, skeletal muscle, breast, ovary, testis, uterus, and umbilical cord. Moreover, the tissue can contain one or more of the following cell types: platelet, myelocyte, erythrocyte, lymphocyte, adipocyte, fibroblast, epithelial cell, endothelial cell, smooth muscle cell, skeletal muscle cell, endocrine cell, glial cell, neuron, secretory cell, barrier function cell, contractile cell, absorptive cell, mucosal cell, limbus cell (from cornea), stem cell (totipotent, pluripotent or multipotent), unfertilized or fertilized oocyte, or sperm.

[0157] In some aspects, one or more agents may have been administered, is/are concurrently administered/administrable, or will later be administered/is subsequently administrable to the patient. Exemplary agents include azathioprine, bortezomib, carfilzomib, cyclophosphamide, dexamethasone, doxorubicin, lenalidomide, melphalan, pomalidomide, prednisolone, thalidomide, and vincristine.

Exemplary agents also include antibiotics. Exemplary agents may also be administered/administrable as part of a therapeutic regimen.

[0158] This disclosure further provides pharmaceutical packs and kits comprising one or more containers, wherein a container can comprise one or more doses of an anti-NAMPT antibody or antigen binding fragment, including compositions that can be used to perform the methods described herein. In certain embodiments, a kit comprises at least one purified anti-NAMPT antibody or an antigen-binding fragment thereof. One skilled in the art will readily recognize that the disclosed anti-NAMPT antibody can be readily incorporated into one of the established kit formats that are well known in the art.

[0159] In certain aspects, the disclosure provides prophylactic and/or therapeutic methods for preventing, reducing and/or reversing the pathophysiological processes that lead to the onset and progression of NAMPT-associated acute and chronic inflammatory in a subject in need thereof, the method comprising administering an effective amount of anti-NAMPT antibody or an antigen-binding fragment thereof (including compositions and pharmaceutical compositions provided herein). As used herein, an “NAMPT-associated acute and chronic inflammatory disorder or condition,” includes any inflammatory condition or biological process which results in inflammation involving NAMPT, e.g., an elevated expression and/or activity of NAMPT (e.g., eNAMPT), including downstream signaling molecules such as inflammatory cytokines. In particular embodiments, the composition comprises a neutralizing humanized anti-NAMPT antibody. In particular embodiments, the subject is a mammal, including but not limited to humans. Methods of treatment and corresponding uses in accordance with the teachings herein may retard, halt or reverse one or more symptoms associated with disorder, and thereby improve the subject's quality of life and/or extend the patient's lifespan.

[0160] In some embodiments, anti-NAMPT antibodies, or fragments thereof, described herein are used to treat a patient having symptoms of an acute or a chronic inflammatory condition or disease (e.g., an inflammatory lung condition or disease) or is at risk for developing an acute or a chronic inflammatory condition or disease (e.g., an inflammatory lung condition or disease).

[0161] A subject in need thereof who would benefit from the methods provided by the disclosure, includes but is not limited to a critically-ill subject; a critically-ill subject with respiratory failure; a critically-ill subject exposed to infection, trauma, and/or sepsis; a subject with radiation exposure; a subject with diagnosis of pulmonary fibrosis (IPF); a subject with pulmonary hypertension; a subject suffering from acute respiratory distress syndrome (ARDS); a subject with a ventilator-induced lung injury (VILI); an intensive care unit (ICU) subject with respiratory failure or at risk for VILI, and/or ARDS/VILI-induced ALI; a subject with pancreatitis; a subject with a smoke inhalation injury, blast injury, and/or trauma-induced acute lung injury (TALI); a subject with a traumatic brain injury; a subject with hemorrhagic shock and resuscitation; a subject with radiation-induced lung injury (including cancer treatment associated radiation-induced lung injury); pregnant subjects with chorioamnionitis (e.g., who are at risk for premature births and maternal/neonatal complications, or complications of pre-

maturity); and subjects with primary and metastatic cancers. Also provided are subjects at risk of developing any of the conditions disclosed herein.

[0162] In certain aspects, the disclosure provides a method for treating a patient suffering from or at risk for inflammatory lung condition or disease, comprising administering to the patient an effective amount of an anti-NAMPT antibody or an antigen-binding fragment thereof (including compositions and pharmaceutical compositions provided herein). This may be based on the patient's symptoms, medical history, or the results of one or more tests. In some cases, a patient has already been diagnosed with an inflammatory condition or disease of the lungs when the patient is administered the anti-NAMPT antibody or antigen binding fragment thereof (including compositions and pharmaceutical compositions provided herein). In other cases, the patient has not been diagnosed with an inflammatory condition or disease of the lungs but the patient is at risk for such a disease or condition. Such a patient includes one who has been placed or will be placed on a ventilator, someone with pneumonia, someone who has experienced bodily trauma, someone with severe bleeding, someone who has aspirated vomit, someone who has inhaled chemicals, someone who has smoked heavily, and/or someone who drinks heavily. For instance, the patient may be placed on a ventilator or have been on a ventilator within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, or 120 hours (or any range derivable therein) and/or 1, 2, 3, 4, 5, 6, or 7 days (or any range derivable therein).

[0163] In certain aspects, the disclosure provides a method for treating a patient suffering from or at risk for acute lung injury (ALI), ventilator-induced lung injury (VILI), or acute respiratory distress syndrome (ARDS) comprising administering to the patient an effective amount of an anti-NAMPT antibody or an antigen-binding fragment thereof (including compositions and pharmaceutical compositions provided herein). At risk patients include, but are not limited to, patients with sepsis or symptoms of sepsis, patients with pneumonia or symptoms of pneumonia, patients with severe bleeding because of an injury to the body, patients who have a severe injury to the chest or head, patients who have breathed harmful fumes or smoke, patients who have inhaled vomit, patients who have had multiple or massive blood transfusions, patients who have fractured long bones (such as the femur), patients who have nearly drowned, patients who have had an adverse reaction to cancer drugs or other medications, patients who have had a drug overdose, patients with pancreatitis, patients who smoke heavily, patients who drink heavily, patients with inflammatory bowel disease, patients with rheumatoid arthritis, patients with colorectal cancer, and patients with obesity-related insulin resistance, or any combination thereof.

[0164] In certain aspects, the disclosure provides a method for preventing ventilator-induced lung injury (VILI) in a patient, the method comprising administering an effective amount of anti-NAMPT antibody or an antigen-binding fragment thereof (including compositions and pharmaceutical compositions provided herein). In particular embodiments, the anti-NAMPT antibody is a neutralizing antibody. In particular embodiments the administration occurs before the patient is placed on a ventilator. In particular embodiments the administration occurs after the patient is placed on a ventilator.

[0165] In certain aspects, the disclosure provides a method of reducing levels of one or more cytokines (e.g., IL-6, TNF- α , IL-1 β , IL-8) in a subject at risk of suffering from or suffering from an NAMPT-associated acute and/or chronic inflammatory disorder.

[0166] In certain aspects, the disclosure provides a method for reducing eNAMPT levels in a subject at risk of suffering from or suffering from an NAMPT-associated acute and/or chronic inflammatory disorder.

[0167] In some embodiments, anti-NAMPT antibodies disclosed herein can be used to treat cancer. In some embodiments, the cancer is prostate cancer (PCa). In particular aspects, the disclosure provides a method for treating PCa in a subject in need thereof by administering to the subject a therapeutically effective amount of an anti-NAMPT antibody or antigen-binding fragment described herein. In some embodiments, the subject having prostate cancer has recurrent PCa, aggressive PCa, or metastatic PCa. In some embodiments, the subject has aggressive PCa that is resistant to androgen deprivation therapy (ADT).

[0168] Alternatively, in some instances, an anti-NAMPT antibody or antigen-binding fragment, can be administered to a subject in combination with ADT. ADT can be administered to the subject prior to, concurrently with, or subsequent to administering an anti-NAMPT antibody or antigen-binding fragment.

[0169] ADT that can be administered to a subject in combination with an anti-NAMPT antibody or antigen-binding fragment, may include one or more of a luteinizing hormone-releasing hormone (LHRH) agonist; a LHRH antagonist; a CYP17 inhibitor; an anti-androgen; and/or an androgen-suppressing drug. In particular embodiments, the LHRH agonist can be Leuprolide (e.g., LUPRONTM ELIGARDTM, etc.), Goserelin (e.g., ZOLADEXTM) Triptorelin (e.g., TRELSTARTM), and/or Histrelin (e.g., VANTASTM); the LHRH antagonist can be Degarelix (e.g., FIRMA-GONTM); the CYP17 inhibitor can be Abiraterone (e.g., ZYTIGATM); the anti-androgen can be Flutamide (e.g., EULEXINTM), Bicalutamide (e.g., CASODEXTM), Nilutamide (e.g., NILANDRONTM), Enzalutamide (e.g., XTANDITM), and/or Apalutamide (e.g., ERLEADATM); and/or the androgen-suppressing drug can be Estrogen and/or Ketoconazole (e.g., NIZORALTM).

[0170] Some embodiments comprise treating Coronavirus disease 2019 (COVID-19) with one or more NAMPT antibodies. COVID-19 is a severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2). SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona. Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. SARS-CoV-2 infection may be asymptomatic or it may cause a wide spectrum of symptoms. Exemplary symptoms include fever, cough, shortness of breath, weakness, fatigue, nausea, vomiting, and changes to taste and smell. Adverse outcomes include diffuse intravascular coagulation; inflamed lung tissues and pulmonary endothelial cells; deep venous thrombosis; pulmonary embolism; thrombotic arterial complications (e.g., limb ischemia; ischemic stroke; myocardial infarction); sepsis; and multi-organ failure. SARS-CoV-2 infection is discussed in greater detail in Wiersinga et al., "Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-2019): A Review," *JAMA*, doi:10.1001/jama.2020.12839

(published online Jul. 10, 2020), which is incorporated herein by reference in its entirety. In some embodiments, the present disclosure provides methods for treating a subject having COVID-19 (e.g., a subject diagnosed with COVID-19 and/or a subject showing one or more symptoms of COVID-19) by administering to the subject an effective amount of an anti-NAMPT antibody or an antigen-binding fragment thereof.

EXAMPLES

[0171] The following examples are included for purpose of illustration only and are not intended to be limiting.

Example 1. Generation of Anti-Human NAMPT Monoclonal Antibodies

[0172] Anti-NAMPT neutralizing murine antibodies were developed by immunizing three mice with recombinant extracellular human NAMPT (hNAMPT; MBL International). Mouse 4C6 and mouse 589 yielded 52 parental clone anti-NAMPT antibodies collectively. Binding of the murine antibodies to hNAMPT was assessed by ELISA. The murine antibodies were also tested for in vitro neutralization by analyzing the effect of the antibodies on hNAMPT-induced phosphorylation of NF κ B. Anti-hNAMPT antibodies AL-303 and AL-310 were selected for their ability to bind recombinant hNAMPT, as well as hNAMPT in lysate from human pulmonary artery endothelial cells (HPAEC). Both AL-303 and AL-310 were also able to inhibit hNAMPT-induced phosphorylation of NF κ B. AL-303 was further able to cross react with recombinant mouse NAMPT (mNAMPT), while AL-310 was not. Furthermore, these antibodies were subjected to in vivo testing, as described below in Examples 4 and 5.

AL-303

[0173] Murine anti-hNAMPT antibody AL-303 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 54, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 55. The heavy chain variable region of AL-303 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5. The light chain variable region of AL-303 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8.

AL-310

[0174] Murine anti-NAMPT antibody AL-310 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 56, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 57. The heavy chain variable region of AL-310 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. The light chain variable region of AL-310 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2

domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

[0175] The amino acid sequences of the heavy and light chain variable regions, as well as the CDRs, of AL-303 and AL-310 is provided in Table 1.

mNAMPT was further tested by assessing the ability of these antibodies to detect recombinant mNAMPT, mNAMPT in lysate from spontaneously breathing mice (“SB”), mNAMPT in lysate from murine lung exposed to LPS, and mNAMPT in lysate from a murine ventilator-induced lung injury (VILI) model.

TABLE 1			
Sequence of murine anti-NAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
AL-303	AL-303 heavy chain variable region (VH) (CDRs underlined)	QVQLQQPGADLVKPGASVKLSCK ASGYTFTSYWMQWVKQRPGQGL EWIGEIDPSNSYTNYNQKFRGKAT LTVDPSSSTAYMQLSSLTSEDSAV YYCARGGYWGQGTTTLTVSS	SEQ ID NO: 54
	AL-303 light chain variable region (VL) (CDRs underlined)	DIVMTQAAFSNPVTLGTSASISCRS SKSLLHSNGITYLYWYLQKPGQSP QLLIYQMSNLASGVPDRFSSSGSG TDFTLRISRVEAEDVGYYCVQNL ELPYTFGGGTKLEIK	SEQ ID NO: 55
	AL-303 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	AL-303 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	AL-303 CDR-H3	ARGGY	SEQ ID NO: 5
	AL-303 CDR-L1	RSSKSLHSNGITYLY	SEQ ID NO: 6
	AL-303 CDR-L2	QMSNLAS	SEQ ID NO: 7
	AL-303 CDR-L3	VQNLLEPYT	SEQ ID NO: 8
	AL-310 heavy chain variable region (VH) (CDRs underlined)	QVQLQQSGAESVMPGASVKLSCK ASGYTFTSYWMHWVKQRPGQGL EWIGEIDPSDSYTNYNQKFKGKST LTVDKSSSTAYMQLSSLTSEDSAV YYCAKSNYVVPWYFDVWGTGTT VTVSS	SEQ ID NO: 56
	AL-310 light chain variable region (VL) (CDRs underlined)	DIVMTQAAFSNPVTLGTSASISCRS SKSLLHSNGITYLYWYLQKPGQSP QLLIYQMSNLASGVPDRFSSSGSG TDFTLRISRVEAEDVGYYCAQNL ELPWTFGGGTKLEIK	SEQ ID NO: 57
AL-310	AL-310 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	AL-310 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	AL-310 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	AL-310 CDR-L1	RSSKSLHSNGITYLY	SEQ ID NO: 6
	AL-310 CDR-L2	QMSNLAS	SEQ ID NO: 7
	AL-310 CDR-L3	AQNLLELPWT	SEQ ID NO: 22

Example 2. Detection of Human and Mouse NAMPT by Murine Anti-NAMPT Antibodies

[0176] To evaluate immunoreactivity of human and mouse NAMPT by murine anti-NAMPT antibodies AL-303 and AL-310, detection of hNAMPT and mNAMPT by these antibodies was tested by Western blot analysis. Immunoreactivity of AL-303 and AL-310 with hNAMPT was also evaluated by assessing the ability of these antibodies to detect recombinant hNAMPT and hNAMPT in HPAEC cell lysate. Immunoreactivity of AL-303 AL-310 with

[0177] Results from the corresponding Western blot analyses is provided in FIG. 1. As shown, AL-303 and AL-310 were strongly immunoreactive with hNAMPT (as compared to other antibodies shown). In comparison, immunoreactivity of these antibodies with mNAMPT was substantially weaker. Of the five murine antibodies tested, only AL-303 and AL-304 (which contained the same sequence as AL-303) were immunoreactive with recombinant mNAMPT, while all of the antibodies were reactive with recombinant hNAMPT and hNAMPT in HPAEC cells.

Example 3. Effect of Murine Anti-NAMPT
Antibodies on hNAMPT-Induced NFκB
Phosphorylation

[0178] Effect of murine anti-NAMPT antibodies AL-303, AL-304, AL-305, AL-309, and AL-310 on hNAMPT-induced NFκB phosphorylation was assessed by Western blot analysis of phospho-NFκB (p-NFκB) expression in cells that were exposed to hNAMPT in absence or presence of these antibodies.

[0179] Recombinant hNAMPT (1 μg/ml) was premixed for 30 min with vehicle, 100 μg/ml of anti-NAMPT polyclonal (pAb), or 100 μg/ml of a murine anti-NAMPT antibody (AL-303, AL-304, AL-305, AL-309, or AL-310). HPAEC cells were stimulated by exposing the cells to the hNAMPT mix for 1 hr. Unstimulated cells (“Unstim”), which were exposed to vehicle, 100 μg/ml of anti-NAMPT pAb, or 100 μg/ml of a murine anti-NAMPT antibody (AL-303, AL-304, AL-305, AL-309, or AL-310) alone, were used as a negative control. HPAEC cells, which were exposed to TNF-α, were used as a positive control. Expression of p-NFκB in lysates from the unstimulated cells, hNAMPT-stimulated cells, and TNF-α-stimulated cells was assessed by Western blot analysis using a p-NFκB specific antibody. Result from the Western blot analysis is provided in FIG. 2.

[0180] As shown in FIG. 2, hNAMPT induced phosphorylation of NFκB in the hNAMPT-stimulated cells, which was substantially attenuated in presence of AL-303, AL-304, AL-305, AL-309, or AL-310. While all of the five antibodies effectively reduced hNAMPT-induced NFκB phosphorylation, the most substantial effect was observed with AL-303 and AL-310. AL-304, AL-304, AL-305, and AL-309 were anti-hNAMPT antibodies also obtained in the initial murine screen.

Example 4. In Vivo Testing of AL-303, AL-304
and AL-305 in Lung Injury Model

[0181] Ability of murine anti-NAMPT antibodies AL-303, AL-304 and AL-305 to treat lung injury was tested in vivo, using a mouse model.

[0182] As described in FIG. 3, C57/B6 mice were intravenously injected with 50 μg, 100 μg, or 200 μg of murine anti-NAMPT antibody, AL-303, AL-304, or AL-305, or with vehicle alone. One hour after the anti-NAMPT antibody injection, the mice were exposed to 40 μg/ml intratracheal hNAMPT (Peprtech). Eight hours post hNAMPT exposure, the anti-NAMPT antibodies were administered again at the same concentrations. Control mice were injected with vehicle and exposed to intratracheal hNAMPT, or injected with vehicle and not exposed to intratracheal hNAMPT. All animals were sacrificed 24 hr after hNAMPT exposure, and assessed for lung injury by analyzing the expression of bronchioalveolar lavage (BAL) protein, and count of BAL-expressing polymorphonuclear neutrophils (PMNs).

[0183] Results from the assessment is provided in FIGS. 4A-4B. As described in FIGS. 4A-4B, the expression of BAL protein (FIG. 4A) and the count of BAL-expressing PMNs (FIG. 4B) was induced in mice that were exposed to intratracheal hNAMPT. Murine anti-NAMPT antibodies AL-303, AL-304 and AL-305 effectively reduced hNAMPT-mediated induction of BAL PMN count, and hNAMPT-induced increase in BAL protein level was substantially attenuated by AL-303. Thus, as described in FIGS. 4A-4B, all of AL-303, AL-304 and AL-305 effectively reduced hNAMPT-induced murine lung injury, while the most sub-

stantial effect was observed with AL-303. Accordingly, AL-303 was selected for subsequent humanization.

Example 5. In Vivo Testing of AL-310 in Lung
Injury

[0184] The ability of murine anti-NAMPT antibody AL-310 to treat lung injury was tested in vivo, using a mouse model.

[0185] As described in FIG. 5, C57/B6 mice were intravenously injected with 10 μg, 25 μg, 50 μg, 100 μg, or 200 μg of murine anti-NAMPT antibody AL-310, 100 μg of anti-NAMPT pAb, or vehicle alone. Concurrent with the antibody injection, the mice were exposed to 1 mg/kg intratracheal LPS. Mice, which were exposed to intratracheal LPS and injected with vehicle or pAb, were used as positive control. Mice, which were injected with vehicle and not exposed to intratracheal LPS, were used as negative control. All animals were sacrificed 6 hr after LPS exposure, and assessed for lung injury by analyzing the expression of BAL protein level.

[0186] Results from the assessment is provided in FIG. 6. As shown in FIG. 6, expression of BAL protein was induced in mice that were exposed to intratracheal LPS. Murine anti-NAMPT antibody AL-310 effectively reduced LPS-mediated induction of BAL protein level, and the effect was substantially more pronounced compared to the effect observed with the positive control. Thus, FIG. 6 shows that AL-310 effectively reduced LPS-induced murine lung injury. Accordingly, AL-310 was selected for subsequent humanization.

Example 6. Humanization of Anti-NAMPT
Antibody AL-303

[0187] Based on the results of in vitro and in vivo testing described in Examples 2-4, murine anti-NAMPT antibody AL-303 was selected for humanization.

1076 Humanized Anti-hNAMPT Antibodies

[0188] The term “1076” collectively refers to humanized versions of anti-hNAMPT antibody AL-303. Specifically, CDRs of VH and VL chains of AL-303 were grafted onto human heavy and light chain acceptor sequences.

[0189] Following grafting, various framework back-mutations were introduced, by de nova synthesis of the variable domain, or mutagenic oligonucleotide primers and polymerase chain reactions, or both, by methods well known in the art. Different combinations of back mutations and other mutations were constructed for heavy and/or light chains of each of the CDR-grafts to generate 1076 humanized anti-hNAMPT antibodies D-1076, G-1076, K-1076, N-1076, P-1076, V-1076 and X-1076.

[0190] Amino acid sequences of the heavy and light chain variable regions of the 1076 humanized anti-hNAMPT antibodies are provided in Table 2. Table 3 provides an alignment of the amino acid sequences of the heavy chain CDRs for 1076 humanized anti-hNAMPT antibodies D-1076, G-1076, K-1076, N-1076, P-1076, V-1076 and X-1076 in comparison to the murine anti-NAMPT antibody AL-303. Table 4 provides an alignment of the amino acid sequences of the light chain CDRs for 1076 humanized anti-hNAMPT antibodies D-1076, G-1076, K-1076, N-1076, P-1076, V-1076 and X-1076 in comparison to the murine anti-NAMPT antibody AL-303. Blank spaces in Tables 3 and 4 indicate that the residue is the same as AL-303.

