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(54) Title: PD-1 PEPTIDE INHIBITORS

(57) Abstract: This disclosure provides peptides which have a strong affinity for the checkpoint receptor "programmed death 1" (PD-1). These peptides block the interaction of PD-1 with its ligand PDL1 and can therefore be used for various therapeutic purposes, such as inhibiting the progression of a hyperproliferative disorder, including cancer, treating infectious diseases, enhancing a response to vaccination, and treating sepsis.

PD-1 PEPTIDE INHIBITORS

[01] This application claims priority to and incorporates by reference in its entirety U.S. Serial No. 62/395,195 filed on September 15, 2016. Each reference cited in this disclosure is incorporated herein in its entirety.

[02] This application incorporates by reference the contents of a 1.38 kb text file created on September 11, 2017 and named "00047900249sequencelisting.txt," which is the sequence listing for this application.

TECHNICAL FIELD

[03] This disclosure relates generally to immunomodulatory peptides.

BRIEF DESCRIPTION OF THE DRAWINGS

[04] **Figure 1**. Graph showing saturatable binding of anti-human PD-1 antibody to Jurkat cells.

[05] **Figure 2**. Graph showing saturatable binding of PD-L1 Fc to Jurkat cells.

[06] **Figures 3A-B**. Graphs showing effect of peptide QP20 on binding of PD-L1 to PD-1. **Figure 3A**, MFI; **Figure 3B**, normalized mean fluorescence intensity (MFI).

[07] **Figures 4A-B**. Graphs showing effect of peptide HD20 on binding of PD-L1 to PD-1. **Figure 4A**, MFI; **Figure 4B**, normalized MFI.

[08] **Figures 5A-B**. Graphs showing effect of peptide WQ20 on binding of PD-L1 to PD-1. **Figure 5A**, MFI; **Figure 5B**, normalized MFI.

[09] **Figures 6A-B**. Graphs showing effect of peptide SQ20 on binding of PD-L1 to PD-1. **Figure 6A**, MFI; **Figure 6B**, normalized MFI.

[10] **Figure 7A**. Graph showing the effect of an anti-human PD-1 antibody on the interaction between PD-1-expressing Jurkat T cells and PD-L1-expressing CHO cells that results in inhibition of a PD-1 mediated suppression of luciferase reporter that is under the control of promoter containing IL-2, NFAT, and NF-kB response elements.

[11] **Figure 7B**. Graph showing the effect of an anti-human PD-1 antibody on the interaction between PD-1-expressing Jurkat T cells and PD-L1-expressing CHO cells (data in 7A expressed as fold inhibition).

[12] **Figure 8A**. Graph showing that PD-1 peptide inhibitors inhibit, in a dose-dependent manner, the interaction between PD-1-expressing Jurkat T cells and PD-L1-expressing CHO cells, which results in increased luciferase reporter expression,.

[13] **Figure 8B**. Graph showing the effect of an anti-human PD-1 antibody on the interaction between PD-1-expressing Jurkat T cells and PD-L1-expressing CHO cells (data in 8B expressed as fold inhibition).

[14] **Figure 9**. Graph showing IL-2 production by peripheral blood mononuclear cells (PBMCs) in a tetanus toxoid recall assay after culture with peptides QP20, HD20, WQ20, SQ20, or CQ-22.

[15] **Figure 10**. Graph showing IL-4 production by PBMCs in a tetanus toxoid recall assay after culture with peptides QP20, HD20, WQ20, SQ20, or CQ-22.

[16] **Figure 11**. Graph showing IL-6 production by PBMCs in a tetanus toxoid recall assay after culture with peptides QP20, HD20, WQ20, SQ20, or CQ-22.

[17] **Figure 12**. Graph showing IL-10 production by PBMCs in a tetanus toxoid recall assay after culture with peptides QP20, HD20, WQ20, SQ20, or CQ-22.

[18] **Figure 13**. Graph showing IL-17a production by PBMCs in a tetanus toxoid recall assay, after culture with peptides QP20, HD20, WQ20, SQ20, or CQ-22.

[19] **Figure 14**. Graph showing IFNγ production by PBMCs in a tetanus toxoid recall assay, after culture with peptides QP20, HD20, WQ20, SQ20, or CQ-22.

[20] **Figure 15**. Graph showing TNFα production by PBMCs in a tetanus toxoid recall assay, after culture with peptides QP20, HD20, WQ20, SQ20, or CQ-22.

[21] **Figure 16.** Graph showing IL-2 production by PBMCs in a tetanus toxoid recall assay, after culture with various combinations of peptides QP20, HD20, WQ20, and SQ20.

[22] **Figure 17.** Graph showing IL-4 production by PBMCs in a tetanus toxoid recall assay, after culture with various combinations of peptides QP20, HD20, WQ20, and SQ20.

[23] **Figure 18.** Graph showing IL-6 production by PBMCs in a tetanus toxoid recall assay, after culture with various combinations of peptides QP20, HD20, WQ20, and SQ20.

[24] **Figure 19.** Graph showing IL-10 production by PBMCs in a tetanus toxoid recall assay, after stimulation with various combinations of peptides QP20, HD20, WQ20, and SQ20.

[25] **Figure 20.** Graph showing IL-17a production by PBMCs after stimulation with various combinations of peptides QP20, HD20, WQ20, and SQ20.

[26] **Figure 21.** Graph showing IFNγ production by PBMCs after culture with various combinations of peptides QP20, HD20, WQ20, and SQ20.