TABLE 2

Sequence of 1076 humanized anti-hNAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
D-1076	D-1076 heavy chain variable region (VH) (CDRs underlined)	QVQLVESGAIEVKKPGASVKLSCK ASGYTFTSYWMQWVRQAPGQRL EWMGEIDPSNSYTNYNQKFRGRV TITVDKSASTAYMELSSLRSEDTA VYYCARGGYWGPGTTVTVSS	SEQ ID NO: 1
	D-1076 light chain variable region (VL) (CDRs underlined)	DIVMTQTPLSLSVTPGQPASISCRS SKSLHLSNGITYLYWYLQKPGQPP QLLIYQMSNLASGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCVQNL ELPYTFGGGTKVDIK	SEQ ID NO: 2
	D-1076 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	D-1076 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	D-1076 CDR-H3	ARGGY	SEQ ID NO: 5
	D-1076 CDR-L1	RSSKSLHLSNGITYLY	SEQ ID NO: 6
	D-1076 CDR-L2	QMSNLAS	SEQ ID NO: 7
G-1076	D-1076 CDR-L3	VQNLLELPYT	SEQ ID NO: 8
	G-1076 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAIEVKKPGASVKVSK ASGYTFTSYWMQWVRQAPGQGL EWMGEIDPSNSYTNYNQKFRGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARGGYWGQGTITVTVSS	SEQ ID NO: 9
	G-1076 light chain variable region (VL) (CDRs underlined)	DIQLTQSPSLSPVTPGEPASISCRSS KSLHLSQGITYLYWYLQKPGQSPQ LLIYQLSNLASGVPDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNL LPYTFGGGTKLEIK	SEQ ID NO: 10
	G-1076 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	G-1076 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	G-1076 CDR-H3	ARGGY	SEQ ID NO: 5
	G-1076 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11
K-1076	G-1076 CDR-L2	QLSNLAS	SEQ ID NO: 12
	G-1076 CDR-L3	VQNLLELPYT	SEQ ID NO: 8
	K-1076 heavy chain variable region (VH) hIgG1 backbone (CDRs underlined)	QVQLVQSGAIEVKKPGASVKVSK ASGYTFTSYWMQWVRQAPGQGL EWMGEIDPSNSYTNYNQKFRGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARGGYWGQGTITVTVSS	SEQ ID NO: 9
	K-1076 light chain variable region (VL) (CDRs underlined)	DIVMTQSPSLSPVTPGEPASISCRSS KSLHLSQGITYLYWYLQKPGQSPQ LLIYQLSNRASGVPDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNL LPYTFGGGTKLEIK	SEQ ID NO: 13
	K-1076 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	K-1076 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	K-1076 CDR-H3	ARGGY	SEQ ID NO: 5
K-1076	K-1076 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11
	K-1076 CDR-L2	QLSNRAS	SEQ ID NO: 14
	K-1076 CDR-L3	VQNLLELPYT	SEQ ID NO: 8

TABLE 2-continued

Sequence of 1076 humanized anti-hNAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
N-1076	N-1076 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSK ASGYTFTSYWMQWVRQAPGQGL EWVGEIDPSNSYTNYNQKFRGRV TLTRDTSTTTVYMELSSLRSED TA VYYCARGGYWGQTTVTVSS	SEQ ID NO: 15
	N-1076 light chain variable region (VL) (CDRs underlined)	DIVMTQTPLSLSVTPGQPASISCRS SKSLHLSNGITYLYWYLQKPGQPP QLLIYQMSNLASGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCVQNL ELPYTFGGGTKVDIK	SEQ ID NO: 2
	N-1076 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	N-1076 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	N-1076 CDR-H3	ARGGY	SEQ ID NO: 5
	N-1076 CDR-L1	RSSKSLHLSNGITYLY	SEQ ID NO: 6
	N-1076 CDR-L2	QMSNLAS	SEQ ID NO: 7
P-1076	N-1076 CDR-L3	VQNLLELPYT	SEQ ID NO: 8
	P-1076 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSK ASGYTFTSYWMQWVRQAPGQGL EWVGEIDPSNSYTNYNQKFRGRV TLTRDTSTTTVYMELSSLRSED TA VYYCARGGYWGQTTVTVSS	SEQ ID NO: 15
	P-1076 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVTGPGEPAISCRSS KSLHLSQGITYLYWYLQKPGQSPQ LLIYQLSNRASGVPDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNL LE LPYTFFGGGTKLEIK	SEQ ID NO: 13
	P-1076 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	P-1076 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	P-1076 CDR-H3	ARGGY	SEQ ID NO: 5
	P-1076 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11
V-1076	P-1076 CDR-L2	QLSNRAS	SEQ ID NO: 14
	P-1076 CDR-L3	VQNLLELPYT	SEQ ID NO: 8
	V-1076 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVKKPGASVKVSK ASGYTFTSYWMQWVRQAPGQGL EWMGEIDPSNSYTNYNQKFRGRV TMTTRDTSTSTVYMELSSLRSED TA VYYCARGGYWGQTTVTVSS	SEQ ID NO: 16
	V-1076 light chain variable region (VL) (CDRs underlined)	DIQLTQSPLSLPVTGPGEPAISCRSS KSLHLSQGITYLYWYLQKPGQSPQ LLIYQLSNLASGVPDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNL LE LPYTFFGGGTKLEIK	SEQ ID NO: 10
	V-1076 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	V-1076 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	V-1076 CDR-H3	ARGGY	SEQ ID NO: 5
	V-1076 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11
	V-1076 CDR-L2	QLSNLAS	SEQ ID NO: 12
	V-1076 CDR-L3	VQNLLELPYT	SEQ ID NO: 8

TABLE 2-continued			
Sequence of 1076 humanized anti-hNAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
X-1076	X-1076 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVKKPGASVKVSCK	SEQ ID NO: 16
		ASGYTFTSYWMQWVRQAPGQGL	
		EWMGEIDPSNSYTNYNQKFRGRV	
		TMTRDTSTSTVYMELSSLRSEDTA	
	X-1076 light chain variable region (VL) (CDRs underlined)	VYYCARGGYWGQTTVTVSS	SEQ ID NO: 2
		DIVMTQTPLSLSVTPGQPASISCRS	
		SKSLLLHSNGITYLYWYLQKPGQPP	
		QLLIYQMSNLAGVDPDRFSGSGSG	
	X-1076 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	X-1076 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
	X-1076 CDR-H3	ARGGY	SEQ ID NO: 5
	X-1076 CDR-L1	RSSKSLLLHSNGITYLY	SEQ ID NO: 6
	X-1076 CDR-L2	QMSNLAG	SEQ ID NO: 7
	X-1076 CDR-L3	VQNLELPYT	SEQ ID NO: 8

TABLE 3																														
Comparison of HC CDRs of 1076 anti-hNAMPT antibodies with HC CDRs of AL-303																														
Heavy Chain (HC) CDR1											SEQ ID NO:		HC CDR2														SEQ ID NO:			
AL-303	G	Y	T	F	T	S	Y	W	M	Q	3	E	I	D	P	S	N	S	Y	T	N	Y	N	Q	K	F	R	G	4	
D-1076											3																		4	
G-1076											3																		4	
K-1076											3																		4	
N-1076											3																		4	
P-1076											3																		4	
V-1076											3																		4	
X-1076											3																		4	
																									HC CDR3				SEQ ID NO:	
																					AL-303		A	R	G	G	Y	5		
																					D-1076							5		
																					G-1076							5		
																					K-1076							5		
																					N-1076							5		
																					P-1076							5		
																					V-1076							5		
																					X-1076							5		

TABLE 4																									
Comparison of LC CDRs of 1076 anti-hNAMPT antibodies with LC CDRs of AL-303																									
Light Chain (LC) CDR1																	SEQ ID NO:		LC CDR2						SEQ ID NO:
AL-303	R	S	S	K	S	L	L	H	S	N	G	I	T	Y	L	Y	6	Q	M	S	N	L	A	S	7
D-1076																	6								7
G-1076										Q							11		L						12
K-1076										Q							11		L		R				14
N-1076																	6								7

TABLE 4-continued

Comparison of LC CDRs of 1076 anti-hNAMPT antibodies with LC CDRs of AL-303										
P-1076	Q	11	L	R						14
V-1076	Q	11	L							12
X-1076		6								7
LC CDR3										SEQ ID NO:
AL-303	V	Q	N	L	E	L	P	Y	T	8
D-1076										8
G-1076										8
K-1076										8
N-1076										8
P-1076										8
V-1076										8
X-1076										8

Example 7. Humanization of Anti-NAMPT Antibody AL-310

[0198] Based on the results of in vitro and in vivo testing described in Examples 2-5, murine anti-NAMPT antibody AL-310 was selected for humanization.

[0199] “1093” refers to a group of humanized antibodies derived from murine anti-NAMPT antibody AL-310. By applying the humanization methodology, the CDR sequences of VH and VL chains of AL-310 were grafted onto different human heavy and light chain acceptor sequences.

[0200] By grafting the corresponding VH and VL CDRs of AL-310 into these acceptor sequences, CDR-grafted, humanized, and modified VH and VL sequences were prepared.

[0201] To generate humanized antibody with potential framework back-mutations, mutations were identified and introduced into the CDR-grafted antibody sequences by de nova synthesis of the variable domain, or mutagenic oligonucleotide primers and polymerase chain reactions, or both, by methods well known in the art. Different combinations of back mutations and other mutations were constructed for heavy and/or light chains of each of the CDR-grafts to generate 1093 humanized anti-hNAMPT antibodies FF-1093, 11-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, and ZZ-1093.

[0202] Amino acid sequences of the heavy and light chain variable regions of the 1093 humanized anti-hNAMPT antibodies are provided in Table 5. Table 6 provides an alignment of the amino acid sequences of the heavy chain CDRs for 1093 humanized anti-hNAMPT antibodies FF-1093, 11-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, and ZZ-1093 in comparison to the murine anti-NAMPT antibody AL-310. Table 7 provides an alignment of the amino acid sequences of the light chain CDRs for 1093 humanized anti-hNAMPT antibodies FF-1093, 11-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, and ZZ-1093 in comparison to the murine anti-NAMPT antibody AL-310. Blank spaces in Tables 6 and 7 indicate that the residue is the same as AL-310.

FF-1093

[0203] 1093 humanized anti-hNAMPT antibody FF-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 17, and a light chain

variable region with an amino acid sequence as set forth in SEQ ID NO: 18. The heavy chain variable region of FF-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of FF-1093, one or more back mutations and other mutations were introduced. The light chain variable region of FF-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

11-1093

[0204] 1093 humanized anti-hNAMPT antibody 11-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 24. The heavy chain variable region of 11-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of 11-1093, one or more back mutations and other mutations were introduced. The light chain variable region of 11-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

NN-1093

[0205] 1093 humanized anti-hNAMPT antibody NN-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 25, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 24. The heavy chain variable region of NN-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of NN-1093, one or more back mutations and other mutations were introduced. The light chain variable region of NN-1093

contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

PP-1093

[0206] 1093 humanized anti-hNMAPT antibody PP-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 25, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 18. The heavy chain variable region of PP-1093 containing a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of PP-1093, one or more back mutations and other mutations were introduced. The light chain variable region of PP-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

SS-1093

[0207] 1093 humanized anti-hNMAPT antibody SS-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 26, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 24. The heavy chain variable region of SS-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of SS-1093, one or more back mutations and other mutations were introduced. The light chain variable region of SS-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

UU-1093

[0208] 1093 humanized anti-hNMAPT antibody UU-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 26, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 18. The heavy chain variable region of

UU-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of UU-1093, one or more back mutations and other mutations were introduced. The light chain variable region of UU-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

XX-1093

[0209] 1093 humanized anti-hNMAPT antibody XX-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 27, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 24. The heavy chain variable region of XX-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of XX-1093, one or more back mutations and other mutations were introduced. The light chain variable region of XX-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

ZZ-1093

[0210] 1093 humanized anti-hNMAPT antibody ZZ-1093 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 27, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 18. The heavy chain variable region of ZZ-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. For the heavy chain of ZZ-1093, one or more back mutations and other mutations were introduced. The light chain variable region of ZZ-1093 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22.

TABLE 5

Sequence of 1093 humanized anti-hNMAPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
FF-1093	FF-1093 heavy chain variable region (VH) (CDRs underlined)	QVQLVESGAIEVKKPGASVKLSCK ASGYTFTSYWMHWVRQAPGQRL EWMGEIDPSDSYTNYNQKFKGRV TITVDKSASTAYMELSSLRSEDTA VYYCAKSNIYVVPWYFDVWGPGT TVTSS	SEQ ID NO: 17
	FF-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGERATLSCRS SKSLLHSNGITYLYWYQQKPGQA PRLLIYQMSNLAGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCAQNL ELPWTFGGGTKLEIK	SEQ ID NO: 18

TABLE 5-continued

Sequence of 1093 humanized anti-hNAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
	FF-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	FF-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	FF-1093 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	FF-1093 CDR-L1	RSSKSLHLSNGITYLY	SEQ ID NO: 6
	FF-1093 CDR-L2	QMSNLAS	SEQ ID NO: 7
	FF-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22
II-1093	II-1093 heavy chain variable region (VH) hIgG1 backbone (CDRs underlined)	QVQLVQSGAEVRKPGASVKVSCK ASGYTFTSYWMHWVRQAPGQGL EWVGEIDPSDSYTNYNQKFKGRV TITADKSTSTAYMELSSLRSEDTD VYYCAKSNYVVPWYFDVWGQGT TVTVSS	SEQ ID NO: 23
	II-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPATLSLSPGERATLSCRS SKSLHLSNGITYLYWYQQKPGQA PRLLIYQMSNLASGIPARFSGSGSG TDFTLTISSELEPEDFAVYYCAQNLE LPWTFGGGTKLEIK	SEQ ID NO: 24
	II-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	II-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	II-1093 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	II-1093 CDR-L1	RSSKSLHLSNGITYLY	SEQ ID NO: 6
	II-1093 CDR-L2	QMSNLAS	SEQ ID NO: 7
	II-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22
NN-1093	NN-1093 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSCK ASGYTFTSYWMHWVRQAPGQGL EWVGEIDPSDSYTNYNQKFKGRV TLTRDTSTTTVYMESSLRSEDTA VYYCAKSNYVVPWYFDVWGQGT TVTVSS	SEQ ID NO: 25
	NN-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPATLSLSPGERATLSCRS SKSLHLSNGITYLYWYQQKPGQA PRLLIYQMSNLASGIPARFSGSGSG TDFTLTISSELEPEDFAVYYCAQNLE LPWTFGGGTKLEIK	SEQ ID NO: 24
	NN-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	NN-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	NN-1093 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	NN-1093 CDR-L1	RSSKSLHLSNGITYLY	SEQ ID NO: 6
	NN-1093 CDR-L2	QMSNLAS	SEQ ID NO: 7
	NN-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22
PP-1093	PP-1093 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSCK ASGYTFTSYWMHWVRQAPGQGL EWVGEIDPSDSYTNYNQKFKGRV TLTRDTSTTTVYMESSLRSEDTA VYYCAKSNYVVPWYFDVWGQGT TVTVSS	SEQ ID NO: 25

TABLE 5-continued

Sequence of 1093 humanized anti-hNAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
	PP-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGERATLSCRS SKSLLLHSNGITYLYWYQQKPGQA PRLLIYQMSNLAGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCAQNL ELPWTFGGGTKLEIK	SEQ ID NO: 18
	PP-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	PP-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	PP-1093 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	PP-1093 CDR-L1	RSSKSLLLHSNGITYLY	SEQ ID NO: 6
	PP-1093 CDR-L2	QMSNLAG	SEQ ID NO: 7
	PP-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22
SS-1093	SS-1093 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESLRISCKA SGYTFTSYWMHWVRQMPGKGLE WMGEIDPSDSYTNYNQKFKGHVT ISADKSISTAYLQWSSLKASDTAM YYCAKSNYVVPWYFDVWGQGT LTVSS	SEQ ID NO: 26
	SS-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPATLSSLSPGERATLSCRS SKSLLLHSNGITYLYWYQQKPGQA PRLLIYQMSNLAGIPARFSGSGSG TDFTLTISSLEPEDFAVYYCAQNL LPWTFGGGTKLEIK	SEQ ID NO: 24
	SS-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	SS-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	SS-1093 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	SS-1093 CDR-L1	RSSKSLLLHSNGITYLY	SEQ ID NO: 6
	SS-1093 CDR-L2	QMSNLAG	SEQ ID NO: 7
	SS-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22
UU-1093	UU-1093 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESLRISCKA SGYTFTSYWMHWVRQMPGKGLE WMGEIDPSDSYTNYNQKFKGHVT ISADKSISTAYLQWSSLKASDTAM YYCAKSNYVVPWYFDVWGQGT LTVSS	SEQ ID NO: 26
	UU-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGERATLSCRS SKSLLLHSNGITYLYWYQQKPGQA PRLLIYQMSNLAGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCAQNL ELPWTFGGGTKLEIK	SEQ ID NO: 18
	UU-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	UU-1093 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	UU-1093 CDR-L1	RSSKSLLLHSNGITYLY	SEQ ID NO: 6
	UU-1093 CDR-L2	QMSNLAG	SEQ ID NO: 7
	UU-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22

Sequence of 1093 humanized anti-hNAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
XX-1093	XX-1093 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYWMHWVRQAPGQGL EWMGEIDPSDSYTNYNQKFGRV TMTRDTSTSTVYMELSSLRSEDTA VYYCAKSNIYVVPWYFDVWGTGT TVTVSS	SEQ ID NO: 27
	XX-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPATLSLSPGERATLSCRS SKSLLSNGITYLYWYQQKPGQA PRLLIYQMSNLAGIPARFSGSGSG TDFTLTISLLEPEDFAVYYCAQNLE LPWTFGGGTKLEIK	SEQ ID NO: 24
	XX-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	XX-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	XX-1093 CDR-H3	AKSNIYVVPWYFDV	SEQ ID NO: 21
	XX-1093 CDR-L1	RSSKSLLSNGITYLY	SEQ ID NO: 6
	XX-1093 CDR-L2	QMSNLAG	SEQ ID NO: 7
	XX-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22
ZZ-1093	ZZ-1093 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYWMHWVRQAPGQGL EWMGEIDPSDSYTNYNQKFGRV TMTRDTSTSTVYMELSSLRSEDTA VYYCAKSNIYVVPWYFDVWGTGT TVTVSS	SEQ ID NO: 27
	ZZ-1093 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGERATLSCRS SKSLLSNGITYLYWYQQKPGQA PRLLIYQMSNLAGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCAQNLE ELPWTFGGGTKLEIK	SEQ ID NO: 18
	ZZ-1093 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	ZZ-1093 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	ZZ-1093 CDR-H3	AKSNIYVVPWYFDV	SEQ ID NO: 21
	ZZ-1093 CDR-L1	RSSKSLLSNGITYLY	SEQ ID NO: 6
	ZZ-1093 CDR-L2	QMSNLAG	SEQ ID NO: 7
	ZZ-1093 CDR-L3	AQNLELPWT	SEQ ID NO: 22

[illegible]

TABLE 6-continued

Comparison of HC CDRs of 1093 anti-hNAMPT antibodies with HC CDRs of AL-310																		
SS-1093	19																	
UU-1093	19																	
XX-1093	19																	
ZZ-1093	19																	
HC CDR2																		SEQ ID NO:
AL-310	E	I	D	P	S	D	S	Y	T	N	Y	N	Q	K	F	K	G	20
FF-1093	20																	
II-1093	20																	
NN-1093	20																	
PP-1093	20																	
SS-1093	20																	
UU-1093	20																	
XX-1093	20																	
ZZ-1093	20																	
HC CDR3																		SEQ ID NO:
AL-310	A	K	S	N	Y	V	V	P	W	Y	F	D	V	21				
FF-1093	21																	
II-1093	21																	
NN-1093	21																	
PP-1093	21																	
SS-1093	21																	
UU-1093	21																	
XX-1093	21																	
ZZ-1093	21																	

TABLE 7

Comparison of LC CDRs of 1093 anti-hNAMPT antibodies with LC CDRs of AL-310																									
Light Chain (LC) CDR1																	SEQ ID NO:	LC CDR2						SEQ ID NO:	
AL-310	R	S	S	K	S	L	L	H	S	N	G	I	T	Y	L	Y	6	Q	M	S	N	L	A	S	7
FF-1093																	6							7	
II-1093																	6							7	
NN-1093																	6							7	
PP-1093																	6							7	
SS-1093																	6							7	
UU-1093																	6							7	

similar to Set 1 or LIN15 peptides, but with residues on positions 10 and 11 replaced by Ala. When a native Ala would occur on either position, it was replaced by Gly.

Set 3 (LIN30)

[0221] Set 3 peptides, also referred to herein as LIN30 peptides, are 30 amino acid long linear peptides that were derived from the target sequence of NAMPT with an offset of one residue.

Set 4 (LOOP7)

[0222] Set 4 peptides, also referred to herein as LOOP7 peptides, are 9 amino acid long constrained peptides. On positions 2-8 are 7-mer peptides derived from the target sequence of NAMPT with an offset of one residue. Cys residues were inserted on positions 1 and 9 and joined by mP2 CLIPST[™] in order to create a loop mimic. Native Cys were replaced by Cys-acm (denoted “2”).

Set 5 (LOOP15)

[0223] Set 5 peptides, also referred to herein as LOOP15 peptides, are 17 amino acid long constrained peptides. On positions 2-16 are 15-mer peptides derived from the target sequence of NAMPT (SEQ ID NO: 60) with an offset of one residue. Cys residues were inserted on positions 1 and 17 and joined by mP2 CLIPST[™] in order to create a loop mimic. Native Cys were replaced by Cys-acm (denoted “2”).

Set 6 (LOOP15.AA)

[0224] Set 6 peptides, also referred to herein as LOOP15.AA peptides, are 17 amino acid long constrained peptides that are similar to Set 5 or LOOP15 peptides, but with residues on positions 10 and 11 replaced by Ala. When a native Ala would occur on either position, it is replaced by Gly.

Set 7 (LOOP25)

[0225] Set 7 peptides, also referred to herein as LOOP25 peptides, are 27 amino acid long constrained peptides. On positions 2-26 are 25-mer peptides derived from the target sequence of NAMPT (SEQ ID NO: 60) with an offset of one residue. Cys residues were inserted on positions 1 and 27 and joined by mP2 CLIPST[™] in order to create a loop mimic. Native Cys were replaced by Cys-acm (denoted “2”).

Set 8 (BET)

[0226] Set 8 peptides, also referred to herein as BET peptides, are 22 amino acid long (3-turn peptide mimics. On positions 2-21 are 20-mer peptides derived from the target sequence of NAMPT (SEQ ID NO: 60) with an offset of one residue. Residues on positions 11 and 12 are replaced by “PG” motif in order to induce the (3-turn formation. Cys residues were inserted on positions 1 and 22 and joined by mP2 CLIPST[™] in order to stabilize the mimic. Native Cys were replaced by Cys-acm (denoted “2”).

Set 9 (HEL.CC)

[0227] Set 9 peptides, also referred to herein as HEL.CC peptides, are 22 amino acid long α -helical peptide mimics derived from residues of the target sequence (NAMPT; SEQ ID NO: 60) with an offset of one residue. Cys residues were

inserted on positions 1 and 5 and joined by means of mP2 CLIPST[™] in order to nucleate an α -helical structure. Native Cys were replaced by Cys-acm (denoted “2”).

Set 10 (HEL.IL)

[0228] Set 10 peptides, also referred to herein as HEL.IL peptides, are 26 amino acid long α -helical peptide mimics derived from residues of the target sequence (NAMPT; SEQ ID NO: 60) with an offset of one residue Leu and Ile residues were inserted in the sequence to facilitate a helical secondary structure without covalent restraints.

Screening Details

[0229] Antibody binding depends on a combination of factors, including concentration of the antibody and the amounts and nature of competing proteins in the ELISA buffer. Also, the pre-coat conditions (the specific treatment of the peptide arrays prior to incubation with the experimental sample) affect binding. These details are summed up in Table 8. For the PEPSCAN[™] Buffer and Preconditioning (SQ), the numbers indicate the relative amount of competing protein (a combination of horse serum and ovalbumin).

TABLE 8

Screening details			
Label	Dilution	Sample buffer	Pre-conditioning
K-1076 (Ab-1076-HC2-LC5)	5 μ g/mL	10% SQ	10% SQ
NN-1093 (NN-1093-HC3-LC3)	2 μ g/mL	1% SQ	1% SQ

[0230] For both antibodies in this study, we observed binding signals in various different regions throughout the NAMPT sequence. This suggests that the epitope for both antibodies are discontinuous epitopes. All signals observed were specific for the antibodies as incubation with secondary antibody alone did not result in any signal on the arrays. For Ab-1076-HC2-LC5, the core sequences derived from overlapping peptide sequences seem to form a binding interface that spans both monomers within an NAMPT dimer. Especially in the plot for the LIN30 mimic a dominant putative binding site can be observed, that is surrounded in the structure by additional sequences derived from lower intensity peaks. Tentative core epitopes for the antibody are listed below. Both antibodies bound the dimeric form of NAMPT.