[27] **Figure 22.** Graph showing TNFα production by PBMCs after culture with various combinations of peptides QP20, HD20, WQ20, and SQ20.

[28] **Figure 23A**. Graph showing IL-2 production by PBMCs from donor A after culture with peptides QP20, HD20, WQ20, and SQ20, or CQ-22.

[29] **Figure 23B**. Graph showing IL-2 production by PBMCs from donor B after culture with peptides QP20, HD20, WQ20, or SQ20 and combinations of these peptides.

[30] **Figure 24A**. Graph showing IL-17a production by PBMCs from donor A after culture with peptides QP20, HD20, WQ20, and SQ20, or CQ-22.

[31] **Figure 24B**. Graph showing IL-17a production by PBMCs from donor B after culture with peptides QP20, HD20, WQ20, or SQ20 and combinations of these peptides.

[32] **Figure 25**. Graph showing number of surface metastases in mice bearing B16-F10-LacZ tumor cells and treated with combinations of peptides.

[33] **Figure 26.** Graph showing the average number ± standard deviation of *Plasmodium yoelii* circumsporozoite protein (PyCS)-specific, IFNγ-secreting CD8 T cells per 0.5×10^6 splenocytes for each cohort tested in Example 8.

[34] **Figure 27.** Graph showing the effect of the combination of QP20, HD20, WQ20, and SQ20 peptides on the mean level of serum HBsAg (hepatitis B surface antigen) at weeks 2 and 3 post infection.

DETAILED DESCRIPTION

[35] This disclosure provides four peptides:

peptide	amino acid sequence	SEQ ID NO:
QP20	QTRTVPMPKI**HHP**PWQNVVP	1
HD20	**HHH**QVYQVRSHWTGMHSGHD	2
WQ20	WNLPASFHN**HHI**RPHEHEWIQ	3
SQ20	SSY**HHF**KMPELHFGKNTFHQ	4

These peptides share a core sequence of HH_, which is shown above in bold, and have a strong affinity for the checkpoint receptor "programmed death 1" (PD-1). These peptides block the interaction of PD-1 with its ligand PD-L1 and can therefore be used to inhibit the progression of a hyperproliferative disorder, including cancer, or to treat infectious diseases, including persistent infections by agents such as HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and *Plasmodium falciparum*, by enhancing, stimulating, and/or increasing an individual's immune response.

Pharmaceutical Compositions

[36] Pharmaceutical compositions comprise up to four of the peptides disclosed herein and a pharmaceutically acceptable vehicle. The "pharmaceutically acceptable vehicle" may comprise one or more substances which do not affect the biological activity of the peptides and, when administered to a patient, does not cause an adverse reaction. Pharmaceutical compositions may be liquid or may be lyophilized. Lyophilized compositions may be provided in a kit with a suitable liquid, typically water for injection (WFI) for use in reconstituting the composition. Pharmaceutical compositions can be administered by any suitable route, including, but not limited to, intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous administration.

[37] In some embodiments, one or more of the disclosed peptides can be conjugated to various moieties, such as albumin and transthyretin, to enhance the peptide's plasma half-life. Methods of preparing such conjugates are well known in the art (*e.g.*, Penchala *et al.*, 2015; Kontermann, 2016; Zorzi *et al.*, 2017).

Therapeutic Uses

[38] Pharmaceutical compositions disclosed herein have a number of therapeutic applications. In some embodiments, a pharmaceutical composition disclosed herein can be administered to a patient to inhibit the progression of a hyperproliferative disorder, such as cancer. Such inhibition may include, for example, reducing proliferation of neoplastic or pre-neoplastic cells; destroying neoplastic or pre-neoplastic cells; and inhibiting metastasis or decreasing the size of a tumor.

[39] Examples of cancers that can be treated using a pharmaceutical composition disclosed herein include, but are not limited to, melanomas, lymphomas, sarcomas, and cancers of the colon, kidney, stomach, bladder, brain (*e.g.*, gliomas, glioblastomas, astrocytomas, medulloblastomas), prostate, bladder, rectum, esophagus, pancreas, liver, lung, breast, uterus, cervix, ovary, blood (*e.g.*, acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, Burkitt's lymphoma, EBV-induced B-cell lymphoma).

[40] In some embodiments, a pharmaceutical composition disclosed herein can be administered in conjunction with a cancer vaccine. A "cancer vaccine" is an immunogenic composition intended to elicit an immune response against a particular antigen in patient to which the cancer vaccine is administered. A cancer vaccine typically contains a tumor antigen which is able to induce or stimulate an immune response against the tumor antigen. A "tumor antigen" is an antigen that is present on the surface of a target tumor. A tumor antigen may be a molecule which is not expressed by a non-tumor cell or may be, for example, an altered version of a molecule expressed by a non-tumor cell (*e.g.*, a protein that is misfolded, truncated, or otherwise mutated). "In conjunction with" includes administration of the pharmaceutical composition may be together with, before, or after administration of the cancer vaccine.

[41] In some embodiments, a pharmaceutical composition disclosed herein can be administered in conjunction with a chimeric antigen receptor (CAR) T cell therapy to treat cancers in order to increase the efficacy of such therapy.

[42] In some embodiments, a pharmaceutical composition disclosed herein can be administered to a patient to treat infectious diseases, including chronic infections, caused, *e.g.*, by viruses, fungi, bacteria, and protozoa, and helminths.

[43] Examples of viral agents include human immunodeficiency virus (HIV), Epstein Barr Virus (EBV), *Herpes simplex* (HSV, including HSV1 and HSV2), Human Papillomavirus (HPV), *Varicella zoster* (VSV) *Cytomegalovirus* (CMV), and hepatitis A, B, and C viruses.

[44] Examples of fungal agents include *Aspergillus*, *Candida*, *Coccidioides*, *Cryptococcus*, *and Histoplasma capsulatum*.

[45] Examples of bacterial agents include *Streptococcal* bacteria (*e.g.*, *pyogenes*, *agalactiae*, *pneumoniae*), *Chlamydia pneumoniae, Listeria monocytogenes*, and *Mycobacterium tuberculosis*.

[46] Examples of protozoa include *Sarcodina* (*e.g.*, *Entamoeba*), *Mastigophora* (*e.g.*, *Giardia*), *Ciliophora* (*e.g.*, *Balantidium*), and *Sporozoa* (*e.g.*, *Plasmodium falciparum*, *Cryptosporidium*).

[47] Examples of helminths include *Platyhelminths* (*e.g.*, trematodes, cestodes), *Acanthocephalins*, and *Nematodes*.

[48] In some embodiments a pharmaceutical composition disclosed herein can be administered as a vaccine adjuvant in conjunction with a vaccine to enhance a response to vaccination (*e.g.*, by increasing effector T cells and/or reducing T cell exhaustion). "In conjunction with" includes administration of the pharmaceutical composition may be together with, before, or after administration of, the vaccine. The vaccine can be, for example, an RNA vaccine (*e.g.*, US 2016/0130345, US 2017/0182150), a DNA vaccine, a recombinant vector, a protein vaccine, or a peptide vaccine. Such vaccines can be delivered, for example, using virus-like particles, as is well known in the art.

[49] In some embodiments a pharmaceutical composition disclosed herein can be administered to treat sepsis.

EXAMPLE 1. Peptide Library Screening

[50] The TriCo-20™ (TRICO-20™) and TriCo-16™ (TRICO-16™) Phage Display Peptide Libraries (Creative Biolabs, 45-1 Ramsey Road, Shirley, NY 11967) were screened to identify binders of soluble recombinant human PD-1 receptor. After the fourth round of panning, obvious enrichment for specific binders was observed, and individual peptides were confirmed as weakly specific binders in a clonal phage ELISA. A fifth round of panning led to greater enrichment. Table 1 lists four peptides which showed strong specific binding in the clonal phage ELISA.

Table 1

	Clonal Phase ELISA			
Clone	coated signal	uncoated signal	peptide sequence	SEQ ID NO:
QP20	0.851	0.446	QTRTVPMPKIHHPPWQNVVP	1
HD20	0.281	0.109	HHHQVYQVRSHWTGMHSGHD	2
WQ20	0.275	0.115	WNLPASFHNHHIRPHEHEWIQ	3
SQ20	0.284	0.159	SSYHHFKMPELHFGKNTFHQ	4

EXAMPLE 2. Competitive PD-1:PD-L1 Binding Inhibition Assay

[51] Briefly, detection of cell surface PD-1 on Jurkat cells was accomplished by incubating cells with the human PD-L1-Fc fusion protein, followed by detection of the recombinant molecule with a fluorescently labeled anti-human Fc antibody. Flow cytometry was performed to detect binding between PD-1 and the PD-L1 recombinant protein. Quantitative binding measurement was then determined by mean fluorescence intensity (MFI).

[52] Jurkat Cell-surface expression of PD1 and binding of PD-L1 to these cells were verified as shown in Figures 1 and 2. The results are shown in Figures 3A-B, 4A-B, 5A-B, and 6A-B.

EXAMPLE 3. Cell-Based Reporter Assay

[53] A cell-based reporter assay was used to assess whether binding of the four peptides identified above was sufficient to block the interaction with PD-1 and its ligand PD-L1. The components of the assay include a Jurkat T cell line that stably expresses human PD-1 and a luciferase reporter, a CHO cell line that stably expressed human PD-L1, and a positive control anti-PD-1 antibody that blocks the interaction of PD-1 and PD-L1, resulting in a measurable effect in the assay. The luciferase reporter in the Jurkat T cell line is triggered by IL-1, NFAT, or NF-κB response elements in the promoter region. The Jurkat T cells are pre-treated with CD3 and immediately cryopreserved for use in the assay. Interaction of the Jurkat T cells with the PD-L1 expressing cell line inhibits the intracellular mechanism by which the luciferase construct is activated, thereby preventing luciferase expression. A molecule that binds to either PD-1 on the Jurkat T cells or to PD-L1 on the CHO cells sufficiently to prevent their interaction permits the Jurkat T cells to produce luciferase. CellTiter-Glo® (CELLTITER-GLO®, Promega) was used to measure luciferase expression.

[54] The results of positive control assays using the anti-PD-1 control antibody are shown in Figures 7A-B. These results demonstrate that the control antibody restores luciferase expression

in a dose-dependent manner, with peak-fold inhibition of approximately 8 at an antibody concentration of 20 μM.

[55] The results of assays of the peptides identified above are shown in Figures 8A-B. These results demonstrate that each of the four peptides restores luciferase expression in a dose-dependent manner, with peak-fold inhibition of approximately 1.5 at a concentration of approximately 25 μM.

EXAMPLE 4. Tetanus Toxoid Recall Assay Using Individual Peptides

[56] Peptides 1-4 were tested in a human PBMC-based tetanus antigen recall assay. "Peptide CQ-22" was used as a negative control.