[0231] The identified epitope candidates for both sequences showed a significant amount of recurring sequence similarities (e.g. ₁₇SYKVTHYKQYPPNTSKVYSYFECREKKT₄₄ (SEQ ID NO: 61) vs. ₁₆₂ATNSREQKK₁₇₀ (SEQ ID NO: 63), ₂₉NTSKVYSYFECREKKTENSKLRK₅₁ (SEQ ID NO: 72) vs. ₃₃₂FPVTENSKGYK₃₄₂ (SEQ ID NO: 67), and ₂₁₆KGTDTVAGLALIKKYYGTK₂₃₄ (SEQ ID NO: 75) vs. ₃₁₆NPLDTVLKVLEILGKK₃₃₁ (SEQ ID NO: 76).

TABLE 9			
List of main epitope candidates found in this study. Top candidates based on an intensity of at least 2x the median intensity value for the linear and conformational peptide arrays.			
Antibody	NAMPT Residue	Main epitope candidates	Sequence identifier
K-1076	17-44	SYKVTHYKQYPNTSKVYSYFECREKKT	SEQ ID NO: 61
	117-127	KAVPEGFV1PR	SEQ ID NO: 62
	162-170	ATNSREQKK	SEQ ID NO: 63
	242-261	VPAAEHSTITAWGKDHEKDA	SEQ ID NO: 64
	262-273	FEHIVTQFSSVP	SEQ ID NO: 65
	289-305	KIWGEDLRHLIVSRSTQ	SEQ ID NO: 66
	332-342	FPVTENSKGYK	SEQ ID NO: 67
	374-389	SIENIAFGSGGGLLQK	SEQ ID NO: 68
	418-425	VADPNKRS	SEQ ID NO: 69
	453-466	YGQDLLHTVFKNGK	SEQ ID NO: 70
	408-417	GLGINVFKDP	SEQ ID NO: 71
NN-1093	29-51	NTSKVYSYFECREKKTENSKLRK	SEQ ID NO: 72
	61-72	GLQYILNKYLKG	SEQ ID NO: 73
	156-170	WYPITVATNSREQKK	SEQ ID NO: 74
	216-234	KGTDTVAGLALIKKYYGTK	SEQ ID NO: 75
	316-331	NPLDTVLEILGKK	SEQ ID NO: 76
	332-342	FPVTENSKGYK	SEQ ID NO: 77
	373-389	WSIENIAFGSGGGLLQK	SEQ ID NO: 78
	417-431	PVADPNKRSKKGRLS	SEQ ID NO: 79
	454-469	GQDLLHTVFKNGKVTK	SEQ ID NO: 80
	470-478	SYSFDEIRK	SEQ ID NO: 81

Example 9. Characterization of Humanized Anti-hNAMPT Antibodies

[0232] 1076 humanized anti-hNAMPT antibodies described in Example 6, and 1093 humanized anti-hNAMPT antibodies described in Example 7 were subjected to in vitro and in vivo and testing for selection of lead humanized anti-hNAMPT antibodies.

Effect of Humanized Anti-hNAMPT Antibodies on hNAMPT-Induced Inflammatory Signaling

[0233] Effect of 1093 humanized anti-hNAMPT antibodies CC-1093, KK-1093, RR-1093, UU-1093, and XX-1093 on hNAMPT-induced inflammatory signaling was assessed by evaluation of NFκB activation in cells that were exposed to hNAMPT in absence or presence of these antibodies.

[0234] Recombinant hNAMPT (1.5 μg/ml) was premixed with vehicle or 100 μg/ml of a 1093 humanized anti-hNAMPT antibody (CC-1093, KK-1093, RR-1093, UU-1093, or XX-1093). Human lung endothelial cells (EC) were stimulated by exposing the cells to the hNAMPT mix for 1 hr. Unstimulated cells, which were not exposed to the hNAMPT mix, served as negative control (“NC”). Stimu-

lated cells, which were exposed to hNAMPT premixed with vehicle alone (“--”), served as positive control. Activation of NFκB in the cells was assessed by evaluating NFκB luciferase activity (NFκB-SecNanoLuc) (n=3–4 for each mAb). Results from the luciferase assay are provided in FIG. 7A.

[0235] As shown in FIG. 7A, hNAMPT induced NFκB activation in the hNAMPT-stimulated cells, which was substantially attenuated in presence of humanized anti-hNAMPT antibodies CC-1093, KK-1093, RR-1093, UU-1093, or XX-1093. While all of the five antibodies effectively reduced hNAMPT-induced activation of NFκB, the most substantial effect was observed with UU-1093 and XX-1093.

Effect of Humanized Anti-hNAMPT Antibodies on hNAMPT-Induced Decline in EC Barrier Integrity

[0236] EC electrical resistance is a reflection of lung EC barrier integrity. Accordingly, the effect of 1093 humanized anti-hNAMPT antibody UU-1093, and 1076 humanized anti-hNAMPT antibodies H-1076, P-1076, N-1076, and D-1076 on hNAMPT-induced decline in EC barrier integrity

was assessed by evaluating electrical resistance in ECs that were exposed to hNAMPT in absence or presence of these antibodies.

[0237] Recombinant hNAMPT (1.5 µg/ml) was premixed with vehicle alone, anti-NAMPT pAb, or a humanized anti-hNAMPT antibody (UU-1093, H-1076, P-1076, N-1076, or D-1076). Human lung ECs were stimulated by exposing the cells to the hNAMPT mix for 1 hr. Stimulated cells, which were exposed to hNAMPT premixed with vehicle alone or to hNAMPT premixed with pAb, served as controls. EC electrical resistance was evaluated as a readout of EC barrier integrity. Results from the testing are provided in FIG. 7B.

[0238] As shown in FIG. 7B, ECs exposed to hNAMPT premixed with each of the humanized anti-hNAMPT antibodies showed substantial induction of EC barrier activity over the control cells. Thus, hNAMPT-mediated decline in EC barrier activity was effectively reversed in presence of 1076 and 1093 humanized anti-hNAMPT antibodies.

In Vivo Testing of Humanized Anti-hNAMPT Antibodies in Lung Injury

[0239] Ability of 1076 humanized anti-hNAMPT antibodies (V-1076, N-1076, K-1076, and P-1076) and 1093 humanized anti-hNAMPT antibodies (SS-1093, CC-1093, XX-1093, and UU-1093) to treat lung injury was tested in vivo, using mouse and rat lung injury models.

[0240] To assess the effect of humanized anti-hNAMPT antibodies on a murine model of lung injury, V-1076, N-1076, K-1076, P-1076, SS-1093, CC-1093, XX-1093, or UU-1093 were injected intravenously at a dose of 0.4 mg/kg to mice that were exposed to LPS for 8 hr and VILI for the final 4 hr. Mice injected with vehicle and exposed to hNAMPT and VILI served as controls. Lung injury in the mice was assessed by analyzing the expression of BAL protein, and count of BAL-expressing cells. Also, edema and inflammatory cell infiltration in lung tissue was assessed by H & E staining, as readout of lung injury. Results from this “two hit” model of lung injury are provided in FIGS. 8A, 8B, and 8D.

[0241] As described in FIG. 8A, compared to the control mice, BAL protein level (FIG. 8A, left panel) and count of BAL-expressing cells (FIG. 8A, right panel) was effectively reduced in mice that were injected with either of the 1076 humanized anti-hNAMPT antibodies. While all of the 1076 humanized anti-hNAMPT antibodies tested effectively reduced lung injury in this “two hit” murine model, the most substantial effect was observed with P-1076.

As described in FIG. 8B, compared to the control mice, BAL protein level (FIG. 8B, left panel) and count of BAL-expressing cells (FIG. 8B, right panel) was effectively reduced in mice that were injected with either of the 1093 humanized anti-hNAMPT antibodies. While all of the 1093 humanized anti-hNAMPT antibodies tested effectively reduced lung injury in this “two hit” murine model, the most substantial effect was observed with UU-1093. Moreover, as described in FIG. 8D, protective effect of UU-1093 in the two-hit lung injury model was further reflected by reduced inflammatory cell infiltration and reduced edema in lung tissue from mice that were injected with UU-1093.

[0242] To assess the effect of humanized anti-hNAMPT antibody on a rat model of lung injury, 40 mg/kg, 80 mg/kg, or 160 mg/kg of P-1076 was injected intravenously to Sprague Dawley rats that were exposed to LPS. Rats

injected with vehicle and exposed to LPS served as positive controls. Rats injected with vehicle alone and not exposed to LPS served as negative controls. Lung injury in the rats was assessed by analyzing the expression of BAL protein, and count of BAL-expressing cells. Results from this rat model of lung injury are provided in FIG. 8C.

[0243] As described in FIG. 8C, compared to control mice (which were injected with vehicle and exposed to LPS), BAL protein level (FIG. 8C, left panel) and count of BAL-expressing cells (FIG. 8C, right panel) was effectively reduced in mice that were injected with humanized anti-hNAMPT antibody P-1076.

[0244] Thus, as described in FIG. 8, while all the tested humanized anti-hNAMPT antibodies effectively reduced lung injury in in vivo lung injury models, the most substantial effect was observed with P-1076 and UU-1093. Accordingly, P-1076 and UU-1093 were selected as the lead humanized and anti-hNAMPT antibodies, and were further modified to generate improved anti-hNAMPT antibodies.

Example 10. Modification of Humanized Anti-hNAMPT Antibody P-1076

[0245] Based on the results of in vitro and in vivo testing described in Example 9, anti-hNAMPT antibody P-1076 was selected for further modification to generate improved 1076 anti-hNAMPT antibodies.

P-1076-Mod Humanized Anti-hNAMPT Antibodies

[0246] P-1076-mod refers to humanized anti-hNAMPT antibodies that were generated by modifying 1076 humanized anti-hNAMPT antibody P-1076.

[0247] To generate improved P-1076-mod anti-hNAMPT antibodies, one or more mutations were introduced into the P-1076 sequence by de nova synthesis of the variable domain, or mutagenic oligonucleotide primers and polymerase chain reactions, or both, by methods well known in the art. These mutations were introduced to remove oxidation sites, to reduce or remove deamidation, to remove potential cleavage or fragmentation sites, to remove potential T-cell epitopes, and/or to reduce binding of potential T-cell epitopes. Different combinations of back mutations and other mutations were constructed for heavy and/or light chains of P-1076 to generate P-1076-mod anti-hNAMPT antibodies P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, and P-1076-mod11.

[0248] Amino acid sequences of the heavy and light chain variable regions of the modified P-1076-mod anti-hNAMPT antibodies are provided in Table 10. In Table 10, mutated residues are in bold font. Table 11 provides an alignment of the amino acid sequences of the heavy chain CDRs for modified P-1076-mod anti-hNAMPT antibodies P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, and P-1076-mod11 in comparison to P-1076. Table 12 provides an alignment of the amino acid sequences of the light chain CDRs for modified P-1076-mod anti-hNAMPT antibodies P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, and P-1076-mod11 in comparison to P-1076. Blank spaces in Tables 11 and 12 indicate that the residue is the

SEQ ID NO: 8. For the light chain of P-1076-mod5, a L-to-V mutation was introduced in the framework region of P-1076 VL to remove a potential T-cell epitope.

P-1076-mod7

[0255] P-1076-mod anti-hNAMPT antibody P-1076-mod7 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 15, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 31. The heavy chain variable region of P-1076-mod7 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5. The heavy chain of P-1076-mod7 is identical to P-1076 VH. The light chain variable region of P-1076-mod7 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 14, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8. For the light chain of P-1076-mod7, a L-to-I mutation was introduced in the framework region of P-1076 VL to remove a potential T-cell epitope.

P-1076-mod8

[0256] P-1076-mod anti-hNAMPT antibody P-1076-mod8 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 15, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 32. The heavy chain variable region of P-1076-mod8 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5. The heavy chain of P-1076-mod8 is identical to P-1076 VH. The light chain variable region of P-1076-mod8 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 33, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8. For the light chain of P-1076-mod8, a L-to-V mutation was introduced in the framework region of P-1076 VL and a L-to-G mutation was introduced in the P-1076 VL CDR2 to remove potential T-cell epitopes.

P-1076-mod9

[0257] P-1076-mod anti-hNAMPT antibody P-1076-mod9 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 15, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 34. The heavy chain variable region of P-1076-mod9 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and

a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5. The heavy chain of P-1076-mod9 is identical to P-1076 VH. The light chain variable region of P-1076-mod9 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 35, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8. For the light chain of P-1076-mod9, a L-to-V mutation was introduced in the framework region of P-1076 VL and a L-to-E mutation was introduced in the P-1076 VL CDR2 to remove potential T-cell epitopes.

P-1076-mod10

[0258] P-1076-mod anti-hNAMPT antibody P-1076-mod10 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 15, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 36. The heavy chain variable region of P-1076-mod10 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5. The heavy chain of P-1076-mod10 is identical to P-1076 VH. The light chain variable region of P-1076-mod10 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 37, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8. For the light chain of P-1076-mod10, a L-to-I mutation was introduced in the framework region of P-1076 VL to remove a potential T-cell epitope, and a L-to-V mutation was introduced in the P-1076 VL CDR2 to reduce the binding of a potential T-cell epitope.

P-1076-mod11

[0259] Modified P-1076-mod anti-hNAMPT antibody P-1076-mod11 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 28, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 13. The heavy chain variable region of P-1076-mod11 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 29, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 5. For the heavy chain of P-1076-mod11, a D-to-E mutation was introduced into the P-1076 VH CDR2 to remove a potential cleavage or fragmentation site. The light chain variable region of P-1076-mod11 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 14, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 8. The light chain of P-1076-mod11 is identical to P-1076 VL.

TABLE 10

Sequence of P-1076-mod anti-hNAMPT antibodies			
Antibody Description		Amino Acid Sequence	Sequence Identifier
P-1076-mod1 heavy chain variable region (VH) (CDRs underlined)	P-1076-mod1	QVQLVQSGAEVTKPGASVKV	SEQ ID NO: 28
	heavy chain	ASGYTFTSYWMQWVRQAPGQGL	
	variable region	EWVGEI <u>EPSNSY</u> TNYNQKFRGRV	
	(VH)	TLTRDTSTTTTVYMELSSLRSEDTA	
	(CDRs underlined)	VYYC <u>ARGGYWGQ</u> GTTVTVSS	

TABLE 10-continued

Sequence of P-1076-mod anti-hNAMPT antibodies			
Antibody Description	Amino Acid Sequence	Sequence Identifier	
P-1076-mod1	P-1076-mod1 light chain variable region (VL) (CDRs underlined)	DIVMTQSP ~~LSLPVTPGEPASIS~~ <u>RSSKSL</u> LHSQGIT ~~YLYWYVQKPG~~ <u>QSPQLLIYQL</u> SNRASGVPDRFSG SGSGTDFTLKISRVEAEDVGVYY <u>CVQNLELPYT</u> FGGGTKLEIK	SEQ ID NO: 30
	P-1076-mod1 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	P-1076-mod1 CDR-H2	EIEPSNSYTNYNQKFRG	SEQ ID NO: 29
	P-1076-mod1 CDR-H3	ARGGY	SEQ ID NO: 5
	P-1076-mod1 CDR-L1	RSSKSL ~~LHSQGIT~~ YLY	SEQ ID NO: 11
	P-1076-mod1 CDR-L2	QLSNRAS	SEQ ID NO: 14
	P-1076-mod1 CDR-L3	VQNLELPYT	SEQ ID NO: 8
	P-1076-mod2 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVS CKASGYTFTSYWMQWVRQAPG <u>QGLEWVGEI</u> EPSNSYTNYNQK <u>FRRVTLTRDTSTTTVYME</u> LSS LRSEDTAVYYC <u>CARGGYWGQGT</u> TVTVSS	SEQ ID NO: 28
	P-1076-mod2 light chain variable region (VL) (CDRs underlined)	DIVMTQSP ~~LSLPVTPGEPASIS~~ <u>CRSSKSL</u> LHSQGIT ~~YLYWYIQK~~ <u>PGQSPQLLIYQL</u> SNRASGVPDR FSGSGSGTDFTLKISRVEAEDV GVYYC <u>VQNLELPYT</u> FGGGTKLEIK	SEQ ID NO: 31
	P-1076-mod2 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
P-1076-mod2	P-1076-mod2 CDR-H2	EIEPSNSYTNYNQKFRG	SEQ ID NO: 29
	P-1076-mod2 CDR-H3	ARGGY	SEQ ID NO: 5
	P-1076-mod2 CDR-L1	RSSKSL ~~LHSQGIT~~ YLY	SEQ ID NO: 11
	P-1076-mod2 CDR-L2	QLSNRAS	SEQ ID NO: 14
	P-1076-mod2 CDR-L3	VQNLELPYT	SEQ ID NO: 8
P-1076-mod3	P-1076-mod3 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG <u>LEWVGEI</u> EPSNSYTNYNQKFRR <u>VTLTRDTSTTTVYME</u> LSSLRSE DTAVYYC <u>CARGGYWGQGT</u> TVTVSS	SEQ ID NO: 28
	P-1076-mod3 light chain variable region (VL) (CDRs underlined)	DIVMTQSP ~~LSLPVTPGEPASIS~~ <u>CRSSKSL</u> LHSQGIT ~~YLYWYVQK~~ <u>PGQSPQLLIYQ</u> SNRASGVPDR FSGSGSGTDFTLKISRVEAEDV GVYYC <u>VQNLELPYT</u> FGGGTKLEIK	SEQ ID NO: 32

TABLE 10-continued

Sequence of P-1076-mod anti-hNAMPT antibodies			
Antibody Description	Amino Acid Sequence	Sequence Identifier	
P-1076-mod3 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3	
P-1076-mod3 CDR-H2	EIEPSNSYTNYNQKFRG	SEQ ID NO: 29	
P-1076-mod3 CDR-H3	ARGGY	SEQ ID NO: 5	
P-1076-mod3 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11	
P-1076-mod3 CDR-L2	QGSNRAS	SEQ ID NO: 33	
P-1076-mod3 CDR-L3	VQNLELPYT	SEQ ID NO: 8	
P-1076-mod4	P-1076-mod4 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVG <u>EIEPSNSYTNYNQKFRR</u> VTLTRDTSTTTVYMELSSLRSE DTAVYYC <u>ARGGYWGQTTVTVS</u> S	SEQ ID NO: 28
	P-1076-mod4 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVTGPGEPAIS <u>CRSSKSLHLSQGITYLYWYVQK</u> PGQSPQLLIY <u>QESNRASGVPDR</u> FSGSGSGTDFTLKISRVEAEDV GVYYCV <u>QNL</u> <u>ELPYTFGGGTKLEIK</u>	SEQ ID NO: 34
P-1076-mod4 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3	
P-1076-mod4 CDR-H2	EIEPSNSYTNYNQKFRG	SEQ ID NO: 29	
P-1076-mod4 CDR-H3	ARGGY	SEQ ID NO: 5	
P-1076-mod4 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11	
P-1076-mod4 CDR-L2	QESNRAS	SEQ ID NO: 35	
P-1076-mod4 CDR-L3	VQNLELPYT	SEQ ID NO: 8	
P-1076-mod5	P-1076-mod5 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVG <u>EIEPSNSYTNYNQKFRR</u> VTLTRDTSTTTVYMELSSLRSE DTAVYYC <u>ARGGYWGQTTVTVS</u> S	SEQ ID NO: 28
	P-1076-mod5 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVTGPGEPAIS <u>CRSSKSLHLSQGITYLYWYIQK</u> PGQSPQLLIY <u>QVSNRASGVPDR</u> FSGSGSGTDFTLKISRVEAEDV GVYYCV <u>QNL</u> <u>ELPYTFGGGTKLEIK</u>	SEQ ID NO: 36
P-1076-mod5 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3	
P-1076-mod5 CDR-H2	EIEPSNSYTNYNQKFRG	SEQ ID NO: 29	

TABLE 10-continued

Sequence of P-1076-mod anti-hNAMPT antibodies		
Antibody Description	Amino Acid Sequence	Sequence Identifier
P-1076-mod5 CDR-H3	ARGGY	SEQ ID NO: 5
P-1076-mod5 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11
P-1076-mod5 CDR-L2	QVSNRAS	SEQ ID NO: 37
P-1076-mod5 CDR-L3	VQNLELPYT	SEQ ID NO: 8
P-1076-mod6 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVGEIDPSNSYTNYNQKFRG RVTLTRDTSTTTVYMELSSLRS EDTAVYYC <u>ARGGY</u> WGQGTTVTVSS	SEQ ID NO: 15
P-1076-mod6 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVTGPGEPAIS <u>CRSSKSLHLSQGITYLY</u> WYVQK PGQSPQLLIY <u>QLSNRAS</u> GVPDR FSGSGSGTDFTLKISRVEAEDV GVYYC <u>VQNLELPYT</u> TFGGGTKLEIK	SEQ ID NO: 30
P-1076-mod6 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
P-1076-mod6 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
P-1076-mod6 CDR-H3	ARGGY	SEQ ID NO: 5
P-1076-mod6 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11
P-1076-mod6 CDR-L2	QLSNRAS	SEQ ID NO: 14
P-1076-mod6 CDR-L3	VQNLELPYT	SEQ ID NO: 8
P-1076-mod7 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVGEIDPSNSYTNYNQKFRG RVTLTRDTSTTTVYMELSSLRS EDTAVYYC <u>ARGGY</u> WGQGTTVTVSS	SEQ ID NO: 15
P-1076-mod7 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVTGPGEPAIS <u>CRSSKSLHLSQGITYLY</u> WYIQK PGQSPQLLIY <u>QLSNRAS</u> GVPDR FSGSGSGTDFTLKISRVEAEDV GVYYC <u>VQNLELPYT</u> TFGGGTKLEIK	SEQ ID NO: 31
P-1076-mod7 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
P-1076-mod7 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
P-1076-mod7 CDR-H3	ARGGY	SEQ ID NO: 5
P-1076-mod7 CDR-L1	RSSKSLHLSQGITYLY	SEQ ID NO: 11