[57] PBMCs were obtained from plasma of human donors and tested *in vitro* for recall of tetanus toxoid. Suitable PBMCs were cryopreserved until needed, then thawed and cultured in a 96-wellplate. Tetanus toxoid was added to the cultures in the presence or absence of peptides 1-4, and the production of cytokines and cell surface T cell activation markers were examined.

[58] The results of these assays are shown in Figures 9-15 and summarized qualitatively in Table 2. In the table, "x" indicates no effect, "-" indicates a possible low effect, "+" indicates some effect, and "++" indicates a definite effect.

Table 2.

peptide	IL-2	IL-4	IL-6	IL-10	IL-17a	IFNγ	TNFα
QP20	x	-	x	x	x	x	x
HD20	-	x	++	x	++	++	++
WQ20	-	++	++	x	++	++	++
SQ20	+	-	++	+	++	++	+

[59] The results demonstrated a trend towards modest enhancement of IL-6, IL-17α, IFNγ, and TNFα production at the highest concentrations of peptides. No significant enhancement of IL-2 production was detected.

EXAMPLE 5. Tetanus Toxoid Recall Assay Using Combinations of Peptides

[60] Combinations of peptides were tested in the antigen recall assay described above, using a different PBMC donor and a different lot number of tetanus toxoid. The results are shown in Figures 16, 17, 18, 19, 20, 21, and 22. These results demonstrated that the combination of the four peptides combination of the four peptides QP20, HD20, WQ20, and SQ20 result in increased IL-2 production and reduced IL-17a production.

[61] The effect of peptides QP20, HD20, WQ20, and QP20 on the production of IL-2 and IL-17a appears to be donor-specific, as shown in Figures 23A-B and 24A-B.

EXAMPLE 6. BIACORE® Assays

[62] BIACORE® assays were carried out using a BIACORE® T-200 at 25°C. The assay and regeneration buffers contained 10 mM HEPES (pH 7.4), 150 mM NaCl, 3mM EDTA, and 0.05% P20. The immobilization buffer was 10mM sodium acetate, pH 5.0. The flow rate used for immobilizing the ligand was 5 µl/min. The flow rate for kinetics analysis was 30 µl/min.

[63] **Scouting**. 12,000 response units (RU) of human and 6000 RU of mouse PD-1 receptors were directly immobilized on flow cell 2 and flow cell 4 of the CM5 chip by amine coupling method (EDC/NHS). The un-occupied sites were blocked with 1M ethanol amine. Scouting was performed at a single analyte concentration of 25 µM to confirm yes/no binding. Flow cell 1 was kept blank and used for reference subtraction. Binding of analyte to the ligand was monitored in real time.

[64] **Full Kinetics**. Based on the scouting results, full kinetics were performed by immobilizing higher RU of the ligand to a new chip and analyte concentration at 25 µM, followed by serial dilution to 12.5, 6.25, 3.125, 1.562, 0.78 and 0 µM concentration or as indicated. Due to fast on rate and off rate, KD was determined by steady state equilibrium kinetics.

[65] Chi square ($\chi 2$) analysis was carried out between the actual sensorgram and a sensorgram generated from the BIANALYSIS® software (black line) to determine the accuracy of the analysis. A $\chi 2$ value within 1- 2 is considered significant (accurate) and below 1 is highly significant (highly accurate).The results are summarized in Table 3.

Table 3

Ligand 10,000 RU	Analyte	Rmax (RU)	KA(1/M)	KD (M)	Conc. (μM)	$\chi 2$
mouse PD-1	WQ-21	270	$1.31x10^{3}$	$7.61x10^{-4}$	0-25	0.0203
mouse PD-1	QP-20	13.4	$1.80x10^{4}$	$5.54x10^{-5}$	0-25	0.0446
mouse PD-1	HD-20	76	$4.25x10^{3}$	$2.35x10^{-4}$	0-25	0.11
mouse PD-1	SQ-20	12.8	$2.14x10^{4}$	$4.68x10^{-5}$	0-25	0.039
human PD-1	WQ-21	84.7	$3.28x10^{3}$	$3.05x10^{-4}$	0-25	0.0309
human PD-1	QP-20	3.83	$9.36x10^{4}$	$1.07x10^{-5}$	0-25	0.0569
human PD-1	HD-20	3.35	$3.18x10^{5}$	$3.41x10^{-6}$	0-12.5	0.0733
human PD-1	SQ-20	4.05	$1.94x10^{5}$	$5.16x10^{-6}$	0-25	0.111
mouse PD-1	Mouse PD-L1	259	$2.75x10^{6}$	$3.64x10^{-7}$	0-50	0.105
human PD-1	Human PD-L1	213	$6.92x10^{6}$	$1.44x10^{-7}$	0-50	2.44

[66] These results indicate that each of the four peptides bind both human and mouse PD-1. QP20 and SQ20 showed the highest affinity towards mouse PD-1. HD20 and SQ20 showed the highest affinity towards human PD-1.

EXAMPLE 7. Experimental Metastasis Model

[67] Efficacy of the peptides was evaluated in a B16-F10-LacZ experimental metastasis model. In this model, B16-F10-LacZ cells, transfected to express the LacZ gene that encodes β-galactoside, an intracellular enzyme, are injected into the tail vein of syngeneic mice. The cells travel through the circulation, settle in the lungs, and form tumors. Mice are terminated 2 weeks after implant. When the enzyme cleaves its substrate, X-gal, the products dimerize and change color and can be detected *ex vivo*. The number of metastatic tumors on the surface of the lung is then quantified by manual counting of tumors under a dissecting microscope.

[68] Briefly, mice (N=7) were implanted on study day 0 with B16-F10-LacZ tumor cells ($5x10^{5}$ or $1x10^{6}$ cells per mouse) by intravenous injection in the tail vein. Mice received a treatment of the peptide combination (200 μg, 20 μg, or 2 μg, each peptide per dose)

intravenously by tail vein injection on study days 2, 5, 7, 9 and 12. Detailed clinical examinations and body weights were recorded regularly during treatment. Mice were terminated on study day 14, and their lungs were removed and stained. The number of tumor metastases were counted. Treatment groups are described in Table 4.

Table 4

Group	N	Implant	Treatment	Dose	Route	Treatment Days
1	7	$5x10^5$	QP-20, SQ-20, HD-20, WQ-20	200 μg	IV	SD 2, 5, 7, 9, 12
2	7	$5x10^5$	QP-20, SQ-20, HD-20, WQ-20	20 μg	IV	SD 2, 5, 7, 9, 1
3	7	$5x10^5$	QP-20, SQ-20, HD-20, WQ-20	2 μg	IV	SD 2, 5, 7, 9, 122
4	7	$5x10^5$	Untreated	--	--	--
5	7	$1x10^6$	QP-20, SQ-20, HD-20, WQ-20	200 μg	IV	SD3, 5, 7, 9, 12
6	7	$1x10^6$	Untreated	--	--	--

[69] The results are shown in Figure 25. A good dose response was observed when mice were implanted at both cell concentrations. Mice treated with the highest dose of peptide mixture (200 μg) had the fewest tumors (average 97), and mice treated with the lowest dose of peptide mixture (2 μg) had the most tumors (average 205). Similarly, in the two groups that were implanted with high tumor numbers, the untreated group had significantly more tumors. This indicates that the 4 peptides in combination showed a dose-dependent efficacy on B16-F10-LacZ tumor growth *in vivo*. Moreover, the peptide combination was well tolerated by the mice and did not have any acute adverse effects on animal health.

EXAMPLE 8. Effect of Peptide Combination on the Immunogenicity of a Malaria Vaccine

[70] Immunogenicity of the peptide combination as a prophylactic vaccine adjuvant was assessed in a mouse model of malaria. Balb/c mice immunized with an adenovirus-based malaria vaccine expressing the *Plasmodium yoelli* circumsporozoite protein (AdPyCS) were given 200μg of the peptide combination, anti-PD-1 mAb, anti-PDL1 mAb, or the negative control peptide ovalbumin (OVA) on days 1, 3, 5, and 7 after immunization with AdPyCS (Table 5). Note that no additional adjuvant was added to the AdPyCS antigen. Spleens were collected 12 days after immunization, and the number of splenic PyCS-specific, IFNγ-secreting $CD8^+$ T cells was determined via ELISpot assay. Note that for the ELISpot assay, splenocytes were stimulated with the SYVPSAEQI peptide (SEQ ID NO:5), an H-2Kd-restricted $CD8^+$ T cell epitope of PyCS.

Table 5

Cohort	Test Sample	# Mice	Route	Treatment days
1	AdPyCS only	5	-	-
2	AdPyCS + control OVA peptide (200 μg)	5	i.p.	0, 1, 3, 5, 7
3	AdPyCS + peptide combo (200 μg)	5	i.p.	0, 1, 3, 5, 7
4	AdPyCS + anti-PD-1 antibody (200 μg)	5	i.p.	0, 1, 3, 5, 7
5	AdPyCS + anti-PDL1 antibody (200 μg)	5	i.p.	0, 1, 3, 5, 7

[71] Figure 26 shows the average number ± standard deviation of CSP-specific, IFNγ-secreting $CD8^+$ T cells per 0.5 x 10^6 splenocytes for each cohort. Significant differences between the AdPyCS alone (Cohort 1) and the peptide combination (Cohort 3), anti-PD-1 antibody (Cohort 4) or anti-PD-L1 antibody (Cohort 5) were detected using the one-way ANOVA test (*** $p < 0.001$, and * $p < 0.05$). These results demonstrate that the peptide combination (Cohort 3) is functionally active *in vivo*, increasing the number of CSP-specific, IFNγ-secreting $CD8^+$ T cells ~1.6-fold relative to AdPyCS alone (Cohort 1), which was similar to changes with anti-PD-1 or -PD-L1 antibody (Cohort 4 and 5).

EXAMPLE 9. Effect of Peptide Combination on Survival in a Model of Sepsis

[72] Sepsis can negatively alter T cell function and survival, however this can be reversed when the PD-1:PDL1 interaction is blocked, which results in improved survival. Thus the efficacy of the peptide combination was assessed in a representative, clinically relevant model of sepsis where CD1 mice are subjected to cecal ligation and puncture (CLP) to induce intra-abdominal peritonitis. For this study, 200μg of either the peptide combination or anti-PD-1 antibody were administered i.v. at 2, 24, 48, 72 and 96 hours after surgery. A vehicle control group was also included. Six mice were in each group. All mice were checked twice daily for signs of morbidity and mortality. Administration of the peptide combination conferred an enhanced survival advantage over the vehicle control group where the peptide combination showed a 2-fold higher survival rate (Table 6). Moreover, survival in the peptide combination group was slightly above treatment with anti-PD-1 antibody.