TABLE 10-continued

Sequence of P-1076-mod anti-hNAMPT antibodies		
Antibody Description	Amino Acid Sequence	Sequence Identifier
P-1076-mod7 CDR-L2	QLSNRAS	SEQ ID NO: 14
P-1076-mod7 CDR-L3	VQNLELPYT	SEQ ID NO: 8
P-1076-mod8 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVGEIDPSNSYTNYNQKFRG RVTLTRDTSTTTVYMELSSLRS EDTAVYYCARGGYWGQTTVTV SS	SEQ ID NO: 15
P-1076-mod8 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVTGPGEPAIS CRSSKSLLSQGITYLYWYVQK PGQSPQLLIYQGSNRASGVPDR FSGSGSGTDFTLKISRVEADV GVYYCVQNLELPYTFGGGTKLE IK	SEQ ID NO: 32
P-1076-mod8 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
P-1076-mod8 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
P-1076-mod8 CDR-H3	ARGGY	SEQ ID NO: 5
P-1076-mod8 CDR-L1	RSSKSLLSQGITYLY	SEQ ID NO: 11
P-1076-mod8 CDR-L2	QGSNRAS	SEQ ID NO: 33
P-1076-mod8 CDR-L3	VQNLELPYT	SEQ ID NO: 8
P-1076-mod9 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVGEIDPSNSYTNYNQKFRG RVTLTRDTSTTTVYMELSSLRS EDTAVYYCARGGYWGQTTVTV SS	SEQ ID NO: 15
P-1076-mod9 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVTGPGEPAIS CRSSKSLLSQGITYLYWYVQK PGQSPQLLIYQESNRASGVPDR FSGSGSGTDFTLKISRVEADV GVYYCVQNL ELPYTFGGGTKLEIK	SEQ ID NO: 34
P-1076-mod9 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
P-1076-mod9 CDR-H2	EIDPSNSYTNYNQKFRG	SEQ ID NO: 4
P-1076-mod9 CDR-H3	ARGGY	SEQ ID NO: 5
P-1076-mod9 CDR-L1	RSSKSLLSQGITYLY	SEQ ID NO: 11
P-1076-mod9 CDR-L2	QESNRAS	SEQ ID NO: 35
P-1076-mod9 CDR-L3	VQNLELPYT	SEQ ID NO: 8

TABLE 10-continued

Sequence of P-1076-mod anti-hNAMPT antibodies			
Antibody	Description	Amino Acid Sequence	Sequence Identifier
P-1076-mod10	P-1076-mod10 heavy chain variable region (VH) (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVG E IDPSNSYTNYN Q KFRG RVTLTRDTSTTTVYME L SSLRS EDTAVYYC ARGGY WGQGT T TVTVSS	SEQ ID NO: 15
	P-1076-mod10 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVT P GEPASIS CRSSK S LLHS Q GITYLYWY I QK PGQSPQ L LIY Q VSNRASGVPDR FSGSGSGTDFTLKISRVEAEDV GVYYC VQ NLELPY T FGGGTKLEIK	SEQ ID NO: 36
	P-1076-mod10 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	P-1076-mod10 CDR-H2	EIDPSNSYTNYN Q KFRG	SEQ ID NO: 4
	P-1076-mod10 CDR-H3	ARGGY	SEQ ID NO: 5
	P-1076-mod10 CDR-L1	RSSK S LLHS Q GITYLY	SEQ ID NO: 11
	P-1076-mod10 CDR-L2	Q VSNRAS	SEQ ID NO: 37
P-1076-mod11	P-1076-mod10 CDR-L3	VQ NLELPYT	SEQ ID NO: 8
	P-1076-mod11 heavy chain variable region (VH) hIgG1 backbone (CDRs underlined)	QVQLVQSGAEVTKPGASVKVSC KASGYTFTSYWMQWVRQAPGQG LEWVG E I E PSNSYTNYN Q KFRG RVTLTRDTSTTTVYME L SSLRS EDTAVYYC ARGGY WGQGT T TVTVSS	SEQ ID NO: 28
	P-1076-mod11 light chain variable region (VL) (CDRs underlined)	DIVMTQSPLSLPVT P GEPASIS CRSSK S LLHS Q GITYLYWY L QK PGQSPQ L LIY Q LSNRASGVPDR FSGSGSGTDFTLKISRVEAEDV GVYYC VQ NLELPY T FGGGTKLEIK	SEQ ID NO: 13
	P-1076-mod11 CDR-H1	GYTFTSYWMQ	SEQ ID NO: 3
	P-1076-mod11 CDR-H2	E I E PSNSYTNYN Q KFRG	SEQ ID NO: 29
	P-1076-mod11 CDR-H3	ARGGY	SEQ ID NO: 5
	P-1076-mod11 CDR-L1	RSSK S LLHS Q GITYLY	SEQ ID NO: 11
P-1076-mod11	P-1076-mod11 CDR-L2	Q LSNRAS	SEQ ID NO: 14
	P-1076-mod11 CDR-L3	VQ NLELPYT	SEQ ID NO: 8

* In Table 10, mutated residues are in bold font.

TABLE 11																																	
Comparison of HC CDRs of P-1076-mod anti-hNAMPT antibodies with HC CDRs of P-1076																																	
Heavy Chain (HC) CDR1											SEQ ID NO:			HC CDR2															SEQ ID NO:				
P-1076	G	Y	T	F	T	S	Y	W	M	Q	3	E	I	D	P	S	N	S	Y	T	N	Y	N	Q	K	F	R	G	4				
P-1076-mod1											3			E															29				
P-1076-mod2											3			E															29				
P-1076-mod3											3			E															29				
P-1076-mod4											3			E															29				
P-1076-mod5											3			E															29				
P-1076-mod6											3																		4				
P-1076-mod7											3																		4				
P-1076-mod8											3																		4				
P-1076-mod9											3																		4				
P-1076-mod10											3																		4				
P-1076-mod11											3			E															29				
																								HC CDR3					SEQ ID NO:				
																		P-1076					A					R	G	G	Y	5	
																		P-1076-mod1															5
																		P-1076-mod2															5
																		P-1076-mod3															5
																		P-1076-mod4															5
																		P-1076-mod5															5
																		P-1076-mod6															5
																		P-1076-mod7															5
																		P-1076-mod8															5
																		P-1076-mod9															5
																		P-1076-mod10															5
																		P-1076-mod11															5

TABLE 12																									
Comparison of LC CDRs of P-1076-mod anti-hNAMPT antibodies with LC CDRs of P-1076																									
Light Chain (LC) CDR1																	SEQ ID NO:		LC CDR2						SEQ ID NO:
P-1076	R	S	S	K	S	L	L	H	S	Q	G	I	T	Y	L	Y	11	Q	L	S	N	R	A	S	14
P-1076 mod1																	11								14
P-1076 mod2																	11								14
P-1076 mod3																	11		G						33
P-1076 mod4																	11		E						35
P-1076 mod5																	11		V						37
P-1076 mod6																	11								14
P-1076 mod7																	11								14
P-1076 mod8																	11		G						33

TABLE 12-continued				
Comparison of LC CDRs of P-1076-mod anti-hNAMPT antibodies with LC CDRs of P-1076				
P-1076 mod9	11	E		35
P-1076 mod10	11	V		37
P-1076 mod11	11			14
LC CDR3				SEQ ID NO:
P-1076	V	Q	N L E L P Y T	8
P-1076-mod1				8
P-1076-mod2				8
P-1076-mod3				8
P-1076-mod4				8
P-1076-mod5				8
P-1076-mod6				8
P-1076-mod7				8
P-1076-mod8				8
P-1076-mod9				8
P-1076-mod10				8
P-1076-mod11				8

TABLE 13					
Biophysical characteristics of P-1076-mod anti-hNAMPT antibodies					
Antibody	Concentration (mg/ml)	Volume (ml)	Total (mg)	Pot. Yield (mg/L)	*Purity
P-1076	1.82	1.34	2.44	97.60	>95%
P-1076-mod6	1.29	1.43	1.84	73.60	>95%
P-1076-mod7	1.27	1.28	1.63	65.20	>95%
P-1076-mod8	1.25	1.36	1.70	68.00	>95%
P-1076-mod9	1.32	1.28	1.69	67.60	>95%
P-1076-mod10	1.23	1.22	1.50	60.00	>95%
P-1076-mod11	1.22	1.26	1.54	61.60	>95%
P-1076-mod1	1.21	1.39	2.85	114.00	>95%
P-1076-mod2	0.89	1.30	1.16	46.40	>95%
P-1076-mod3	1.07	1.34	1.43	57.20	>95%
P-1076-mod4	1.17	1.38	1.61	64.40	>95%
P-1076-mod5	0.77	1.34	1.03	41.20	>95%

Example 11. Modification of Humanized Anti-hNAMPT Antibody UU-1093

[0260] Based on the results of in vitro and in vivo testing described in Example 9, anti-hNAMPT antibody UU-1093 was selected for further modification to generate modified 1093 anti-hNAMPT antibodies.

UU-1093-Mod Humanized Anti-hNAMPT Antibodies

[0261] UU-1093-mod refers to humanized anti-hNAMPT antibodies that were generated by modifying 1093 humanized anti-hNAMPT antibody UU-1093.

[0262] To generate improved UU-1093-mod anti-hNAMPT antibodies, one or more mutations were introduced into the UU-1093 amino acid sequence by de nova synthesis of the variable domain, or mutagenic oligonucleotide primers and polymerase chain reactions, or both, by methods well known in the art. These mutations were introduced to remove oxidation sites, to reduce or remove deamidation, to remove potential cleavage or fragmentation sites, to remove potential T-cell epitopes, and/or to reduce

the binding of potential T-cell epitopes. Different combinations of back mutations and other mutations were constructed for heavy and/or light chains of UU-1093 to generate modified UU-1093-mod anti-hNAMPT antibodies UU-1093-mod1, UU-1093-mod2, UU-1093-mod3, UU-1093-mod4, UU-1093-mod5, UU-1093-mod6, UU-1093-mod7, UU-1093-mod8, UU-1093-mod9, UU-1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093-mod13, UU-1093-mod14, UU-1093-mod15, UU-1093-mod16, UU-1093-mod17, UU-1093-mod18, and UU-1093-mod19.

[0263] Amino acid sequences of the heavy and light chain variable regions of the modified P-1076-mod anti-hNAMPT antibodies are provided in Table 14. In Table 14, mutated residues are in bold font. Table 15 provides an alignment of the amino acid sequences of the heavy chain CDRs for modified UU-1093-mod anti-hNAMPT antibodies UU-1093-mod1, UU-1093-mod2, UU-1093-mod3, UU-1093-mod4, UU-1093-mod5, UU-1093-mod6, UU-1093-mod7, UU-1093-mod8, UU-1093-mod9, UU-1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093-mod13, UU-1093-mod14, UU-1093-mod15, UU-1093-mod16, UU-1093-mod17, UU-1093-mod18, and UU-1093-mod19 in comparison to UU-1093. Table 16 provides an alignment of the amino acid sequences of the light chain CDRs for modified UU-1093-mod anti-hNAMPT antibodies UU-1093-mod1, UU-1093-mod2, UU-1093-mod3, UU-1093-mod4, UU-1093-mod5, UU-1093-mod6, UU-1093-mod7, UU-1093-mod8, UU-1093-mod9, UU-1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093-mod13, UU-1093-mod14, UU-1093-mod15, UU-1093-mod16, UU-1093-mod17, UU-1093-mod18, and UU-1093-mod19 in comparison to UU-1093. Blank spaces in Tables 15 and 16 indicate that the residue is the same as UU-1093.

UU-1093-mod1

[0264] UU-1093-mod anti-hNAMPT antibody UU-1093-mod1 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 38, and a light chain

and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22. The light chain of UU-1093-mod13 is identical to UU-1093 VL.

UU-1093-mod14

[0277] UU-1093-mod anti-hNAMPT antibody UU-1093-mod14 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 40, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 18. The heavy chain variable region of UU-1093-mod14 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 39, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 41. For the heavy chain of UU-1093-mod14, a D-to-E mutation was introduced into the UU-1093 VH CDR2 to remove a potential cleavage or fragmentation site, and a S-to-T mutation was introduced into the UU-1093 VH CDR3 to remove a potential T-cell epitope. The light chain variable region of UU-1093-mod14 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22. The light chain of UU-1093-mod14 is identical to UU-1093 VL.

UU-1093-mod15

[0278] UU-1093-mod anti-hNAMPT antibody UU-1093-mod15 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 42, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 18. The heavy chain variable region of UU-1093-mod15 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 43, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 39, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 44. For the heavy chain of UU-1093-mod15, a M-to-I mutation was introduced into the UU-1093 VH CDR1 to remove an oxidation site; a M-to-V mutation was introduced into the UU-1093 VH framework region 2 to remove an oxidation site and a potential T-cell epitope; a D-to-E mutation was introduced into the UU-1093 VH CDR2 to remove a potential cleavage or fragmentation site; a M-to-V mutation was introduced into the UU-1093 VH framework region 3 to remove an oxidation site; and a K-to-R mutation was introduced into the UU-1093 VH CDR3 to reduce the binding of a potential T-cell epitope. The light chain variable region of UU-1093-mod15 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22. The light chain of UU-1093-mod15 is identical to UU-1093 VL.

UU-1093-mod16

[0279] UU-1093-mod anti-hNAMPT antibody UU-1093-mod16 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 45, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 18. The heavy chain variable region of UU-1093-mod16 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 46, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 39, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 41. For the heavy chain of

UU-1093-mod16, a W-to-F mutation and a M-to-I mutation were introduced into the UU-1093 VH CDR1 to remove an oxidation site; a M-to-V mutation was introduced into the UU-1093 VH framework region 2 to remove an oxidation site and a potential T-cell epitope; a D-to-E mutation was introduced into the UU-1093 VH CDR2 to remove a potential cleavage or fragmentation site; a M-to-V mutation was introduced into the UU-1093 VH framework region 3 to remove an oxidation site; and a S-to-T mutation was introduced into the UU-1093 VH CDR3 to remove a potential T-cell epitope. The light chain variable region of UU-1093-mod16 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22. The light chain of UU-1093-mod16 is identical to UU-1093 VL.

UU-1093-mod17

[0280] UU-1093-mod anti-hNAMPT antibody UU-1093-mod17 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 26, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 47. The heavy chain variable region of UU-1093-mod17 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. The heavy chain of UU-1093-mod17 is identical to UU-1093 VH. The light chain variable region of UU-1093-mod17 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22. For the light chain of UU-1093-mod17, a N-to-Q mutation was introduced into the UU-1093 VL CDR1 to reduce or remove deamidation.

UU-1093-mod18

[0281] UU-1093-mod anti-hNAMPT antibody UU-1093-mod18 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 26, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 48. The heavy chain variable region of UU-1093-mod18 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. The heavy chain of UU-1093-mod18 is identical to UU-1093 VH. The light chain variable region of UU-1093-mod18 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 49, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 50, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 22. For the light chain of UU-1093-mod18, a G-to-A mutation was introduced into the UU-1093 VL CDR1 to reduce or remove deamidation; a I-to-V mutation was introduced into the UU-1093 VL framework region 2 to reduce the binding of a potential T-cell epitope; a M-to-V mutation was introduced into the UU-1093 VL CDR2 to reduce the binding of a potential T-cell epitope and to remove an oxidation site; and a I-to-V mutation was introduced into the UU-1093 VH framework region 3 to reduce the binding of a potential T-cell epitope.

UU-1093-mod19

[0282] UU-1093-mod anti-hNAMPT antibody UU-1093-mod19 has a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 26, and a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 51. The heavy chain variable region of UU-1093-mod19 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 19, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 20, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 21. The heavy chain of UU-1093-mod17 is identical to UU-1093 VH. The light chain variable region of UU-1093-mod19 contains a CDR1 domain with an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain with an amino acid sequence as set forth in SEQ ID NO: 52, and a CDR3 domain with an amino acid sequence as set forth in SEQ ID NO: 53. For the light chain of UU-1093-mod19, a N-to-Q mutation was introduced into the UU-1093 VL CDR1 to reduce or remove deamidation; a I-to-V mutation was introduced into the UU-1093 VL framework region 2 to remove a potential T-cell epitope; a M-to-V mutation was introduced into the UU-1093 VL CDR2 to remove a potential T-cell epitope and to remove an oxidation site; a A-to-G mutation was introduced into the UU-1093 VL CDR2 to remove a potential T-cell epitope; and a W-to-F mutation was introduced into the UU-1093 VL CDR3 to remove an oxidation site.

TABLE 14

Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
UU-1093-mod1	UU-1093-mod1 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSYWMHW VRQMPGKGLEWMGEI <u>EPS</u> DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCA <u>KS</u> NYVVPWYFD <u>VWGQ</u> GLVTVSS	SEQ ID NO: 38
	UU-1093-mod1 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL <u>LHSQGIT</u> YLYWYQQKPGQAPRLLIY QMSNLASGIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCA <u>QNL</u> ELPWTFGGG <u>TK</u> LEIK	SEQ ID NO: 47
	UU-1093-mod1 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093-mod1 CDR-H2	EI <u>EPS</u> DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod1 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	UU-1093-mod1 CDR-L1	RSSKSL <u>LHSQGIT</u> YLY	SEQ ID NO: 11
	UU-1093-mod1 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod1 CDR-L3	AQNL <u>ELPWT</u>	SEQ ID NO: 22

TABLE 14-continued

Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
UU-1093-mod2	UU-1093-mod2 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSYWMHW VRQMPGKGLEWMGEI <u>EPS</u> DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCA <u>KT</u> NYVVPWYFD <u>VWGQ</u> GLVTVSS	SEQ ID NO: 40
	UU-1093-mod2 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL <u>LHSQGIT</u> YLYWYQQKPGQAPRLLIY QMSNLASGIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCA <u>QNL</u> ELPWTFGGG <u>TK</u> LEIK	SEQ ID NO: 47
	UU-1093-mod2 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093-mod2 CDR-H2	EI <u>EPS</u> DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod2 CDR-H3	AK <u>T</u> NYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod2 CDR-L1	RSSKSL <u>LHSQGIT</u> YLY	SEQ ID NO: 11
	UU-1093-mod2 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod2 CDR-L3	AQNL <u>ELPWT</u>	SEQ ID NO: 22
UU-1093-mod3	UU-1093-mod3 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY <u>WI</u> HW VRQVPGKGLEWMGEI <u>EPS</u> DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYYCA <u>RS</u> NYVVPWYFD <u>VWGQ</u> GLVTVSS	SEQ ID NO: 42
	UU-1093-mod3 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL <u>LHSQGIT</u> YLYWYQQKPGQAPRLLIY QMSNLASGIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCA <u>QNL</u> ELPWTFGGG <u>TK</u> LEIK	SEQ ID NO: 47
	UU-1093-mod3 CDR-H1	GYTFTSY <u>WI</u> H	SEQ ID NO: 43
	UU-1093-mod3 CDR-H2	EI <u>EPS</u> DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod3 CDR-H3	ARSNYVVPWYFDV	SEQ ID NO: 44
	UU-1093-mod3 CDR-L1	RSSKSL <u>LHSQGIT</u> YLY	SEQ ID NO: 11
	UU-1093-mod3 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod3 CDR-L3	AQNL <u>ELPWT</u>	SEQ ID NO: 22

TABLE 14-continued

Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
UU-1093-mod4	UU-1093-mod4 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY FI HW VRQVPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYYCA KTNYVVPWYFD VWGQGTLVTVSS	SEQ ID NO: 45
	UU-1093-mod4 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSQG IT YLYWYQQKPGQAPRLLIY QMSN L ASGIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCA QNL ELPWTFGGGTK LEIK	SEQ ID NO: 47
	UU-1093-mod4 CDR-H1	GYTFTSY FIH	SEQ ID NO: 46
	UU-1093-mod4 CDR-H2	E IE PSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod4 CDR-H3	AK T NYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod4 CDR-L1	RSSKSL LHSQ GITYLY	SEQ ID NO: 11
	UU-1093-mod4 CDR-L2	QMSN L AS	SEQ ID NO: 7
	UU-1093-mod4 CDR-L3	A QNL ELPWT	SEQ ID NO: 22
	UU-1093-mod5 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY W MIHW VRQMPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCA KSNYVVPWYFD VWGQGTLVTVSS	SEQ ID NO: 38
	UU-1093-mod5 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSNA IT YLYWYQQKPGQAPRLLVY QVS N LASGVPDRFSGSGS GTDFTLTISRLEPEDFAV YYCA QNL ELPWTFGGGTK LEIK	SEQ ID NO: 48
UU-1093-mod5	UU-1093-mod5 CDR-H1	GYTFTSY W MH	SEQ ID NO: 19
	UU-1093-mod5 CDR-H2	E IE PSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod5 CDR-H3	AK S NYVVPWYFDV	SEQ ID NO: 21
	UU-1093-mod5 CDR-L1	RSSKSL LHSNA ITYLY	SEQ ID NO: 49
	UU-1093-mod5 CDR-L2	QVS N LAS	SEQ ID NO: 50
	UU-1093-mod5 CDR-L3	A QNL ELPWT	SEQ ID NO: 22

TABLE 14-continued

Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
UU-1093-mod6	UU-1093-mod6 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY W MIHW VRQMPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCA KTNYVVPWYFD VWGQGTLVTVSS	SEQ ID NO: 40
	UU-1093-mod6 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSNA IT YLYWYQQKPGQAPRLLVY QVS N LASGVPDRFSGSGS GTDFTLTISRLEPEDFAV YYCA QNL ELPWTFGGGTK LEIK	SEQ ID NO: 48
	UU-1093-mod6 CDR-H1	GYTFTSY W MH	SEQ ID NO: 19
	UU-1093-mod6 CDR-H2	E IE PSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod6 CDR-H3	AK T NYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod6 CDR-L1	RSSKSL LHSNA ITYLY	SEQ ID NO: 49
	UU-1093-mod6 CDR-L2	QVS N LAS	SEQ ID NO: 50
	UU-1093-mod6 CDR-L3	A QNL ELPWT	SEQ ID NO: 22
UU-1093-mod7	UU-1093-mod7 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY W MIHW VRQVPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYYCA RSNYVVPWYFD VWGQGTLVTVSS	SEQ ID NO: 42
	UU-1093-mod7 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSNA IT YLYWYQQKPGQAPRLLVY QVS N LASGVPDRFSGSGS GTDFTLTISRLEPEDFAV YYCA QNL ELPWTFGGGTK LEIK	SEQ ID NO: 48
	UU-1093-mod7 CDR-H1	GYTFTSY W IH	SEQ ID NO: 43
	UU-1093-mod7 CDR-H2	E IE PSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod7 CDR-H3	A R SNYVVPWYFDV	SEQ ID NO: 44
	UU-1093-mod7 CDR-L1	RSSKSL LHSNA ITYLY	SEQ ID NO: 49
	UU-1093-mod7 CDR-L2	QVS N LAS	SEQ ID NO: 50
UU-1093-mod7	UU-1093-mod7 CDR-L3	A QNL ELPWT	SEQ ID NO: 22

TABLE 14-continued			
Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
UU-1093-mod8	UU-1093-mod8 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY FIHW VRQVPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVY YCAKTNYVVPWYFDVWGQ GTLVTVSS	SEQ ID NO: 45
	UU-1093-mod8 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSNAIT YLYWYQQKPGQAPRLLVY QVSNLASGVPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELP WTF GGG TK LEIK	SEQ ID NO: 48
	UU-1093-mod8 CDR-H1	GYTFTSY FIH	SEQ ID NO: 46
	UU-1093-mod8 CDR-H2	E IEPS DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod8 CDR-H3	AKTNYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod8 CDR-L1	RSSKSL LHSNAIT YLY	SEQ ID NO: 49
	UU-1093-mod8 CDR-L2	QVSNLAS	SEQ ID NO: 50
	UU-1093-mod8 CDR-L3	AQNLELP WTF	SEQ ID NO: 22
	UU-1093-mod9 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY WMIHW VRQMPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCAKSNYVVPWYFD VWGQGTSLVTVSS	SEQ ID NO: 38
	UU-1093-mod9 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSQG IT YLYWYQQKPGQAPRLLVY QVSNLGS G IPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELP FTF GGG TK LEIK	SEQ ID NO: 51
UU-1093-mod9	UU-1093-mod9 CDR-H1	GYTFTSY WMIH	SEQ ID NO: 19
	UU-1093-mod9 CDR-H2	E IEPS DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod9 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	UU-1093-mod9 CDR-L1	RSSKSL LHSQG ITYLY	SEQ ID NO: 11
	UU-1093-mod9 CDR-L2	QVSNLGS	SEQ ID NO: 52
	UU-1093-mod9 CDR-L3	AQNLELP FTF	SEQ ID NO: 53
	UU-1093-mod11 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY WMIHW VRQMPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYYCARSNYVVPW YFDVWGQGTSLVTVSS	SEQ ID NO: 42
	UU-1093-mod11 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSQG IT YLYWYQQKPGQAPRLLVY QVSNLGS G IPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELP FTF GGG TK LEIK	SEQ ID NO: 51
	UU-1093-mod11 CDR-H1	GYTFTSY WMIH	SEQ ID NO: 43
	UU-1093-mod11 CDR-H2	E IEPS DSYTNYNQKFKG	SEQ ID NO: 39
UU-1093-mod11	UU-1093-mod11 CDR-H3	ARSNYVVPWYFDV	SEQ ID NO: 44
	UU-1093-mod11 CDR-L1	RSSKSL LHSQG ITYLY	SEQ ID NO: 11
	UU-1093-mod11 CDR-L2	QVSNLGS	SEQ ID NO: 52
	UU-1093-mod11 CDR-L3	AQNLELP FTF	SEQ ID NO: 53
	UU-1093-mod12 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY FIHW VRQVPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYCAKSNYVVPWYFD VWGQGTSLVTVSS	SEQ ID NO: 45
	UU-1093-mod12 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSQG IT YLYWYQQKPGQAPRLLVY QVSNLGS G IPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELP FTF GGG TK LEIK	SEQ ID NO: 51
	UU-1093-mod12 CDR-H1	GYTFTSY FIH	SEQ ID NO: 46
	UU-1093-mod12 CDR-H2	E IEPS DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod12 CDR-H3	AKTNYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod12 CDR-L1	RSSKSL LHSNAIT YLY	SEQ ID NO: 49

TABLE 14-continued			
Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
UU-1093-mod10	UU-1093-mod10 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY WMIHW VRQMPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCAKTNYVVPWYFD VWGQGTSLVTVSS	SEQ ID NO: 40
	UU-1093-mod10 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSQG IT YLYWYQQKPGQAPRLLVY QVSNLGS G IPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELP FTF GGG TK LEIK	SEQ ID NO: 51
	UU-1093-mod10 CDR-H1	GYTFTSY WMIH	SEQ ID NO: 19
	UU-1093-mod10 CDR-H2	E IEPS DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod10 CDR-H3	AKTNYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod10 CDR-L1	RSSKSL LHSQG ITYLY	SEQ ID NO: 11
	UU-1093-mod10 CDR-L2	QVSNLGS	SEQ ID NO: 52
	UU-1093-mod10 CDR-L3	AQNLELP FTF	SEQ ID NO: 53
	UU-1093-mod11 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY WMIHW VRQMPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYYCARSNYVVPW YFDVWGQGTSLVTVSS	SEQ ID NO: 42
	UU-1093-mod11 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSQG IT YLYWYQQKPGQAPRLLVY QVSNLGS G IPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELP FTF GGG TK LEIK	SEQ ID NO: 51
UU-1093-mod11	UU-1093-mod11 CDR-H1	GYTFTSY WMIH	SEQ ID NO: 43
	UU-1093-mod11 CDR-H2	E IEPS DSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod11 CDR-H3	ARSNYVVPWYFDV	SEQ ID NO: 44
	UU-1093-mod11 CDR-L1	RSSKSL LHSQG ITYLY	SEQ ID NO: 11
	UU-1093-mod11 CDR-L2	QVSNLGS	SEQ ID NO: 52
	UU-1093-mod11 CDR-L3	AQNLELP FTF	SEQ ID NO: 53
	UU-1093-mod12 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSY FIHW VRQVPGKGLEWMGE IEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYCAKSNYVVPWYFD VWGQGTSLVTVSS	SEQ ID NO: 45
	UU-1093-mod12 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSSLSPGER ATLSCRSSKSL LHSQG IT YLYWYQQKPGQAPRLLVY QVSNLGS G IPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELP FTF GGG TK LEIK	SEQ ID NO: 51
	UU-1093-mod12 CDR-H1	GYTFTSY FIH	SEQ ID NO: 46
	UU-1093-mod12 CDR-H2	E IEPS DSYTNYNQKFKG	SEQ ID NO: 39

TABLE 14-continued			
Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
	variable region (VH) (CDRs underlined)	VRQVPKGLEWMGEIEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYYCAKTNYVVPWYFD VWGQGTLVTVSS	
	UU-1093-mod12 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSLSPGER SEQ ID ATLSCRSSSKSLHSGIT NO: 51 YLYWYQQKPGQAPRLLVY QVSNLGS GIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELPFTFGGGTK LEIK	
	UU-1093-mod12 CDR-H1	GYTFTSYFIH	SEQ ID NO: 46
	UU-1093-mod12 CDR-H2	EIEPSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod12 CDR-H3	AKTNYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod12 CDR-L1	RSSKSLHSGITYLY	SEQ ID NO: 11
	UU-1093-mod12 CDR-L2	QVSNLGS	SEQ ID NO: 52
	UU-1093-mod12 CDR-L3	AQNLELPFT	SEQ ID NO: 53
UU-1093-mod13	UU-1093-mod13 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSYWMHW NO: 38 VRQMPKGLEWMGEIEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCAKSNYVVPWYFD VWGQGTLVTVSS	SEQ ID NO: 38
	UU-1093-mod13 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSLSPGER SEQ ID ATLSCRSSSKSLHSGIT NO: 18 YLYWYQQKPGQAPRLLIY QMSNLAS GIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELPWTFGGGTK LEIK	SEQ ID NO: 18
	UU-1093-mod13 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093-mod13 CDR-H2	EIEPSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod13 CDR-H3	AKSNYVVPWYFDV	SEQ ID NO: 21
	UU-1093-mod13 CDR-L1	RSSKSLHSGITYLY	SEQ ID NO: 6
	UU-1093-mod13 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod13 CDR-L3	AQNLELPWT	SEQ ID NO: 22
UU-1093-mod14	UU-1093-mod14 heavy chain variable	EVQLVQSGAEVKKPGESL RISCKASGYTFTSYWMHW NO: 40 VRQMPKGLEWMGEIEPS	SEQ ID NO: 40

TABLE 14-continued			
Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
	region (VH) (CDRs underlined)	DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAMYYCAKTNYVVPWYFD VWGQGTLVTVSS	
	UU-1093-mod14 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSLSPGER SEQ ID ATLSCRSSSKSLHSGIT NO: 18 YLYWYQQKPGQAPRLLIY QMSNLAS GIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELPWTFGGGTK LEIK	
	UU-1093-mod14 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093-mod14 CDR-H2	EIEPSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod14 CDR-H3	AKTNYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod14 CDR-L1	RSSKSLHSGITYLY	SEQ ID NO: 6
	UU-1093-mod14 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod14 CDR-L3	AQNLELPWT	SEQ ID NO: 22
UU-1093-mod15	UU-1093-mod15 heavy chain variable region (VH) (CDRs underlined)	EVQLVQSGAEVKKPGESL RISCKASGYTFTSYWIIHW NO: 42 VRQVPKGLEWMGEIEPS DSYTNYNQKFKGHVTISA DKSISTAYLQWSSLKASD TAVYYCARSNYVVPWYFD VWGQGTLVTVSS	SEQ ID NO: 42
	UU-1093-mod15 light chain variable region (VL) (CDRs underlined)	EIVLTQSPGTLSLSPGER SEQ ID ATLSCRSSSKSLHSGIT NO: 18 YLYWYQQKPGQAPRLLIY QMSNLAS GIPDRFSGSGS GTDFTLTISRLEPEDFAV YYCAQNLELPWTFGGGTK LEIK	SEQ ID NO: 18
	UU-1093-mod15 CDR-H1	GYTFTSYWIIH	SEQ ID NO: 43
	UU-1093-mod15 CDR-H2	EIEPSDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod15 CDR-H3	ARSNYVVPWYFDV	SEQ ID NO: 44
	UU-1093-mod15 CDR-L1	RSSKSLHSGITYLY	SEQ ID NO: 6
	UU-1093-mod15 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod15 CDR-L3	AQNLELPWT	SEQ ID NO: 22
UU-1093-mod16	UU-1093-mod16 heavy chain	EVQLVQSGAEVKKPGESL RISCKASGYTFTSYFIHW NO: 45 VRQVPKGLEWMGEIEPS	SEQ ID NO: 45

TABLE 14-continued			
Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
	variable region (VH) (CDRs underlined)	<u>DSYTNYNQKFKGHVTISA</u> <u>DKSISTAYLQWSSLKASD</u> <u>TAVYYCAKTNYVVPWYFD</u> <u>VWGQGTTLVTVSS</u>	
	UU-1093-mod16 light chain variable region (VL) (CDRs underlined)	<u>EIVLTQSPGTL</u> <u>SLSPGER</u> <u>ATLSCRSSKSL</u> <u>LHSGIT</u> <u>YLYWYQQKPGQAPRLLIY</u> <u>QMSNLASGIPDRFSGSGS</u> <u>GTDFTLTISRLEPEDFAV</u> <u>YYCAQNLELPWTFGGGTK</u> <u>LEIK</u>	SEQ ID NO: 18
	UU-1093-mod16 CDR-H1	GYTFTSY FIH	SEQ ID NO: 46
	UU-1093-mod16 CDR-H2	E I EPDSYTNYNQKFKG	SEQ ID NO: 39
	UU-1093-mod16 CDR-H3	AK T NYVVPWYFDV	SEQ ID NO: 41
	UU-1093-mod16 CDR-L1	RSSKSLHSGIT Y LY	SEQ ID NO: 6
	UU-1093-mod16 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod16 CDR-L3	AQNLELPWT	SEQ ID NO: 22
UU-1093-mod17	UU-1093-mod17 heavy chain variable region (VH) (CDRs underlined)	<u>EVQLVQSGAEVKKPGESL</u> <u>RISCKASGYTFTSYWMHW</u> <u>VRQMPGKGLEWMGEIDPS</u> <u>DSYTNYNQKFKGHVTISA</u> <u>DKSISTAYLQWSSLKASD</u> <u>TAMYYCAKSNIYVVPWYFD</u> <u>VWGQGTTLVTVSS</u>	SEQ ID NO: 26
	UU-1093-mod17 light chain variable region (VL) (CDRs underlined)	<u>EIVLTQSPGTL</u> <u>SLSPGER</u> <u>ATLSCRSSKSL</u> <u>LHSQGIT</u> <u>YLYWYQQKPGQAPRLLIY</u> <u>QMSNLASGIPDRFSGSGS</u> <u>GTDFTLTISRLEPEDFAV</u> <u>YYCAQNLELPWTFGGGTK</u> <u>LEIK</u>	SEQ ID NO: 47
	UU-1093-mod17 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093-mod17 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	UU-1093-mod17 CDR-H3	AKSNIYVVPWYFDV	SEQ ID NO: 21
	UU-1093-mod17 CDR-L1	RSSKSLHSG Q ITYLY	SEQ ID NO: 11
	UU-1093-mod17 CDR-L2	QMSNLAS	SEQ ID NO: 7
	UU-1093-mod17 CDR-L3	AQNLELPWT	SEQ ID NO: 22
UU-1093-mod18	UU-1093-mod18 heavy chain variable region	<u>EVQLVQSGAEVKKPGESL</u> <u>RISCKASGYTFTSYWMHW</u> <u>VRQMPGKGLEWMGEIDPS</u> <u>DSYTNYNQKFKGHVTISA</u>	

TABLE 14-continued			
Amino acid sequences of improved UU-1093-mod anti-hNAMPT antibodies			
Anti-body	Description	Amino Acid Sequence	Se-quence Identifier
	(VH) (CDRs underlined)	<u>DKSISTAYLQWSSLKASD</u> <u>TAMYYCAKSNIYVVPWYFD</u> <u>VWGQGTTLVTVSS</u>	SEQ ID NO: 26
	UU-1093-mod18 light chain variable region (VL) (CDRs underlined)	<u>EIVLTQSPGTL</u> <u>SLSPGER</u> <u>ATLSCRSSKSL</u> <u>LHSNAIT</u> <u>YLYWYQQKPGQAPRLLVY</u> <u>QVSNLASGVPDRFSGSGS</u> <u>GTDFTLTISRLEPEDFAV</u> <u>YYCAQNLELPWTFGGGTK</u> <u>LEIK</u>	SEQ ID NO: 48
	UU-1093-mod18 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093-mod18 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	UU-1093-mod18 CDR-H3	AKSNIYVVPWYFDV	SEQ ID NO: 21
	UU-1093-mod18 CDR-L1	RSSKSLHSG NA ITYLY	SEQ ID NO: 49
	UU-1093-mod18 CDR-L2	QVSNLAS	SEQ ID NO: 50
	UU-1093-mod18 CDR-L3	AQNLELPWT	SEQ ID NO: 22
UU-1093-mod19	UU-1093-mod19 heavy chain variable region (VH) (CDRs underlined)	<u>EVQLVQSGAEVKKPGESL</u> <u>RISCKASGYTFTSYWMHW</u> <u>VRQMPGKGLEWMGEIDPS</u> <u>DSYTNYNQKFKGHVTISA</u> <u>DKSISTAYLQWSSLKASD</u> <u>TAMYYCAKSNIYVVPWYFD</u> <u>VWGQGTTLVTVSS</u>	SEQ ID NO: 26
	UU-1093-mod19 light chain variable region (VL) (CDRs underlined)	<u>EIVLTQSPGTL</u> <u>SLSPGER</u> <u>ATLSCRSSKSL</u> <u>LHSQGIT</u> <u>YLYWYQQKPGQAPRLLVY</u> <u>QVSNLGS</u> <u>GIPDRFSGSGS</u> <u>GTDFTLTISRLEPEDFAV</u> <u>YYCAQNLELPFT</u> <u>LEIK</u>	SEQ ID NO: 51
	UU-1093-mod19 CDR-H1	GYTFTSYWMH	SEQ ID NO: 19
	UU-1093-mod19 CDR-H2	EIDPSDSYTNYNQKFKG	SEQ ID NO: 20
	UU-1093-mod19 CDR-H3	AKSNIYVVPWYFDV	SEQ ID NO: 21
	UU-1093-mod19 CDR-L1	RSSKSLHSG Q ITYLY	SEQ ID NO: 11
	UU-1093-mod19 CDR-L2	QVSNL GS	SEQ ID NO: 52
	UU-1093-mod19 CDR-L3	AQNLELP FT	SEQ ID NO: 53

In Table 14, mutated residues are in bold font.

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TABLE 15-continued

Comparison of FIC CDRs of UU-1093-mod anti-hNAMPT antibodies with FIC CDRs of UU-1093														
UU-1093-mod13	E													39
UU-1093-mod14	E													39
UU-1093-mod15	E													39
UU-1093-mod16	E													39
UU-1093-mod17														20
UU-1093-mod18														20
UU-1093-mod19														20
HC CDR3														SEQ ID NO:
UU-1093	A	K	S	N	Y	V	V	P	W	Y	F	D	V	21
UU-1093-mod1														21
UU-1093-mod2			T											41
UU-1093-mod3		R												44
UU-1093-mod4			T											41
UU-1093-mod5														21
UU-1093-mod6			T											41
UU-1093-mod7		R												44
UU-1093-mod8			T											41
UU-1093-mod9														21
UU-1093-mod10			T											41
UU-1093-mod11		R												44
UU-1093-mod12			T											41
UU-1093-mod13														21
UU-1093-mod14			T											41
UU-1093-mod15		R												44
UU-1093-mod16			T											41
UU-1093-mod17														21
UU-1093-mod18														21
UU-1093-mod19														21

TABLE 16

Comparison of LC CDRs of UU-1093-mod anti-hNAMPT antibodies with LC CDRs of UU-1093																												
Light Chain (LC) CDR1															SEQ ID NO:	LC CDR2						SEQ ID NO:						
UU-1093-	R	S	S	K	S	L	L	H	S	N	G	I	T	Y	L	Y	6	Q	M	S	N	L	A	S	7			
UU-1093-mod1	Q										11																	7

TABLE 16-continued

Comparison of LC CDRs of UU-1093-mod anti-hNAMPT antibodies with LC CDRs of UU-1093										
UU-1093-mod2	Q	11								7
UU-1093-mod3	Q	11								7
UU-1093-mod4	Q	11								7
UU-1093-mod5	A	49	V							50
UU-1093-mod6	A	49	V							50
UU-1093-mod7	A	49	V							50
UU-1093-mod8	A	49	V							50
UU-1093-mod9	Q	11	V				G			52
UU-1093-mod10	Q	11	V				G			52
UU-1093-mod11	Q	11	V				G			52
UU-1093-mod12	Q	11	V				G			52
UU-1093-mod13		6								7
UU-1093-mod14		6								7
UU-1093-mod15		6								7
UU-1093-mod16		6								7
UU-1093-mod17	Q	11								7
UU-1093-mod18	A	49	V							50
UU-1093-mod19	Q	11	V				G			52
LC CDR3										SEQ ID NO:
UU-1093	A	Q	N	L	E	L	P	W	T	22
UU-1093-mod1										22
UU-1093-mod2										22
UU-1093-mod3										22
UU-1093-mod4										22
UU-1093-mod5										22
UU-1093-mod6										22
UU-1093-mod7										22
UU-1093-mod8										22
UU-1093-mod9								F		53
UU-1093-mod10								F		53
UU-1093-mod11								F		53
UU-1093-mod12								F		53
UU-1093-mod13										22
UU-1093-mod14										22
UU-1093-mod15										22
UU-1093-mod16										22
UU-1093-mod17										22
UU-1093-mod18										22
UU-1093-mod19								F		53

Example 12. Tissue Expression of NAMPT in Human Invasive PCa

[0284] To assess the role of NAMPT in prostate cancer (PCa) invasiveness and progression, the NAMPT expression was studied in PCa tissue.

[0285] Expression of NAMPT was assessed by immuno-histochemical (IHC) staining in normal prostate tissue, in

prostatic adenocarcinoma confined to the prostate and without capsular invasion, and in prostatic adenocarcinomas with capsular invasion into peri-prostatic adipose tissues. Representative micrographs are provided in FIGS. 9A-9C. Additionally, NAMPT expression was evaluated by IHC staining in benign prostate tissues, tissues from PCa patients with organ-confined disease (T2 disease; n=12), and tissues from PCa patients with capsule invasive disease (T3 disease; n=14); a cumulative analysis is provided in FIG. 9D.

[0286] As depicted in FIG. 9, IHC analysis of the normal and PCa tissues showed virtual absence of NAMPT expression in normal prostate tissue (FIG. 9A), and minimal expression of NAMPT in prostatic adenocarcinoma confined to the prostate and without capsular invasion (FIG. 9B). In contrast, prostatic adenocarcinomas with capsular invasion into peri-prostatic adipose tissues show significantly robust NAMPT staining (FIG. 9C). Moreover, comparative analysis of benign prostate tissues and tissues from 26 PCa patients with T2 and T3 disease showed increased expression of NAMPT with increased PCa invasiveness (FIG. 9D). Thus, increased expression of NAMPT was observed in invasive PCa in human.

Example 13. Effect of Radiation Exposure on NAMPT Expression

[0287] Radiation therapy is a mainstay of PCa therapy. As extracellular NAMPT (eNAMPT) functions as a damage-associated molecular pattern protein (DAMP) in innate immunity, effect of radiation on NAMPT expression was assessed by evaluating the expression of NAMPT in radiation-exposed murine and human tissues.

[0288] To assess the effect of radiation-induced tissue injury and damage on NAMPT expression in murine tissues, C57/B6 mice were exposed to a single dose of thoracic radiation (20 Gy) for 1 week. Effect of radiation on inflammation, vascular leak and inflammatory lung injury was assessed by H&E staining of the murine lung tissues following radiation exposure. Representative micrographs are provided in FIG. 10A. NAMPT expression was evaluated in the lung tissues before and after radiation by IHC staining. Representative micrographs are provided in FIGS. 10B and 10C. To assess the effect of radiation on NAMPT expression in human tissues, normal human epithelial tissues (tonsil) were exposed to radiation (8 Gy) for 24 hours, and NAMPT expression was evaluated by IHC staining. Representative micrographs are provided in FIG. 10D.

[0289] As depicted in FIG. 10, after 1 week of radiation exposure, an increase in inflammation, vascular leak and inflammatory injury was observed in murine lung tissues (FIG. 10A). The radiation-induced lung injury was accompanied by prominent NAMPT expression (FIG. 10B), especially in alveolar macrophages and epithelial cells (FIG. 10C). Consistent with radiation as a stimulus for NAMPT tissue expression in mouse, marked increase in NAMPT expression was observed in normal human epithelial tissues (tonsil) 24 hours after radiation exposure (FIG. 10D). Thus, radiation-induced tissue injury significantly induced NAMPT expression.

Example 14. Role of NAMPT in PCa Cell Migration

[0290] An in vitro assay of PCa cell migration through human smooth muscle cells was used to assess the role of NAMPT on migration of PCa cells.

[0291] To assess the role of NAMPT in PCa cell migration, NAMPT (100 ng/mL) was added to a culture of human DU-145 PCa cells. Following 24 hours of NAMPT exposure, migration of the PCa cells was assessed. A summary of the observation is provided in FIG. 11A, and representative micrographs are provided in FIG. 11B.

[0292] As observed in FIG. 11, NAMPT served as a potent chemoattractant for human DU-145 PCa cells and induced PCa cell migration over a 24-hour period.

Example 15. Characterization of Humanized Anti-hNAMPT Antibody

[0293] Ability of 1076 humanized anti-hNAMPT antibodies (N-1076, K-1076, and P-1076) and 1093 humanized anti-hNAMPT antibodies (SS-1093, XX-1093, and UU-1093) to treat lung injury was tested in vivo, using two murine lung injury models: a “one hit” model of lung injury that was developed by intratracheal delivery of LPS into mice, and a “two hit” model of lung injury that was developed by exposing mice to LPS and mechanical VILI. Either of the humanized anti-hNAMPT antibodies was administered to these mice in order to assess the capacity of the antibodies to attenuate acute inflammation and injury. Results from the testing is provided in FIG. 12.

[0294] As depicted in FIG. 12A, analysis of integrated lung injury score showed that all of the tested anti-hNAMPT antibodies were effective in reducing lung injury in the LPS-induced “one hit” model. However, the most substantial effect was observed with anti-hNAMPT antibody P-1076. As described in FIG. 12B, analysis of integrated lung injury score showed that all of the tested anti-hNAMPT antibodies were effective in reducing lung injury in the LPS/VILI-induced “two hit” model. However, the most substantial effect was observed with anti-hNAMPT antibody P-1076. As described in FIG. 12C, anti-hNAMPT antibody P-1076 was effective in reducing histologic injury indices in the LPS/VILI-induced “two hit” model of acute inflammatory injury.

Example 16. Effect of Humanized Anti-hNAMPT Antibody P-1076 on PCa Cell Invasion

[0295] To assess the effect of humanized anti-hNAMPT antibody P-1076 on PCa cell invasion, peritoneal invasion of human PCa cells was evaluated in severe combined immunodeficient (SCID) mice.