Table 6

Group	% Survival
Vehicle Control	50%
Anti-PD-1 antibody	83%
PD-1 Peptide Combo	100%

EXAMPLE 10. Effect of Peptide Combination on Serum HBsAg Levels in HBV-Infected Mice

[73] The combination of QP20, HD20, WQ20, and SQ20 peptides was assessed in a hepatitis B virus (HBV) mouse model where the role of PD-1 in T cell exhaustion and immunotolerance is documented (Tzeng et al., 2012; Ye et al., 2015). PD-1 is elevated in the hepatic T cells of mice with persistent HBV infection but not in animals that have cleared the infection. In this model, it has been shown that inhibition of the PD-1/PD-L1 interaction with an anti-PD-1 mAb both increases antigen-specific IFNγ production by hepatic T cells and reverses HBV persistence (Tzeng et al., 2012). This mouse model of persistent HBV presented an opportunity to test whether the combination of QP20, HD20, WQ20, and SQ20 peptides can reverse T cell exhaustion *in vivo* and aid the immune system in controlling viral infection.

[74] Mice infected with HBV were treated with saline (negative control), 200μg of QP20, HD20, WQ20, and SQ20 peptides combined, or 200μg anti-PD-1 mAb at 9 time points, 2 days prior to infection and days 1, 3, 6, 9, 12, 14, 17 and 20 post infection. The level of serum HB surface antigen (HBsAg) was monitored by ELISA on days 7, 14, and 21 to follow the infection (higher levels of serum HBsAg are reflective of higher viral titer) and detect the immune enhancement activity of the combination of QP20, HD20, WQ20, and SQ20 peptides. The group treated with the combination of QP20, HD20, WQ20, and SQ20 peptides showed significantly lower mean level of serum HBsAg at weeks 2 and 3 post infection ($p<0.05$, 1-way ANOVA, Tukey's Multiple Comparison Test) compared to the saline negative control (Figure 27).

REFERENCES

[75] Kontermann, "Half-life extended biotherapeutics," Expert Opin. Biol. Ther. 16, 903-15, 2016.

[76] Penchala *et al.*, "A biomimetic approach for enhancing the in vivo half-life of peptides," Nat. Chem. Biol. 11, 793–98, 2015.

[77] Tzeng *et al.*, "PD-1 blockage reverses immune dysfunction and hepatitis B viral persistence in a mouse animal model," PLoS One 7(6):e39179, 2012.

[78] Ye *et al.*, "T-cell exhaustion in chronic hepatitis B infection: current knowledge and clinical significance," Cell Death Dis. Mar 19;6:e1694, 2015.

[79] Zorzi *et al.*, "Acylated heptapeptide binds albumin with high affinity and application as tag furnishes long-acting peptides," Nature Communications 8, 16092, 2017.

CLAIMS

1. A pharmaceutical composition, comprising:

(a) up to four peptides selected from the group consisting of:

(i) a peptide consisting of the amino acid sequence SEQ ID NO:1;

(ii) a peptide consisting of the amino acid sequence SEQ ID NO:2;

(iii) a peptide consisting of the amino acid sequence SEQ ID NO:3; and

(iv) a peptide consisting of the amino acid sequence SEQ ID NO:4; and

(b) a pharmaceutically acceptable vehicle.

2. The pharmaceutical composition of claim 1, which comprises only one of the four peptides.

3. The pharmaceutical composition of claim 1, which comprises only two of the four peptides, wherein the two peptides are selected from the group consisting of:

(a) the peptide consisting of the amino acid sequence SEQ ID NO:1 and the peptide consisting of the amino acid sequence SEQ ID NO:2;

(b) the peptide consisting of the amino acid sequence SEQ ID NO:1 and the peptide consisting of the amino acid sequence SEQ ID NO:3;

(c) the peptide consisting of the amino acid sequence SEQ ID NO:1 and the peptide consisting of the amino acid sequence SEQ ID NO:4;

(d) the peptide consisting of the amino acid sequence SEQ ID NO:2 and the peptide consisting of the amino acid sequence SEQ ID NO:3;

(e) the peptide consisting of the amino acid sequence SEQ ID NO:2 and the peptide consisting of the amino acid sequence SEQ ID NO:4; and

(f) the peptide consisting of the amino acid sequence SEQ ID NO:3 and the peptide consisting of the amino acid sequence SEQ ID NO:4..

4. The pharmaceutical composition of claim 1, which comprises only three of the four peptides, wherein the three peptides are selected from the group consisting of:

(a) the peptide consisting of the amino acid sequence SEQ ID NO:1, the peptide consisting of the amino acid sequence SEQ ID NO:2, and the peptide consisting of the amino acid sequence SEQ ID NO:3;

(b) the peptide consisting of the amino acid sequence SEQ ID NO:1, the peptide consisting of the amino acid sequence SEQ ID NO:2, and the peptide consisting of the amino acid sequence SEQ ID NO:4;

(c) the peptide consisting of the amino acid sequence SEQ ID NO:2, the peptide consisting of the amino acid sequence SEQ ID NO:3, and the peptide consisting of the amino acid sequence SEQ ID NO:4; and

(d) the peptide consisting of the amino acid sequence SEQ ID NO:1, the peptide consisting of the amino acid sequence SEQ ID NO:3, and the peptide consisting of the amino acid sequence SEQ ID NO:4.