[0296] To assess the role of humanized anti-hNAMPT antibody P-1076 on PCa cell invasion, metastatic human PCa cells, PC3, were injected intraperitoneally (I.P.) into SCID mice. The mice were injected two times a week with 2 µg of humanized anti-hNAMPT antibody P-1076 or vehicle alone. Peritoneal invasion of the PC3 cells was evaluated 6 weeks after the PC3 cell injection. Representative micrographs and a summary of the results are provided in FIG. 13.

[0297] As depicted in FIG. 13, injection of human PCa cell line caused substantial peritoneal muscle invasion (FIG. 13A), while PC3-challenged SCID mice receiving humanized anti-hNAMPT antibody P-1076 exhibited marked reductions in PC3 invasion of the smooth muscle peritoneum (FIG. 13B).

[0298] Thus, as summarized in FIG. 13C, observations from this study strongly implicate a role for NAMPT in PCa cell invasiveness and a critical potential for humanized anti-hNAMPT antibody P-1076 to temporize this invasive behavior.

Example 17. In Vivo Treatment of RILI Using Anti-NAMPT Antibodies

[0299] The ability impact of anti-NAMPT administration on RILI was assessed using in vivo experiments in C57/B6

mice. The mice were divided into four groups: mice that received 20Gy thoracic radiation and were injected intraperitoneally with a polyclonal NAMPT-neutralizing antibody (pAb); mice that received 20Gy thoracic radiation and were injected intraperitoneally with a monoclonal anti-NAMPT antibody (mAb) (P-1076-mod1); and non-irradiated mice injected with vehicle alone ("Ctrl"); and irradiated mice injected with vehicle alone ("Ctrl"). Amount of BAL protein was measured and count of BAL-expressing cells was obtained. Lung tissues were also subjected to H&E staining to assess lung inflammation. Moreover, acute lung injury (ALI) severity score was assessed based on BAL indices and H&E staining. Results from the corresponding analyses are provided in FIGS. 14A-E.

[0300] As shown in FIG. 14A, H&E staining of lung tissues from irradiated control mice (injected with vehicle alone) displayed diffuse alveolar damage 4 weeks after radiation exposure (FIG. 14A, left panel), compared to lung tissues from non-irradiated control mice (inset of FIG. 14A, left panel). In contrast, lung tissues from mice that were injected with anti-NAMPT pAb (FIG. 14A, middle panel) or anti-NAMPT mAb (FIG. 14A, right panel) demonstrated reduced H&E staining, indicating less alveolar damage in anti-NAMPT Ab treated mice following radiation exposure. FIG. 14B summarizes H&E staining in lung tissues of non-irradiated control mice, irradiated control mice, and irradiated mice that were injected with anti-NAMPT pAb or mAb. As shown in FIG. 14B, H&E stained area was increased in lung tissues from irradiated control mice compared to that from non-irradiated control mice. However, compared to irradiated control mice, a significant reduction in H&E stained area was observed in lung tissues from mice that were injected with anti-NAMPT pAb or mAb ($p < 0.05$), suggesting a role of NAMPT in development of RILI. FIG. 14C shows BAL protein levels in lung tissues of non-irradiated control mice, irradiated control mice, and irradiated mice that were injected with anti-NAMPT pAb or mAb. As shown in FIG. 14C, compared to non-irradiated control mice, mice that were exposed to radiation displayed increased BAL protein levels. However, irradiated mice that were injected with anti-NAMPT pAb or mAb demonstrated significantly reduced BAL protein level compared to the irradiated control mice ($p < 0.05$), with more pronounced reduction observed in irradiated mice that were treated with anti-NAMPT mAb. Similarly, count of BAL cells increased in mice that were exposed to irradiation, although irradiated mice that were injected with anti-NAMPT pAb or mAb demonstrated markedly reduced BAL cell count compared to the irradiated control mice ($p < 0.05$), with more pronounced reduction observed in irradiated mice that were treated with anti-NAMPT mAb. Furthermore, as shown in FIG. 14E, compared to control mice, mice that were exposed to radiation displayed increased ALI severity score; however, irradiated mice that were injected with anti-NAMPT pAb or mAb demonstrated significantly reduced ALI severity score compared to the irradiated control mice, with more pronounced reduction observed in irradiated mice that were treated with anti-NAMPT mAb. Thus, the results show attenuation of RILI following treatment with anti-NAMPT Abs, underscoring NAMPT as a potential therapeutic target in RILI.

Example 18. Radiolabeled Anti-NAMPT Antibody
Identifies Increased NAMPT Expression in
Inflamed Lung Tissues

[0301] Radiolabeled anti-NAMPT antibodies were developed with the goal of non-invasively detecting NAMPT

signaling pathway and NAMPT expression in different tissues in vivo. Imaging the mouse models with RILI using radiolabeled anti-NAMPT mAb (P-1076-mod1) would enable defining the optimal time for deploying anti-NAMPT mAb as a therapeutic intervention and to survey the major organs for inflammation and cellular apoptosis, employing other specific radiolabels, following total body irradiation (TBI) or partial body irradiation (PBI), such as in a nuclear incident. To test the detection of NAMPT expression by the radiolabeled anti-NAMPT antibody, ^{99m}Tc -labeled anti-NAMPT mAb probe was injected into control mice and mice that were exposed to 8Gy PBI, and rapid autoradiograph imaging was performed. Results from the analysis are described in FIGS. 15A-D.

[0302] As shown in FIGS. 15A-B, higher radioactive uptake was observed in lungs of irradiated mice compared to non-irradiated control mice, indicating higher NAMPT expression induced by RILI. Furthermore, uptake of radiolabeled anti-NAMPT antibody was used as a measure of lung activity in irradiated mice or non-irradiated control mice. As shown in FIG. 15C, a significant increase in lung activity over tissue background was observed in both right and left lungs from irradiated mice compared to those from non-irradiated control mice ($p < 0.05$). Moreover, level of radioactivity in irradiated mice or non-irradiated control mice was determined to assess uptake of the radiolabeled anti-NAMPT mAb. As shown in FIG. 15D, a significant increase in radioactivity was observed in irradiated mice compared to non-irradiated control mice ($p < 0.05$), thus confirming increased uptake of the radiolabeled anti-NAMPT mAb in irradiated mice.

[0303] Thus, the radiolabeled anti-NAMPT antibody was effective in detecting increased NAMPT expression in inflamed lung tissues. This underscores the potentials of utilizing the radiolabeled anti-NAMPT antibody as a tool for detection of NAMPT, which could be pivotal in using NAMPT as a biomarker in RILI.

Example 19. Validating NAMPT as a Therapeutic
Target in RILI Using an In Vivo Model of
Radiation-Induced Lung Fibrosis

[0304] To further validate NAMPT as a therapeutic target in RILI, WT C57/B6 mice were exposed to 20Gy WTLI. The irradiated mice were intraperitoneally injected with 10 μg of an anti-NAMPT mAb (P-1076-mod1) or vehicle control. The mice were evaluated for radiation-induced lung fibrosis (RILF) 18 weeks post radiation exposure by assessing BAL cell count, collagen deposition, and expression of lung tissue smooth muscle actin (SMA), which is a reflection of myofibroblast transition and fibrosis. The results are shown in FIGS. 16A-C.

[0305] As shown in FIGS. 16A-C, the anti-NAMPT mAb significantly reduced IR-induced RILI, which was reflected by decreased BAL cell count (FIG. 16A), decreased expression of lung tissue SMA (detected by western blot analyses, shown in FIG. 16B), and decreased collagen deposition (detected by Trichrome staining of lung tissues, shown in FIG. 16C) in Ab-treated mice compared to vehicle-treated control mice.

[0306] Thus, the results underscore the role of an anti-NAMPT Ab in attenuating RILF, further validating NAMPT as a therapeutic target in RILI.

Example 20. Evaluating the Efficacy of an Anti-NAMPT mAb in Pre-Clinical Models of Lung Injury

[0307] The efficacy of an anti-NAMPT mAb was validated in a rat model of trauma (blast)/ventilator-induced lung injury (VILI). Sprague Dawley rats were challenged with trauma (blast) followed by 4 hours of mechanical ventilation. Rats were injected with an anti-NAMPT mAb (P-1076-mod1, 100 μ g, intravenously (IV)) 30 minute following the blast. Rats, which were exposed to trauma (blast)/VILI and injected with vehicle, served as control. Lungs were removed from the rats ~5 hours after onset of blast and evaluated for injury. Also, edema and inflammatory cell infiltration in lung tissue were assessed by hematoxylin and eosin (H&E) staining, as readout of lung injury. Results from this trauma (blast)/VILI lung injury model are provided in FIGS. 17A-C.

[0308] As shown in FIG. 17A, compared to non-challenged rats (FIG. 17A, inset in rightmost box), lung tissues from vehicle injected control trauma/VILI rats showed inflammatory cell infiltration and edema, which was indicative of trauma/VILI induced lung injury. In contrast, as shown in FIG. 17B, lung tissues from anti-NAMPT mAb treated trauma/VILI rats showed marked reduction in inflammatory cell infiltration and edema, thus indicating attenuation of trauma/VILI-induced lung injury by the anti-NAMPT mAb. The effect of the anti-NAMPT mAb on trauma/VILI-induced lung injury is summarized in FIG. 17C, which shows lung injury score of the rats, as assessed from the H&E staining indices. As shown in FIG. 17C, lung injury score was significantly reduced in rats that were treated with anti-NAMPT mAb compared to rats that were injected with vehicle control ($p < 0.05$). Thus, the results outlined in FIGS. 17A-C show the efficacy of a NAMPT neutralizing mAb in attenuating trauma/VILI-induced lung injury.

[0309] Next, the efficacy of the anti-NAMPT mAb was validated in a murine model of LPS/VILI. Mice were challenged with LPS for 18 hours followed by 4 hours of mechanical ventilation. Mice were injected with an anti-NAMPT mAb (P-1076-mod1, 10 μ g, IV), an anti-NAMPT polyclonal antibody (pAb), or vehicle control (PBS). Mice, which were not exposed to LPS/VILI, served as control. Edema and inflammatory cell infiltration in lung tissue from the mice were then assessed by H&E staining, as readout of lung injury. Results from this LPS/VILI lung injury model are provided in FIGS. 18A-C.

[0310] As shown in FIG. 18A, compared to non-challenged mice (FIG. 18A, inset), lung tissues from vehicle injected control mice showed inflammatory cell infiltration and edema, which was indicative of LPS/VILI induced lung injury. In contrast, as shown in FIG. 18B, lung tissues from anti-NAMPT mAb treated mice showed marked reduction in inflammatory cell infiltration and edema, thus indicating attenuation of LPS/VILI-induced lung injury by the anti-NAMPT mAb. The effect of the anti-NAMPT mAb on trauma/VILI-induced lung injury is summarized in FIG. 18C, which shows acute lung injury (ALI) severity score of the mice, as assessed from the H&E staining indices. As shown in FIG. 18C, ALI was markedly reduced in mice treated with anti-NAMPT pAb or mAb compared to vehicle injected mice, with most robust reduction in ALI severity score observed in mice that were treated with the anti-NAMPT mAb ($p < 0.001$). Thus, the results outlined in FIGS.

18A-C show the efficacy of a NAMPT neutralizing mAb in attenuating trauma/VILI-induced lung injury.

[0311] Accordingly, the results demonstrate the effectiveness of the anti-NAMPT mAb in reducing lung injury in pre-clinical in vivo lung injury models.

Example 21. Radiolabeled Anti-NAMPT Antibody Identifies Increased NAMPT Expression in Inflamed Lung Tissues

[0312] A humanized anti-NAMPT mAb (K-1076) was radiolabeled to develop an imaging probe that would be capable of non-invasively detecting NAMPT signaling pathway and NAMPT expression in different tissues in vivo. Considering the potentials of NAMPT as a diagnostic and/or prognostic biomarker in acute inflammatory conditions (e.g., COVID-19, ARDS and lung injury), the radiolabeled anti-NAMPT mAb could be used as a diagnostic tool in subjects who are at risk of developing such conditions, or for selecting subjects likely to respond to treatment of such inflammatory conditions with an anti-NAMPT mAb. The present example describes detection of NAMPT expression in inflamed tissues, such as LPS-challenged and ionizing radiation-exposed lungs, using the radiolabeled anti-NAMPT mAb.

[0313] First, to test the detection of NAMPT expression by the radiolabeled anti-NAMPT antibody, ^{99m}Tc -labeled anti-NAMPT mAb probe or radiolabeled IgG control Ab was injected into mice that were exposed to 20Gy whole thoracic lung irradiation (WTLI), and rapid autoradiograph imaging were performed.

[0314] As shown in FIG. 19A, markedly higher radioactive uptake was observed in irradiated mice injected with radiolabeled anti-NAMPT mAb (PRONAMPTOR) (FIG. 19A, right panel) compared to irradiated mice injected with the radiolabeled IgG control (FIG. 19A, left panel). Thus, the results shown in FIG. 19A demonstrate the ability of the radiolabeled anti-NAMPT imaging probe in detecting radiation-induced NAMPT expression.

[0315] To further assess the detection of NAMPT expression by radiolabeled anti-NAMPT imaging probe, ^{99m}Tc -labeled anti-NAMPT mAb was injected into vehicle challenged control mice or LPS challenged mice 3 hours or 18 hours after LPS challenge, and rapid autoradiograph imaging was performed. Results from the analysis are shown in FIGS. 19B-D.

[0316] As shown in FIG. 19B, compared to control mice (FIG. 19B, left panel), LPS challenged mice showed markedly higher uptake of the radiolabeled anti-NAMPT imaging probe 3 hours after LPS challenge (FIG. 19B, right panel). Autoradiograph imaging of lungs from LPS challenged mice or control mice further confirmed this observation; compared to control mice (FIG. 19C, left panel), lungs of LPS challenged mice showed markedly higher uptake of the radiolabeled anti-NAMPT imaging probe 3 hour after LPS challenge (FIG. 19C, right panel). Moreover, as shown in FIG. 19D, compared to control mice, LPS challenged mice showed significantly higher radioactivity 3 hours and 18 hours after LPS challenge ($p < 0.05$), indicating higher uptake of the radiolabeled anti-NAMPT imaging probe. Thus, the results described in FIGS. 19B-D demonstrate the ability of the radiolabeled anti-NAMPT imaging probe in detecting LPS-induced NAMPT expression.

[0317] Accordingly, the radiolabeled anti-NAMPT antibody was effective in detecting increased NAMPT expres-

sion in inflamed tissues. This underscores the potentials of utilizing the radiolabeled anti-NAMPT antibody as a tool for detection of NAMPT, which could be pivotal in using NAMPT as a diagnostic and/or prognostic biomarker in acute inflammatory conditions. Moreover, by virtue of detecting increased NAMPT expression in inflamed tissues, this radiolabeled anti-NAMPT imaging probe could be useful for selecting subjects who are likely to respond to treatment of acute inflammatory conditions with a neutralizing anti-NAMPT mAb.

Example 22. Anti-NAMPT Antibody Reduces PAH
Manifestation in a Rat Model

[0318] To explore the potentials of NAMPT as a therapeutic target in PAH, a rat monocrotaline (MCT) model of PAH was used. One dose of MCT (60 mg/kg body weight) was subcutaneously injected to Sprague-Dawley rats (190-200 g). The MCT-challenged rats were then injected twice weekly with either an anti-NAMPT mAb (P-1076-mod1, i.p., 100 µg/rat) or vehicle control (control MCT rats). The rats were then assessed for right ventricular systolic pressure (RVSP) and pulmonary artery remodeling. The results are shown in FIGS. 20A and 20B.

[0319] RVSP was determined in anti-NAMPT Ab treated MCT rats or control MCT rats by right heart catheterization using a Millar pressure transducer catheter. As shown in FIG. 20A, a significant decrease in RVSP was observed in

MCT rats that were treated with anti-NAMPT mAb compared to control MCT rats (p<0.05).

[0320] Pulmonary artery remodeling was assessed using APERIO IMAGESCOPE software after lungs from anti-NAMPT Ab treated MCT rats or control MCT rats were stained with H&E. As shown in FIG. 20B, a marked decrease in pulmonary artery thickness was observed in anti-NAMPT mAb treated MCT rats compared to control MCT rats.

[0321] The results demonstrate that neutralization of NAMPT by anti-NAMPT mAb reverses vascular remodeling and RV dysfunction in a rat model of PAH, thus indicating the effectiveness of NAMPT as a therapeutic target in PAH.

[0322] Unless otherwise specified, the disclosure of every patent, patent application, and publication cited herein is hereby incorporated herein by reference to the extent the references set forth information relevant to the instant disclosure. While this invention has been disclosed with reference to particular embodiments, it is apparent that some embodiments and variations of this invention can be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims include all such embodiments and equivalent variations.

[0323] Sequences disclosed herein and/or relevant to the present invention are listed in the Sequence Summary Table (Table 17) below.

TABLE 17

Sequence Summary Table		
Sequence Identifier	Description	Sequence
SEQ ID NO: 1	heavy chain variable region (VH): D-1076	QVQLVESGAEVKKPGASVKLSCK ASGYTFTSYWMQWVRQAPGQRL EWMGEIDPSNSYTNYNQKFRGRV TITVDKSASTAYMELSSLRSEDTA VYYCARGGYWGPGTTVTVSS
SEQ ID NO: 2	light chain variable region (VL): D-1076, N-1076, X-1076	DIVMTQTPLSLSVTPGQPASISCRS SKSLLHSNGITYLYWYLQKPGQPP QLLIYQMSNLASGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCVQNL ELPYTFGPGTKVDIK
SEQ ID NO: 3	CDR-H1: D-1076, G-1076, K-1076, N-1076, P-1076, V-1076, X-1076, P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, P-1076-mod11, AL-303	<u>GYTFTSYWMQ</u>
SEQ ID NO: 4	CDR-H2: D-1076, G-1076, K-1076, N-1076, P-1076, V-1076, X-1076, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, AL-303	<u>EIDPSNSYTNYNQKFRG</u>
SEQ ID NO: 5	CDR-H3: D-1076, G-1076, K-1076, N-1076, P-1076, V-1076, X-1076, P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, P-1076-mod11, AL-303	<u>ARGGY</u>

TABLE 17-continued

Sequence Summary Table		
Sequence Identifier	Description	Sequence
SEQ ID NO: 6	CDR-L1: D-1076, N-1076, X-1076, FF-1093, II-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, ZZ-1093, AL-303, UU-1093-mod13, UU-1093-mod14, UU-1093-mod15, UU-1093-mod16, AL-303, AL-310	<u>RSSKSLHNSGITYLY</u>
SEQ ID NO: 7	CDR-L2: D-1076, N-1076, X-1076, FF-1093, II-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, ZZ-1093, UU-1093-mod1, UU-1093-mod2, UU-1093-mod3, UU-1093-mod4, UU-1093-mod13, UU-1093-mod14, UU-1093-mod15, UU-1093-mod16, UU-1093-mod17,,AL-303, AL-310	<u>QMSNLAS</u>
SEQ ID NO: 8	CDR-L3: D-1076, G-1076, K-1076, N-1076, P-1076, V-1076, X-1076, P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, P-1076-mod11,,AL-303	<u>VQNLELPYT</u>
SEQ ID NO: 9	heavy chain variable region (VH): G-1076, K-1076	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYWMQWVRQAPGQGL EWMGEIDPSNSYTNYNQKFRGRV TMTTDTSTSTAYMELRSLRSDDTA VYYC <u>ARGGYWGQGTTTVTVSS</u>
SEQ ID NO: 10	light chain variable region (VL): G-1076, V-1076	DIQLTQSPLSLPVTGPGEPAISCRSS <u>KSLLLHSQGITYLYWYLQKPGQSPQ</u> LLIY <u>QLSNLAS</u> GVDPDRFSGSGSGTD FTLKISRVEAEDVGVYYC <u>VQNLEL</u> <u>PYTFGGGTKLEIK</u>
SEQ ID NO: 11	CDR-L1: G-1076, K-1076, P-1076, V-1076, P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10, P-1076-mod11, UU-1093-mod1, UU-1093-mod2, UU-1093-mod3, UU-1093-mod4, UU-1093-mod9, UU-1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093-mod17, UU-1093-mod19,	<u>RSSKSLLLHSQGITYLY</u>
SEQ ID NO: 12	CDR-L2: G-1076, V-1076	<u>QLSNLAS</u>
SEQ ID NO: 13	light chain variable region (VL): K-1076, P-1076, P-1076-mod11	DIVMTQSPLSLPVTGPGEPAISCRSS <u>KSLLLHSQGITYLYWYLQKPGQSPQ</u> LLIY <u>QLSNRAS</u> GVDPDRFSGSGSGT DFTLKISRVEAEDVGVYYC <u>VQNLE</u> <u>LPYTFGGGTKLEIK</u>
SEQ ID NO: 14	CDR-L2: K-1076, P-1076, P-1076-mod1, P-1076-mod2, P-1076-mod6, P-1076-mod7, P-1076-mod11	<u>QLSNRAS</u>
SEQ ID NO: 15	heavy chain variable region (VH): N-1076, P-1076, P-1076-mod6, P-1076-mod7, P-1076-mod8, P-1076-mod9, P-1076-mod10	QVQLVQSGAEVTKPGASVKVSCK ASGYTFTSYWMQWVRQAPGQGL EWVGEIDPSNSYTNYNQKFRGRV TLTRDTSTTTVYMELSSLSRSEDTA VYYC <u>ARGGYWGQGTTTVTVSS</u>

TABLE 17-continued

Sequence Summary Table		
Sequence Identifier	Description	Sequence
SEQ ID NO: 16	heavy chain variable region (VH): V-1076, X-1076	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYWMQWVRQAPGQGL EWMGEIDPSNSYTNYNQKFRGRV TMTRDTSTSTVYMELSSLRSEDTA VYYCARGGYWGQGTTTVTVSS
SEQ ID NO: 17	heavy chain variable region (VH): FF-1093	QVQLVESGAEVKKPGASVKLSCK ASGYTFTSYWMHWVRQAPGQRL EWMGEIDPSDSYTNYNQKFKGRV TITVDKSASTAYMELSSLRSEDTA VYYCAKSNIYVVPWYFDVWGPGT TVTVSS
SEQ ID NO: 18	light chain variable region (VL): FF-1093, PP-1093, UU-1093, ZZ-1093, UU-1093-mod13, UU-1093-mod14, UU-1093-mod15, UU-1093-mod16	EIVLTQSPGTLSSLSPGERATLSCRSS KSLLLHSNGITYLYWYQQKPGQAP RLLIYQMSNLASGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCAQNLEL PWTFGGGTKLEIK
SEQ ID NO: 19	CDR-H1: FF-1093, II-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, ZZ-1093, UU-1093-mod1, UU-1093-mod2, UU-1093-mod5, UU-1093-mod6, UU-1093-mod9, UU-1093-mod10, UU-1093-mod13, UU-1093-mod14, UU-1093-mod17, UU-1093-mod18, UU-1093-mod19,, AL-310	<u>GYTFTSYWMH</u>
SEQ ID NO: 20	CDR-H2: FF-1093, II-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, ZZ-1093, UU-1093-mod17, UU-1093-mod18, UU-1093-mod19, AL-310	<u>EIDPSDSYTNYNQKFKG</u>
SEQ ID NO: 21	CDR-H3: FF-1093, II-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, ZZ-1093, UU-1093-mod1, UU-1093-mod5, UU-1093-mod9, UU-1093-mod13, UU-1093-mod17, UU-1093-mod18, UU-1093-mod19,, AL-310	<u>AKSNIYVVPWYFDV</u>
SEQ ID NO: 22	CDR-L3: FF-1093, II-1093, NN-1093, PP-1093, SS-1093, UU-1093, XX-1093, ZZ-1093, UU-1093-mod1, UU-1093-mod2, UU-1093-mod3, UU-1093-mod4, UU-1093-mod5, UU-1093-mod6, UU-1093-mod7, UU-1093-mod8, UU-1093-mod 13, UU-1093-mod14, UU-1093-mod15, UU-1093-mod16, UU-1093-mod17, UU-1093-mod18,, AL-310	<u>AQNLELPWT</u>
SEQ ID NO: 23	heavy chain variable region (VH): II-1093	QVQLVQSGAEVRKPGASVKVSCK ASGYTFTSYWMHWVRQAPGQGL EWVGEIDPSDSYTNYNQKFKGRV TITADKSTSTAYMELSSLRSEDTD VYYCAKSNIYVVPWYFDVWGQGT TVTVSS
SEQ ID NO: 24	light chain variable region (VL): II-1093, NN-1093, SS-1093, XX-1093	EIVLTQSPATLSSLSPGERATLSCRSS KSLLLHSNGITYLYWYQQKPGQAP RLLIYQMSNLASGIPARFSGSGSGT DFTLTISSLEPEDFAVYYCAQNLEL PWTFGGGTKLEIK

TABLE 17-continued

Sequence Summary Table		
Sequence Identifier	Description	Sequence
SEQ ID NO: 25	heavy chain variable region (VH): NN-1093, PP-1093	QVQLVQSGAEVTKPGASVKV SCK ASGYTFTSYWMHWVRQAPGQGL EWVGEIDPSDSYTNYNQKFKGRV TLTRDTSTTTVYMESSLRSEDTA VYYCAKSNYVVPWYFDVWGQGT TVTVSS
SEQ ID NO: 26	heavy chain variable region (VH): SS-1093, UU-1093, UU-1093-mod17, UU-1093-mod 18, UU-1093-mod19	EVQLVQSGAEVKKPGESLRISCKA SGYTFTSYWMHWVRQMPGKGLE WMGEIDPSDSYTNYNQKFKGHVT ISADKSISTAYLQWSSLKASDTAM YYCAKSNYVVPWYFDVWGQGT LTVVSS
SEQ ID NO: 27	heavy chain variable region (VH): XX-1093, ZZ-1093	QVQLVQSGAEVKKPGASVKV SCK ASGYTFTSYWMHWVRQAPGQGL EWMGEIDPSDSYTNYNQKFKGRV TMTTRDTSTSTVYMESSLRSEDTA VYYCAKSNYVVPWYFDVWG TGT TVTVSS
SEQ ID NO: 28	heavy chain variable region (VH): P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod11	QVQLVQSGAEVTKPGASVKV SCK ASGYTFTSYWMQWVRQAPGQGL EWVGEI EPSNSYTNYNQKFRGRVT LTRDTSTTTVYMESSLRSEDTAV YYCARGGYWGQGT TVTVSS
SEQ ID NO: 29	CDR-H2: P-1076-mod1, P-1076-mod2, P-1076-mod3, P-1076-mod4, P-1076-mod5, P-1076-mod11	EIEPSNSYTNYNQKFRG
SEQ ID NO: 30	light chain variable region (VL): P-1076-mod1, P-1076-mod6	DIVMTQSPLSLPVTPGEPASISCRSS KSLLLHSQGITYLYWYVQKPGQSPQ LLIYQLSNRASGV PDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNLE LPYTFGGG TKLEIK
SEQ ID NO: 31	light chain variable region (VL): P-1076-mod2, P-1076-mod7	DIVMTQSPLSLPVTPGEPASISCRSS KSLLLHSQGITYLYWYIQKPGQSPQ LLIYQLSNRASGV PDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNLE LPYTFGGG TKLEIK
SEQ ID NO: 32	light chain variable region (VL): P-1076-mod3, P-1076-mod8	DIVMTQSPLSLPVTPGEPASISCRSS KSLLLHSQGITYLYWYVQKPGQSPQ LLIYQGSNRASGV PDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNLE LPYTFGGG TKLEIK
SEQ ID NO: 33	CDR-L2: P-1076-mod3, P-1076-mod8	QGSNRAS
SEQ ID NO: 34	light chain variable region (VL): P-1076-mod4, P-1076-mod9	DIVMTQSPLSLPVTPGEPASISCRSS KSLLLHSQGITYLYWYVQKPGQSPQ LLIYQESNRASGV PDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNLE LPYTFGGG TKLEIK
SEQ ID NO: 35	CDR-L2: P-1076-mod4, P-1076-mod9	QESNRAS
SEQ ID NO: 36	light chain variable region (VL): P-1076-mod5, P-1076-mod10	DIVMTQSPLSLPVTPGEPASISCRSS KSLLLHSQGITYLYWYIQKPGQSPQ LLIYQVSNRASGV PDRFSGSGSGT DFTLKISRVEAEDVGVYYCVQNLE LPYTFGGG TKLEIK
SEQ ID NO: 37	CDR-L2: P-1076-mod5, P-1076-mod10	QVSNRAS

TABLE 17-continued

Sequence Summary Table		
Sequence Identifier	Description	Sequence
SEQ ID NO: 38	heavy chain variable region (VH): UU-1093-mod1, UU-1093-mod5, UU-1093-mod9, UU-1093-mod13	EVQLVQSGAEVKKPGESLRISCKA SGYTFTSYWMHWVRQMPGKGLE WMGEIEPSDSYTNYNQKFKGHVTI SADKSISTAYLQWSSLKASDTAMY YCAKSNYVVPWYFDVWGQGTLV TVSS
SEQ ID NO: 39	CDR-H2: UU-1093-mod1, UU- 1093-mod2, UU-1093-mod3, UU- 1093-mod4, UU-1093-mod5, UU- 1093-mod6, UU-1093-mod7, UU- 1093-mod8, UU-1093-mod9, UU- 1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093- mod13, UU-1093-mod 14, UU- 1093-mod 15, UU-1093-mod16	<u>EIEPSDSYTNYNQKFKG</u>
SEQ ID NO: 40	heavy chain variable region (VH): UU-1093-mod2, UU-1093-mod6, UU-1093-mod10, UU-1093- mod14	EVQLVQSGAEVKKPGESLRISCKA SGYTFTSYWMHWVRQMPGKGLE WMGEIEPSDSYTNYNQKFKGHVTI SADKSISTAYLQWSSLKASDTAMY YCAKTNVVPWYFDVWGQGTLV TVSS
SEQ ID NO: 41	CDR-H3: UU-1093-mod2, UU- 1093-mod4, UU-1093-mod6, UU- 1093-mod8, UU-1093-mod10, UU-1093-mod12, UU-1093- mod14, UU-1093-mod16	<u>AKTNVVPWYFDV</u>
SEQ ID NO: 42	heavy chain variable region (VH): UU-1093-mod3, UU-1093-mod7, UU-1093-mod11, UU-1093- mod15	EVQLVQSGAEVKKPGESLRISCKA SGYTFTSYWIHWVRQVPGKGLEW MGEIEPSDSYTNYNQKFKGHVTIS ADKSISTAYLQWSSLKASDTAVYY CARSNYVVPWYFDVWGQGTLV VSS
SEQ ID NO: 43	CDR-H1: UU-1093-mod3, UU- 1093-mod7, UU-1093-mod11, UU-1093-mod15	<u>GYTFTSYWIH</u>
SEQ ID NO: 44	CDR-H3: UU-1093-mod3, UU- 1093-mod7, UU-1093-mod11, UU-1093-mod15	<u>ARSNYVVPWYFDV</u>
SEQ ID NO: 45	heavy chain variable region (VH): UU-1093-mod4, UU-1093-mod8, UU-1093-mod12, UU-1093- mod16	EVQLVQSGAEVKKPGESLRISCKA SGYTFTSYFIHWVRQVPGKGLEW MGEIEPSDSYTNYNQKFKGHVTIS ADKSISTAYLQWSSLKASDTAVYY CAKTNVVPWYFDVWGQGTLV VSS
SEQ ID NO: 46	CDR-H1: UU-1093-mod4, UU- 1093-mod8, UU-1093-mod12, UU-1093-mod16	<u>GYTFTSYFIH</u>
SEQ ID NO: 47	light chain variable region (VL): UU-1093-mod1, UU-1093-mod2, UU-1093-mod3, UU-1093-mod4, UU-1093-mod17	EIVLTQSPGTLSSLSPGERATLSCRSS KSLLLHSQGITYLYWYQQKPGQAP RLLIYQMSNLASGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCAQNLEL PWTFGGGTKLEIK
SEQ ID NO: 48	light chain variable region (VL): UU-1093-mod5, UU-1093-mod6, UU-1093-mod7, UU-1093-mod8, UU-1093-mod18	EIVLTQSPGTLSSLSPGERATLSCRSS KSLLLHSNAITYLYWYQQKPGQAP RLLVYQVSNLASGVPDRFSGSGSG TDFTLTISRLEPEDFAVYYCAQNLE LPWTFGGGTKLEIK
SEQ ID NO: 49	CDR-L1: UU-1093-mod5, UU- 1093-mod6, UU-1093-mod7, UU- 1093-mod8, UU-1093-mod18	<u>RSSKSLLLHSNAITYLY</u>

TABLE 17-continued

Sequence Summary Table		
Sequence Identifier	Description	Sequence
SEQ ID NO: 50	CDR-L2: UU-1093-mod5, UU-1093-mod6, UU-1093-mod7, UU-1093-mod8, UU-1093-mod18	<u>QVSNLAS</u>
SEQ ID NO: 51	light chain variable region (VL): UU-1093-mod9, UU-1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093-mod19	EIVLTQSPGTL ~~SL~~ SPGERATL ~~SCR~~ <u>SS</u> KSL ~~LHS~~ <u>QG</u> ITYLYWYQQKPGQAP RL ~~LVYQ~~ <u>VSNL</u> SGSIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCA <u>QNLE</u> <u>LPFTFGGGTKLEIK</u>
SEQ ID NO: 52	CDR-L2: UU-1093-mod9, UU-1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093-mod19	<u>QVSNLGS</u>
SEQ ID NO: 53	CDR-L3: UU-1093-mod9, UU-1093-mod10, UU-1093-mod11, UU-1093-mod12, UU-1093-mod19	<u>AQNLELPFT</u>
SEQ ID NO: 54	heavy chain variable region (VH): AL-303	QVQLQQPGADLVKPGASVKLSCK ASGYTFTSYWMQWVKQRPQGGL EWIGEIDPSNSYTNYNQKFRGKAT LTVDPSSSTAYMQLSSLTSEDSAV YYC <u>ARGGYWGQ</u> TTTLTVSS
SEQ ID NO: 55	light chain variable region (VL): AL-303	DIVMTQAAFSNPVTLGTSASISCRS SKSL ~~LHS~~ <u>NG</u> ITYLYWYLQKPGQSP QLLIYQMSNLASGVPDRFSSSGSG TDFTLRISRVEAEDVGYYCV <u>QNL</u> <u>ELPYTFGGG</u> TKLEIK
SEQ ID NO: 56	heavy chain variable region (VH): AL-310	QVQLQQSGAESVMPGASVKLSCK ASGYTFTSYWMHWVKQRPQGGL EWIGEIDPSDSYTNYNQKFKGKST LTVDKSSSTAYMQLSSLTSEDSAV YYCAKSNYVVPWYFDVWGTGTT VTVSS
SEQ ID NO: 57	light chain variable region (VL): AL-310	DIVMTQAAFSNPVTLGTSASISCRS SKSL ~~LHS~~ <u>NG</u> ITYLYWYLQKPGQSP QLLIYQMSNLASGVPDRFSSSGSG TDFTLRISRVEAEDVGYYCA <u>QNL</u> <u>ELPWTFGGG</u> TKLEIK
SEQ ID NO: 58	IgG ₁ heavy chain constant region	ASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVTP SSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSD GSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 59	kappa light chain constant region	RTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKSTYLSST LTLKADYEKKHKVYACEVTHQGL SSPVTKSFNRGEC
SEQ ID NO: 60	NAMPT	MNPAAEAEFNILLATDSYKVTHY KQYPNTSKVYSYFECREKKTENS KL ~~RK~~ VKYEETVFYGLQYILNKYL KGKVVTKEKIQEAKDVYKEHFQD DVFNEKGWNYILEKYDGHLP ~~IE~~ IK AVPEGFVI ~~PR~~ GNVLF ~~T~~ VENTDPEC

TABLE 17-continued

Sequence Summary Table		
Sequence Identifier	Description	Sequence
		YWLTNWIETILVQSWYPITVATNS REQKKILAKYLLETSGNLDGLEYS LHDFGYRGVSSQETAGIGASAHV NFKGTDTVAGLALIKKYYGKDP VPGYSVPAAEHSTITAWGKDHEK DAFEHIVTQFSSVPVSVVSDSYDIY NACEKIWGEDLRHLIVSRSTQAPLI IRPDSGNPLDTVLRKLEILGKKFPV TENSKGYKLLPPYLRVIQGDGVDI NTLQEIIVEGMKQKMWSIENIAFGS GGLLQKLTRDLLNCSFKCSYVVT NGLGINVFKDPVADPNKRSKKGR LSLHRTFAGNFVTLEEGKGDLEEY GQDLLHTVFKNGKVTKSYSFDEIR KNAQLNIELEAAHH
SEQ ID NO: 61	K-1076 epitope (residue 17-44)	SYKVTHYKQYPPNTSKVYSYFECR EKKT
SEQ ID NO: 62	K-1076 epitope (residue 117-127)	KAVPEGFVIPR
SEQ ID NO: 63	K-1076 epitope (residue 162-170)	ATNSREQKK
SEQ ID NO: 64	K-1076 epitope (residue 242-261)	VPAAEHSTITAWGKDHEKDA
SEQ ID NO: 65	K-1076 epitope (residue 262-273)	FEHIVTQFSSVP
SEQ ID NO: 66	K-1076 epitope (residue 289-305)	KIWGEDLRHLIVSRSTQ
SEQ ID NO: 67	K-1076 epitope (residue 332-342)	FPVTENSKGYK
SEQ ID NO: 68	K-1076 epitope (residue 374-389)	SIENIAFGSGGGLLQK
SEQ ID NO: 69	K-1076 epitope (residue 418-425)	VADPNKRS
SEQ ID NO: 70	K-1076 epitope (residue 453-466)	YGQDLLHTVFKNGK
SEQ ID NO: 71	K-1076 epitope (residue 408-417)	GLGINVFKDP
SEQ ID NO: 72	NN-1093 epitope (residue 29-51)	NTSKVYSYFECREKKTENSKLRK
SEQ ID NO: 73	NN-1093 epitope (residue 61-72)	GFQYIFNKYLKG
SEQ ID NO: 74	NN-1093 epitope (residue 156-170)	WYPITVATNSREQKK
SEQ ID NO: 75	NN-1093 epitope (residue 216-234)	KGTDTVAGLALIKKYYGTK
SEQ ID NO: 76	NN-1093 epitope (residue 316-331)	NPLDTVLRKLEILGKK
SEQ ID NO: 77	NN-1093 epitope (residue 332-342)	FPVTENSKGYK
SEQ ID NO: 78	NN-1093 epitope (residue 373-389)	WSIENIAFGSGGGLLQK
SEQ ID NO: 79	NN-1093 epitope (residue 417-431)	PVADPNKRSKKGRLS

TABLE 17-continued

Sequence Summary Table		
Sequence Identifier	Description	Sequence
SEQ ID NO: 80	NN-1093 epitope (residue 454-469)	GQDLLHTVFKNGKVTK
SEQ ID NO: 81	NN-1093 epitope (residue 470-478)	SYSFDEIRK

SEQUENCE LISTING

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Sequence total quantity: 81
SEQ ID NO: 1          moltype = AA  length = 112
FEATURE              Location/Qualifiers
REGION              1..112
                    note = Description of Artificial Sequence:
                      Syntheticpolypeptide
source              1..112
                    mol_type = protein
                    organism = synthetic construct

SEQUENCE: 1
QVQLVESGAE VKKPGASVKL SCKASGYTFT SYWMQWVRQA PGQRLEWMGE IDPSNSYTN  60
NQKFRGRVTI TVDKSASTAY MELSSLRSED TAVYYCARGG YWGP GTTVTV SS      112

SEQ ID NO: 2          moltype = AA  length = 112
FEATURE              Location/Qualifiers
REGION              1..112
                    note = Description of Artificial Sequence:
                      Syntheticpolypeptide
source              1..112
                    mol_type = protein
                    organism = synthetic construct

SEQUENCE: 2
DIVMTQTPLS LSVTPGQPAS ISCRSSKSL L HSN GITYLYW YLQKPGQPPQ LLIYQMSNLA  60
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCVQNLELP YTFGPGTKVD IK      112

SEQ ID NO: 3          moltype = AA  length = 10
FEATURE              Location/Qualifiers
REGION              1..10
                    note = Description of Artificial Sequence: Syntheticpeptide
source              1..10
                    mol_type = protein
                    organism = synthetic construct

SEQUENCE: 3
GYTFTSYWMQ                                         10

SEQ ID NO: 4          moltype = AA  length = 17
FEATURE              Location/Qualifiers
REGION              1..17
                    note = Description of Artificial Sequence: Syntheticpeptide
source              1..17
                    mol_type = protein
                    organism = synthetic construct

SEQUENCE: 4
EIDPSNSYTN YNQKFRG                                         17

SEQ ID NO: 5          moltype = AA  length = 5
FEATURE              Location/Qualifiers
REGION              1..5
                    note = Description of Artificial Sequence: Syntheticpeptide
source              1..5
                    mol_type = protein
                    organism = synthetic construct

SEQUENCE: 5
ARGGY                                         5

SEQ ID NO: 6          moltype = AA  length = 16
FEATURE              Location/Qualifiers
REGION              1..16

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-continued

source	note = Description of Artificial Sequence: Syntheticpeptide 1..16 mol_type = protein organism = synthetic construct	
SEQUENCE: 6 RSSKSLLSN GITYLY		16
SEQ ID NO: 7 FEATURE REGION	moltype = AA length = 7 Location/Qualifiers 1..7 note = Description of Artificial Sequence: Syntheticpeptide	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 7 QMSNLAS		7
SEQ ID NO: 8 FEATURE REGION	moltype = AA length = 9 Location/Qualifiers 1..9 note = Description of Artificial Sequence: Syntheticpeptide	
source	1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 8 VQNLLEPYT		9
SEQ ID NO: 9 FEATURE REGION	moltype = AA length = 112 Location/Qualifiers 1..112 note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112 mol_type = protein organism = synthetic construct	
SEQUENCE: 9 QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYWMQWVRQA PGQGLEWMGE IDPSNSYTNV NPKFRGRVTM TTDSTSTAY MELRSLRSDD TAVYYCARGG YWGQGTITVTV SS		60 112
SEQ ID NO: 10 FEATURE REGION	moltype = AA length = 112 Location/Qualifiers 1..112 note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112 mol_type = protein organism = synthetic construct	
SEQUENCE: 10 DIQLTQSPLS LPVTPGEPAS ISCRSSKSL HSQGITYLYW YLQKPGQSPQ LLIYQLSNLA SGVPDRFSGS GSGTDFTLKI SRVEAEDGVV YYCVQNLLEP YTFGGGTKLE IK		60 112
SEQ ID NO: 11 FEATURE REGION	moltype = AA length = 16 Location/Qualifiers 1..16 note = Description of Artificial Sequence: Syntheticpeptide	
source	1..16 mol_type = protein organism = synthetic construct	
SEQUENCE: 11 RSSKSLLSN GITYLY		16
SEQ ID NO: 12 FEATURE REGION	moltype = AA length = 7 Location/Qualifiers 1..7 note = Description of Artificial Sequence: Syntheticpeptide	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 12 QLSNLAS		7
SEQ ID NO: 13 FEATURE REGION	moltype = AA length = 112 Location/Qualifiers 1..112 note = Description of Artificial Sequence: Syntheticpolypeptide	

-continued

source	1..112	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 13		
DIVMTQSPLS LPVTPGEPAS	ISCRSSKSL L HSQGITYLYW YLQKPGQSPQ LLIYQLSNRA	60
SGVPDRFSGS GSGTDFTLKI	SRVEAEDVG V YYCVQNLELP YTFGGGTKLE IK	112
SEQ ID NO: 14	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
REGION	1..7	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 14		
QLSNRAS		7
SEQ ID NO: 15	moltype = AA length = 112	
FEATURE	Location/Qualifiers	
REGION	1..112	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 15		
QVQLVQSGAE VTKPGASVKV	SCKASGYTFT SYWMQWVRQA PGQGLEWVGE IDPSNSYTN Y	60
NQKFRGRVTL TRDTSTTVY	MELSSLRSED TAVYYCARGG YWGQTTTVTV SS	112
SEQ ID NO: 16	moltype = AA length = 112	
FEATURE	Location/Qualifiers	
REGION	1..112	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 16		
QVQLVQSGAE VKKPGASVKV	SCKASGYTFT SYWMQWVRQA PGQGLEWMGE IDPSNSYTN Y	60
NQKFRGRVTM TRDTSTTVY	MELSSLRSED TAVYYCARGG YWGQTTTVTV SS	112
SEQ ID NO: 17	moltype = AA length = 120	
FEATURE	Location/Qualifiers	
REGION	1..120	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..120	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 17		
QVQLVESGAE VKKPGASVKL	SCKASGYTFT SYWMHWVRQA PGQRLEWMGE IDPSDSYTN Y	60
NQKFKGRVTI TVDKSASTAY	MELSSLRSED TAVYYCAKSN YVVPWYFDVW GP GTTVTVSS	120
SEQ ID NO: 18	moltype = AA length = 112	
FEATURE	Location/Qualifiers	
REGION	1..112	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 18		
EIVLTQSPGT LSLSPGERAT	LSCRSSKSL L HSNGITYLYW YQQKPGQAPR LLIYQMSNLA	60
SGIPDRFSGS GSGTDFTLTI	SRLEPEDFAV YYCAQNLELP WTFGGGTKLE IK	112
SEQ ID NO: 19	moltype = AA length = 10	
FEATURE	Location/Qualifiers	
REGION	1..10	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..10	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 19		
GYTFTSYWMH		10
SEQ ID NO: 20	moltype = AA length = 17	