5. The pharmaceutical composition of claim 1, which comprises all four of the peptides.

6. A method of inhibiting progression of a hyperproliferative disorder, to treat an infectious disease, or to treat sepsis, comprising administering to a patient in need thereof an effective amount of the pharmaceutical composition of any of claims 1-5.

7. The method of claim 6, wherein the composition is administered to inhibit progression of a hyperproliferative disorder.

8. The method of claim 7, wherein the hyperproliferative disorder is a cancer.

9. The method of claim 8, wherein the cancer is a melanoma.

10. The method of claim 8, further comprising administering a cancer vaccine to the patient.

11. The method of claim 7, further comprising administering a chimeric antigen receptor (CAR) T cell therapy to the patient.

12. The method of claim 6, wherein the composition is administered to treat an infectious disease.

13. The method of claim 12, wherein the infectious disease is malaria.

14. The method of claim 12, wherein the infectious disease is hepatitis B.

15. The method of claim 12, wherein the composition is administered as a vaccine adjuvant to a vaccine against the infectious disease.

16. The method of claim 6, wherein the composition is administered to treat sepsis.

17. Use of the pharmaceutical composition of any of claims 1-5 in the manufacture of a medicament to inhibit progression of a hyperproliferative disorder, to treat an infectious disease, or to treat sepsis.

18. The pharmaceutical composition of any of claims 1-5 for use in inhibiting progression of a hyperproliferative disorder, to treat an infectious disease, or to treat sepsis.

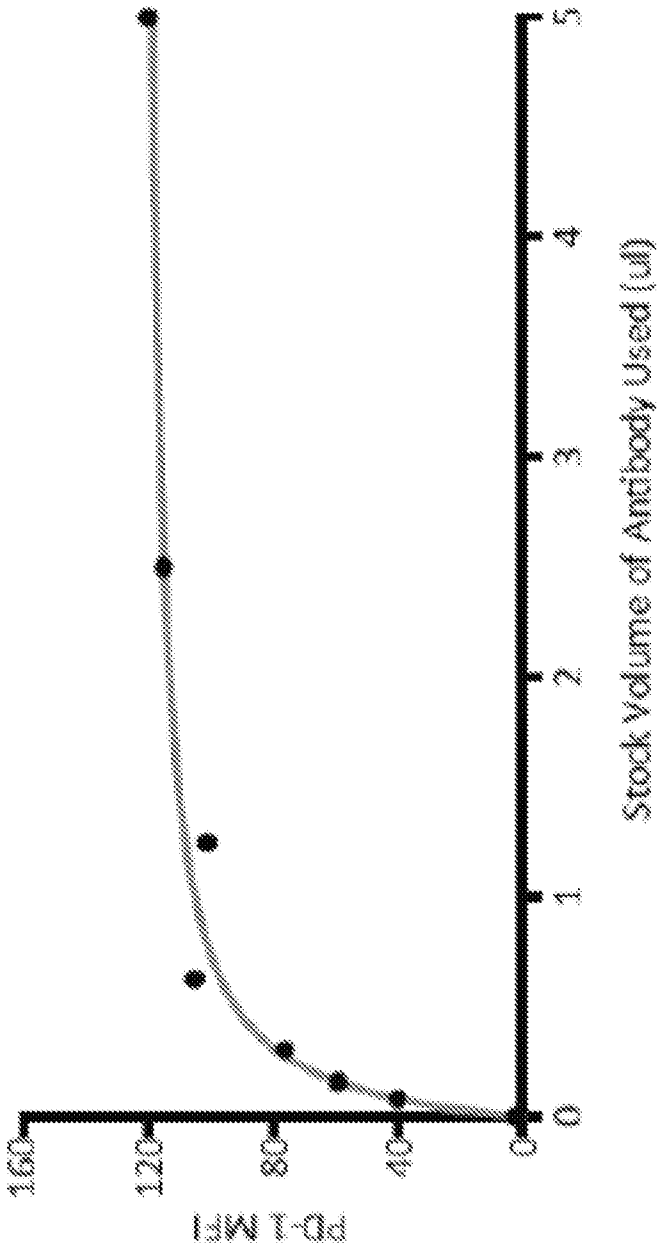

PD-1 MFI
160
120
80
40
0
0
1
2
3
4
5
Stock Volume of Antibody Used (ul)