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FEATURE	Location/Qualifiers	
REGION	1..17	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..17	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 20		
EIDPSDSYTN YNQKFKG		17
SEQ ID NO: 21	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 21		
AKSNYVVPWY FDV		13
SEQ ID NO: 22	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
REGION	1..9	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..9	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 22		
AQNLELPWT		9
SEQ ID NO: 23	moltype = AA length = 120	
FEATURE	Location/Qualifiers	
REGION	1..120	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..120	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 23		
QVQLVQSGAE VRKPGASVKV SCKASGYTFT SYWMHWVRQA PGQGLEWVGE IDPSDSYTN		60
NQKFKGRVTI TADKSTSTAY MELSSLRSED TDVYYCAKSN YVVPWYFDVW GQGTTVTVSS		120
SEQ ID NO: 24	moltype = AA length = 112	
FEATURE	Location/Qualifiers	
REGION	1..112	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 24		
EIVLTQSPAT LSLSPGERAT LSCRSSKSL L HSN GITYLYW YQKPGQAPR LLIYQMSNLA		60
SGIPARFSGS GSGTDFTLTI SSLEPEDFAV YYCAQNLELP WTFGGGTKLE IK		112
SEQ ID NO: 25	moltype = AA length = 120	
FEATURE	Location/Qualifiers	
REGION	1..120	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..120	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 25		
QVQLVQSGAE VTKPGASVKV SCKASGYTFT SYWMHWVRQA PGQGLEWVGE IDPSDSYTN		60
NQKFKGRVTL TRDTSTTTVY MELSSLRSED TAVYYCAKSN YVVPWYFDVW GQGTTVTVSS		120
SEQ ID NO: 26	moltype = AA length = 120	
FEATURE	Location/Qualifiers	
REGION	1..120	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..120	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 26		
EVQLVQSGAE VKKPGESLRI SCKASGYTFT SYWMHWVRQM PGKGLEWMGE IDPSDSYTN		60
NQKFKGHVTI SADKSISTAY LQWSSLKASD TAMYCAKSN YVVPWYFDVW GQGTLVTVSS		120

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SEQ ID NO: 27 moltype = AA length = 120
FEATURE Location/Qualifiers
REGION 1..120
 note = Description of Artificial Sequence:
 Syntheticpolypeptide
source 1..120
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 27
QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYWMHWVRQA PGQGLEWMGE IDPSDSYTNV 60
NQKFKGRVTM TRDTSTSTVY MELSSLRSED TAVYYCAKSN YVVPWFYFDVW GTGTTVTTVSS 120

SEQ ID NO: 28 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
 note = Description of Artificial Sequence:
 Syntheticpolypeptide
source 1..112
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 28
QVQLVQSGAE VTKPGASVKV SCKASGYTFT SYWMQWVRQA PGQGLEWVGE IEPSNSYTNV 60
NQKFRGRVTL TRDTSTTTVY MELSSLRSED TAVYYCARGG YWQGTTTVTV SS 112

SEQ ID NO: 29 moltype = AA length = 17
FEATURE Location/Qualifiers
REGION 1..17
 note = Description of Artificial Sequence: Syntheticpeptide
source 1..17
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 29
EIEPSNSYTN YNQKFRG 17

SEQ ID NO: 30 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
 note = Description of Artificial Sequence:
 Syntheticpolypeptide
source 1..112
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 30
DIVMTQSPLS LPVTPGEPAS ISCRSSKSLL HSQGITYLYW YVQKPGQSPQ LLIYQLSNRA 60
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCVQNLELP YTFGGGTKLE IK 112

SEQ ID NO: 31 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
 note = Description of Artificial Sequence:
 Syntheticpolypeptide
source 1..112
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 31
DIVMTQSPLS LPVTPGEPAS ISCRSSKSLL HSQGITYLYW YIQKPGQSPQ LLIYQLSNRA 60
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCVQNLELP YTFGGGTKLE IK 112

SEQ ID NO: 32 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
 note = Description of Artificial Sequence:
 Syntheticpolypeptide
source 1..112
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 32
DIVMTQSPLS LPVTPGEPAS ISCRSSKSLL HSQGITYLYW YVQKPGQSPQ LLIYQGSNRA 60
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCVQNLELP YTFGGGTKLE IK 112

SEQ ID NO: 33 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
 note = Description of Artificial Sequence: Syntheticpeptide
source 1..7

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	mol_type = protein organism = synthetic construct	
SEQUENCE: 33 QGSNRAS		7
SEQ ID NO: 34 FEATURE REGION	moltype = AA length = 112 Location/Qualifiers 1..112 note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112 mol_type = protein organism = synthetic construct	
SEQUENCE: 34 DIVMTQSPLS LPVTPGEPAS ISCRSSKSLL HSQGITYLYW YVQKPGQSPQ LLIYQESNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCVQNLLELP YTFGGGTKLE IK	60 112	
SEQ ID NO: 35 FEATURE REGION	moltype = AA length = 7 Location/Qualifiers 1..7 note = Description of Artificial Sequence: Syntheticpeptide	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 35 QESNRAS		7
SEQ ID NO: 36 FEATURE REGION	moltype = AA length = 112 Location/Qualifiers 1..112 note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..112 mol_type = protein organism = synthetic construct	
SEQUENCE: 36 DIVMTQSPLS LPVTPGEPAS ISCRSSKSLL HSQGITYLYW YIQKPGQSPQ LLIYQVSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCVQNLLELP YTFGGGTKLE IK	60 112	
SEQ ID NO: 37 FEATURE REGION	moltype = AA length = 7 Location/Qualifiers 1..7 note = Description of Artificial Sequence: Syntheticpeptide	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 37 QVSNRAS		7
SEQ ID NO: 38 FEATURE REGION	moltype = AA length = 120 Location/Qualifiers 1..120 note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..120 mol_type = protein organism = synthetic construct	
SEQUENCE: 38 EVQLVQSGAE VKKPGESLRI SCKASGYTFT SYWMHWVRQM PGKGLEWMGE IEPDSYNTNY NQKFKGHVTI SADKSISTAY LQWSSLKASD TAMYCAKSN YVVPWYFDVW GQGLVTVSS	60 120	
SEQ ID NO: 39 FEATURE REGION	moltype = AA length = 17 Location/Qualifiers 1..17 note = Description of Artificial Sequence: Syntheticpeptide	
source	1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 39 IEPDSYTN YNQKFKG		17
SEQ ID NO: 40 FEATURE REGION	moltype = AA length = 120 Location/Qualifiers 1..120 note = Description of Artificial Sequence: Syntheticpolypeptide	

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source	1..120	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 40		
EVQLVQSGAE VKKPGESLRI	SCKASGYTFT SYWMHWVRQM PGKGLEWMGE IEPDSYTN	60
NQKFKGHVTI SADKSISTAY	LQWSSLKASD TAMYCAKTN YVVPWYFDVW GQGLVTVSS	120
SEQ ID NO: 41	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 41		
AKTNYVVPWY FDV		13
SEQ ID NO: 42	moltype = AA length = 120	
FEATURE	Location/Qualifiers	
REGION	1..120	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..120	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 42		
EVQLVQSGAE VKKPGESLRI	SCKASGYTFT SYWIHWVRQV PGKGLEWMGE IEPDSYTN	60
NQKFKGHVTI SADKSISTAY	LQWSSLKASD TAVYYCARSN YVVPWYFDVW GQGLVTVSS	120
SEQ ID NO: 43	moltype = AA length = 10	
FEATURE	Location/Qualifiers	
REGION	1..10	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..10	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 43		
GYTFTSYWIH		10
SEQ ID NO: 44	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 44		
ARSNYVVPWY FDV		13
SEQ ID NO: 45	moltype = AA length = 120	
FEATURE	Location/Qualifiers	
REGION	1..120	
	note = Description of Artificial Sequence: Syntheticpolypeptide	
source	1..120	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 45		
EVQLVQSGAE VKKPGESLRI	SCKASGYTFT SYFIHWVRQV PGKGLEWMGE IEPDSYTN	60
NQKFKGHVTI SADKSISTAY	LQWSSLKASD TAVYYCAKTN YVVPWYFDVW GQGLVTVSS	120
SEQ ID NO: 46	moltype = AA length = 10	
FEATURE	Location/Qualifiers	
REGION	1..10	
	note = Description of Artificial Sequence: Syntheticpeptide	
source	1..10	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 46		
GYTFTSYFIH		10
SEQ ID NO: 47	moltype = AA length = 112	
FEATURE	Location/Qualifiers	
REGION	1..112	
	note = Description of Artificial Sequence: Syntheticpolypeptide	

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source 1..112
mol_type = protein
organism = synthetic construct

SEQUENCE: 47
EIVLTQSPGT LSLSPGERAT LSCRSSKSL L HSQGITYLYW YQKPGQAPR LLIYQMSNLA 60
SGIPDRFSGS GSGTDFTLTI SRLEPEDFAV YYCAQNLELP WTFGGGTKLE IK 112

SEQ ID NO: 48 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = Description of Artificial Sequence:
Syntheticpolypeptide

source 1..112
mol_type = protein
organism = synthetic construct

SEQUENCE: 48
EIVLTQSPGT LSLSPGERAT LSCRSSKSL L HSNAITYLYW YQKPGQAPR LLVYQVSNLA 60
SGVPDRFSGS GSGTDFTLTI SRLEPEDFAV YYCAQNLELP WTFGGGTKLE IK 112

SEQ ID NO: 49 moltype = AA length = 16
FEATURE Location/Qualifiers
REGION 1..16
note = Description of Artificial Sequence: Syntheticpeptide

source 1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 49
RSSKSL LHSN AITYLY 16

SEQ ID NO: 50 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = Description of Artificial Sequence: Syntheticpeptide

source 1..7
mol_type = protein
organism = synthetic construct

SEQUENCE: 50
QVSNLAS 7

SEQ ID NO: 51 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = Description of Artificial Sequence:
Syntheticpolypeptide

source 1..112
mol_type = protein
organism = synthetic construct

SEQUENCE: 51
EIVLTQSPGT LSLSPGERAT LSCRSSKSL L HSQGITYLYW YQKPGQAPR LLVYQVSNLG 60
SGIPDRFSGS GSGTDFTLTI SRLEPEDFAV YYCAQNLELP FTFGGGTKLE IK 112

SEQ ID NO: 52 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = Description of Artificial Sequence: Syntheticpeptide

source 1..7
mol_type = protein
organism = synthetic construct

SEQUENCE: 52
QVSNLGS 7

SEQ ID NO: 53 moltype = AA length = 9
FEATURE Location/Qualifiers
REGION 1..9
note = Description of Artificial Sequence: Syntheticpeptide

source 1..9
mol_type = protein
organism = synthetic construct

SEQUENCE: 53
AQNLELPFT 9

SEQ ID NO: 54 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = Description of Artificial Sequence:
Syntheticpolypeptide

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source	1..112				
	mol_type = protein				
	organism = synthetic construct				
SEQUENCE: 54					
QVQLQQPGAD LVKPGASVKL	SCKASGYTFT SYWMQWVKQR	PGQGLEWIGE IDPSNSYTN	60		
NQKFRGKATL TVDPSSSTAY	MLSSLTSED SAVYVCARGG	YWGQTTTLTV SS	112		
SEQ ID NO: 55	moltype = AA length = 112				
FEATURE	Location/Qualifiers				
REGION	1..112				
	note = Description of Artificial Sequence:				
	Syntheticpolypeptide				
source	1..112				
	mol_type = protein				
	organism = synthetic construct				
SEQUENCE: 55					
DIVMTQAAPS NPVTLGTSAS	ISCRSSKSLH HSNQITYLYW	YLQKPGQSPQ LLIYQMSNLA	60		
SGVPDRFSSS GSGTDFTLRI	SRVEAEDVGV YYCVQNLRLP	YTFGGGTKLE IK	112		
SEQ ID NO: 56	moltype = AA length = 120				
FEATURE	Location/Qualifiers				
REGION	1..120				
	note = Description of Artificial Sequence:				
	Syntheticpolypeptide				
source	1..120				
	mol_type = protein				
	organism = synthetic construct				
SEQUENCE: 56					
QVQLQQSGAE SVMPGASVKL	SCKASGYTFT SYWMHWVKQR	PGQGLEWIGE IDPSDSYTN	60		
NQKFKGKSTL TVDKSSSTAY	MLSSLTSED SAVYVCAKSN	YVVPWFYFDVW GTGTTVTVSS	120		
SEQ ID NO: 57	moltype = AA length = 112				
FEATURE	Location/Qualifiers				
REGION	1..112				
	note = Description of Artificial Sequence:				
	Syntheticpolypeptide				
source	1..112				
	mol_type = protein				
	organism = synthetic construct				
SEQUENCE: 57					
DIVMTQAAPS NPVTLGTSAS	ISCRSSKSLH HSNQITYLYW	YLQKPGQSPQ LLIYQMSNLA	60		
SGVPDRFSSS GSGTDFTLRI	SRVEAEDVGV YYCAQNLRLP	WTFGGGTKLE IK	112		
SEQ ID NO: 58	moltype = AA length = 330				
FEATURE	Location/Qualifiers				
REGION	1..330				
	note = Description of Artificial Sequence:				
	Syntheticpolypeptide				
source	1..330				
	mol_type = protein				
	organism = synthetic construct				
SEQUENCE: 58					
ASTKGPSVFP LAPSSKSTSG	GTAALGCLVK DYFPEPTVS	WNSGALTSGV HTFPAVLQSS	60		
GLYSLSSVVT VPSSSLGTQT	YICNVNHKPS NTKVDKKVEP	KSCDKTHTCP PCPAPELLGG	120		
PSVFLFPPKP KDTLMISRTP	EVTCTVVVDVS HEDPEVKFNW	YVDGVEVHNA KTKPREEQYN	180		
STYRVVSVLT VLNQDNLNGK	EYKCKVSNKA LPAPIKTIS	KAKGQPREPQ VYTLPPSRDE	240		
LTKNQVSLTC LVKGFYPSDI	AVEWESNGQP ENNYKTTTPV	LDSDGSFFLY SKLTVDKSRW	300		
QQGNVFSCSV MHEALHNHYT	QKSLSLSPGK		330		
SEQ ID NO: 59	moltype = AA length = 107				
FEATURE	Location/Qualifiers				
REGION	1..107				
	note = Description of Artificial Sequence:				
	Syntheticpolypeptide				
source	1..107				
	mol_type = protein				
	organism = synthetic construct				
SEQUENCE: 59					
RTVAAPSVFI FPPSDEQLKS	GTASVVCLLN NFYPREAKVQ	WKVDNALQSG NSQESVTEQD	60		
SKDSTYSLSS TLTLKADYE	KHKVYACEVT HQGLSSPVTK	SFNRGEC	107		
SEQ ID NO: 60	moltype = AA length = 491				
FEATURE	Location/Qualifiers				
source	1..491				
	mol_type = protein				
	organism = Homo sapiens				

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SEQUENCE: 60		
MNPAAEAEFN	ILLATDSYKV THYKQYPPNT SKVYSYFECR EKKTENSKLR KVKYEETV FY	60
GLQYILNKYL	KGKVVTKKEI QEAKDVYKEH FQDDVFNEKG WNYILEKYDG HLP I EIKAVP	120
EGFVIPRGNV	LFTVENTDPE CYWLTNWIET ILVQSWYPIT VATNSREQKK ILAKYLLETS	180
GNLDGLEYKL	HDFGYRGVSS QETAGIGASA HLVNFKGTD T VAGLALIKKY YGTDKDPVPGY	240
SVPAAEHSTI	TAWGKDHEKD AFEHIVTQFS SVPVSVVSDS YDIYNACEKI WGEDLRHLIV	300
SRSTQAPLII	RPDSGNPLDT VLKVL EILGK KFPVTENSKG YKLLPPYLRV IQGDGVDINT	360
LQEIVEGMKQ	KMWSIENIAF GSGGGLLQKL TRDLLNCSFK CSYVVTNGLG INVFKDPVAD	420
PNKRSKKGRL	SLHRTPAGNF VTLEEGKGD L EEYGQDLLHT VFKNGKVTKS YSFDEIRKNA	480
QLNIELEAAH	H	491
SEQ ID NO: 61	moltype = AA length = 28	
FEATURE	Location/Qualifiers	
source	1..28	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 61		
SYKVTHYKQY	PPNTSKVYSY FECREKKT	28
SEQ ID NO: 62	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
source	1..11	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 62		
KAVPEGFVIP	R	11
SEQ ID NO: 63	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
source	1..9	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 63		
ATNSREQKK		9
SEQ ID NO: 64	moltype = AA length = 20	
FEATURE	Location/Qualifiers	
source	1..20	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 64		
VPAAEHSTIT	AWGKDHEKDA	20
SEQ ID NO: 65	moltype = AA length = 12	
FEATURE	Location/Qualifiers	
source	1..12	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 65		
FEHIVTQFSS	VP	12
SEQ ID NO: 66	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 66		
KIWGEDLRHL	IVSRSTQ	17
SEQ ID NO: 67	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
source	1..11	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 67		
FPVTENSKGY	K	11
SEQ ID NO: 68	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 68		
SIENIAFGSG	GGLLQK	16
SEQ ID NO: 69	moltype = AA length = 8	

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FEATURE	Location/Qualifiers	
source	1..8 mol_type = protein organism = Homo sapiens	
SEQUENCE: 69 VADPNKRS		8
SEQ ID NO: 70 FEATURE	moltype = AA length = 14 Location/Qualifiers	
source	1..14 mol_type = protein organism = Homo sapiens	
SEQUENCE: 70 YGQDLLHTVF KNGK		14
SEQ ID NO: 71 FEATURE	moltype = AA length = 10 Location/Qualifiers	
source	1..10 mol_type = protein organism = Homo sapiens	
SEQUENCE: 71 GLGINVFKDP		10
SEQ ID NO: 72 FEATURE	moltype = AA length = 23 Location/Qualifiers	
source	1..23 mol_type = protein organism = Homo sapiens	
SEQUENCE: 72 NTSKVYSYFE CREKKTENSK LRK		23
SEQ ID NO: 73 FEATURE	moltype = AA length = 12 Location/Qualifiers	
source	1..12 mol_type = protein organism = Homo sapiens	
SEQUENCE: 73 GLQYILNKYL KG		12
SEQ ID NO: 74 FEATURE	moltype = AA length = 15 Location/Qualifiers	
source	1..15 mol_type = protein organism = Homo sapiens	
SEQUENCE: 74 WYPITVATNS REQKK		15
SEQ ID NO: 75 FEATURE	moltype = AA length = 19 Location/Qualifiers	
source	1..19 mol_type = protein organism = Homo sapiens	
SEQUENCE: 75 KGTDTVAGLA LIKKYYGTK		19
SEQ ID NO: 76 FEATURE	moltype = AA length = 16 Location/Qualifiers	
source	1..16 mol_type = protein organism = Homo sapiens	
SEQUENCE: 76 NPLDVLKVL EILGKK		16
SEQ ID NO: 77 FEATURE	moltype = AA length = 11 Location/Qualifiers	
source	1..11 mol_type = protein organism = Homo sapiens	
SEQUENCE: 77 FPVTENSKGY K		11
SEQ ID NO: 78 FEATURE	moltype = AA length = 17 Location/Qualifiers	
source	1..17 mol_type = protein organism = Homo sapiens	

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SEQUENCE: 78		
WSIENIAFGS GGGLLQK		17
SEQ ID NO: 79	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 79		
PVADPNKRSK KGRLS		15
SEQ ID NO: 80	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 80		
GQDLLHTVFK NGKVTK		16
SEQ ID NO: 81	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
source	1..9	
	mol_type = protein	
	organism = Homo sapiens	
SEQUENCE: 81		
SYSFDEIRK		9

1. A method of treating a subject having Coronavirus disease 2019 (COVID-19), the method comprising administering to the subject an effective amount of an isolated antibody, or an antigen-binding fragment thereof, that binds to human nicotinamide phosphoribosyltransferase (NAMPT).

2-27. (canceled)

28. The method of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NOs: 4 or 29; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; and
- (ii) a light chain variable region comprising a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6 or 11; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 7, 12, 14, 33, 35 or 37; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8.

29. The method of claim 1, wherein a heavy chain variable region of the isolated antibody comprises:

- (a) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 4, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5; or
- (b) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 3, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 29, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 5.

30. The method of claim 1, wherein a light chain variable region of the isolated antibody comprises:

- (a) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an

- amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
- (b) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 12, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
- (c) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 14, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
- (d) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 33, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
- (e) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 35, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
- (f) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 6, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 37, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
- (g) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 7, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
- (h) a CDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 11, a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 12, and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;

- [illegible]

sequence as set forth in SEQ ID NO: 11; a CDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 37; and a CDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8.

32. The method of claim 1, wherein the isolated antibody or antigen-binding fragment thereof is humanized.

33. The method of claim 1, wherein the isolated antibody contains a light chain variable region with an amino acid sequence as set forth in SEQ ID NO: 2, 10, 13, 30, 31, 32, 34 or 36.

34. The method of claim 1, wherein the isolated antibody contains a heavy chain variable region with an amino acid sequence as set forth in SEQ ID NO: 1, 9, 15, 16 or 28.

35. The method of claim 1, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 15, and a light chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 13.

36. The method of claim 1, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 26, and a light chain comprising a variable region comprising the amino acid sequence as set forth in SEQ ID NO: 18.

37. The method of claim 1, wherein the isolated antibody or antigen-binding fragment thereof comprises a humanized heavy chain variable region derived from murine antibody AL-303 or AL-310, and a humanized light chain variable region derived from murine antibody AL-303 or AL-310.

38. The method of claim 1, wherein the isolated antibody or antigen-binding fragment thereof binds to human NAMPT in a homodimeric conformation, wherein the antibody binds an epitope on human NAMPT comprising either

- a) an epitope on human NAMPT comprising at least one amino acid in amino acid residues 17-44 of SEQ ID NO: 60; at least one amino acid in amino acid residues 117-127 of SEQ ID NO: 60; at least one amino acid in

- amino acid residues 162-170 of SEQ ID NO: 60; at least one amino acid in amino acid residues 242-261 of SEQ ID NO: 60; at least one amino acid in amino acid residues 262-273 of SEQ ID NO: 60; at least one amino acid in amino acid residues 289-305 of SEQ ID NO: 60; at least one amino acid in amino acid residues 332-342 of SEQ ID NO: 60; at least one amino acid in amino acid residues 374-389 of SEQ ID NO: 60; at least one amino acid in amino acid residues 418-425 of SEQ ID NO: 60; at least one amino acid in amino acid residues 453-466 of SEQ ID NO: 60; and at least one amino acid in amino acid residues 408-416 of SEQ ID NO: 60; or
- b) an epitope on human NAMPT comprising at least one amino acid in amino acid residues 29-51 of SEQ ID NO: 60; at least one amino acid in amino acid residues 61-72 of SEQ ID NO: 60; at least one amino acid in amino acid residues 156-170 of SEQ ID NO: 60; at least one amino acid in amino acid residues 216-234 of SEQ ID NO: 60; at least one amino acid in amino acid residues 316-331 of SEQ ID NO: 60; at least one amino acid in amino acid residues 332-342 of SEQ ID NO: 60; at least one amino acid in amino acid residues 373-389 of SEQ ID NO: 60; at least one amino acid in amino acid residues 417-431 of SEQ ID NO: 60; at least one amino acid in amino acid residues 454-469 of SEQ ID NO: 60; and at least one amino acid in amino acid residues 470-478 of SEQ ID NO: 60.

39. The method of claim 1, wherein the isolated antibody or antigen-binding fragment thereof comprises an Fc domain.

40. The method of claim 1, wherein the antibody or antigen-binding fragment thereof is a monoclonal antibody.

41. The method of claim 1, wherein the antibody or antigen-binding fragment thereof is an IgG antibody.

42. The method of claim 1, wherein the antibody or antigen-binding fragment thereof is an IgG1 or an IgG4 antibody.

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