FIG. 1

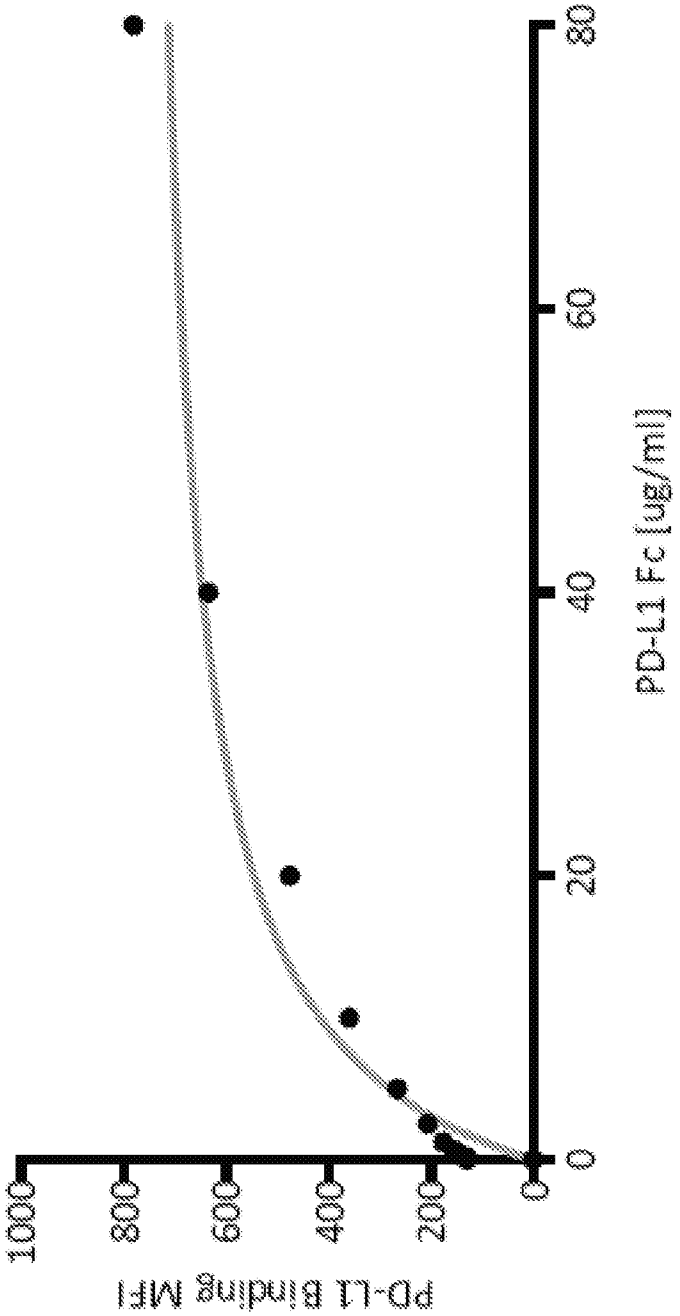


FIG. 2

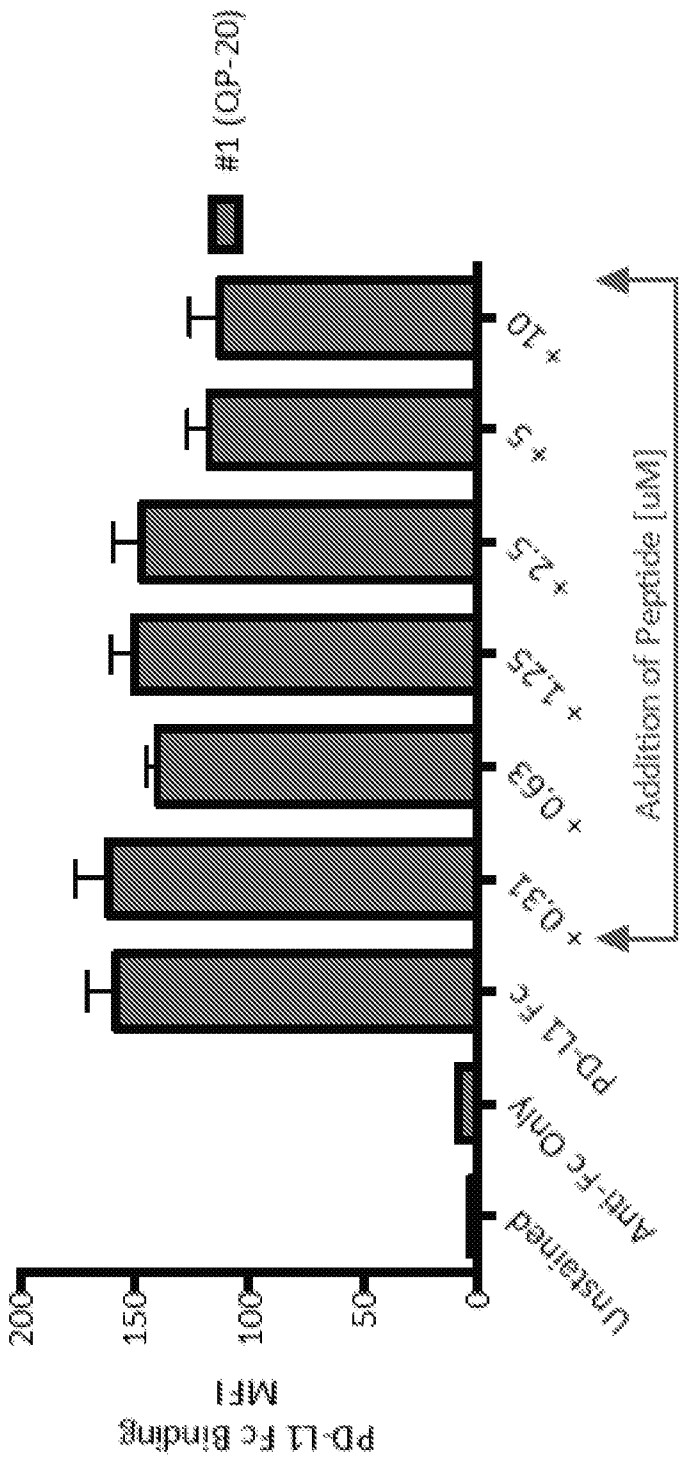

PD-L1 Fc Binding
MFI
200
150
100
50
0
Unstained
Anti-Fc Only
PD-L1 Fc
+0.31
+0.63
+1.25
+2.5
+5
+10
Addition of Peptide [uM]
#1 (QP-20)

FIG. 3A

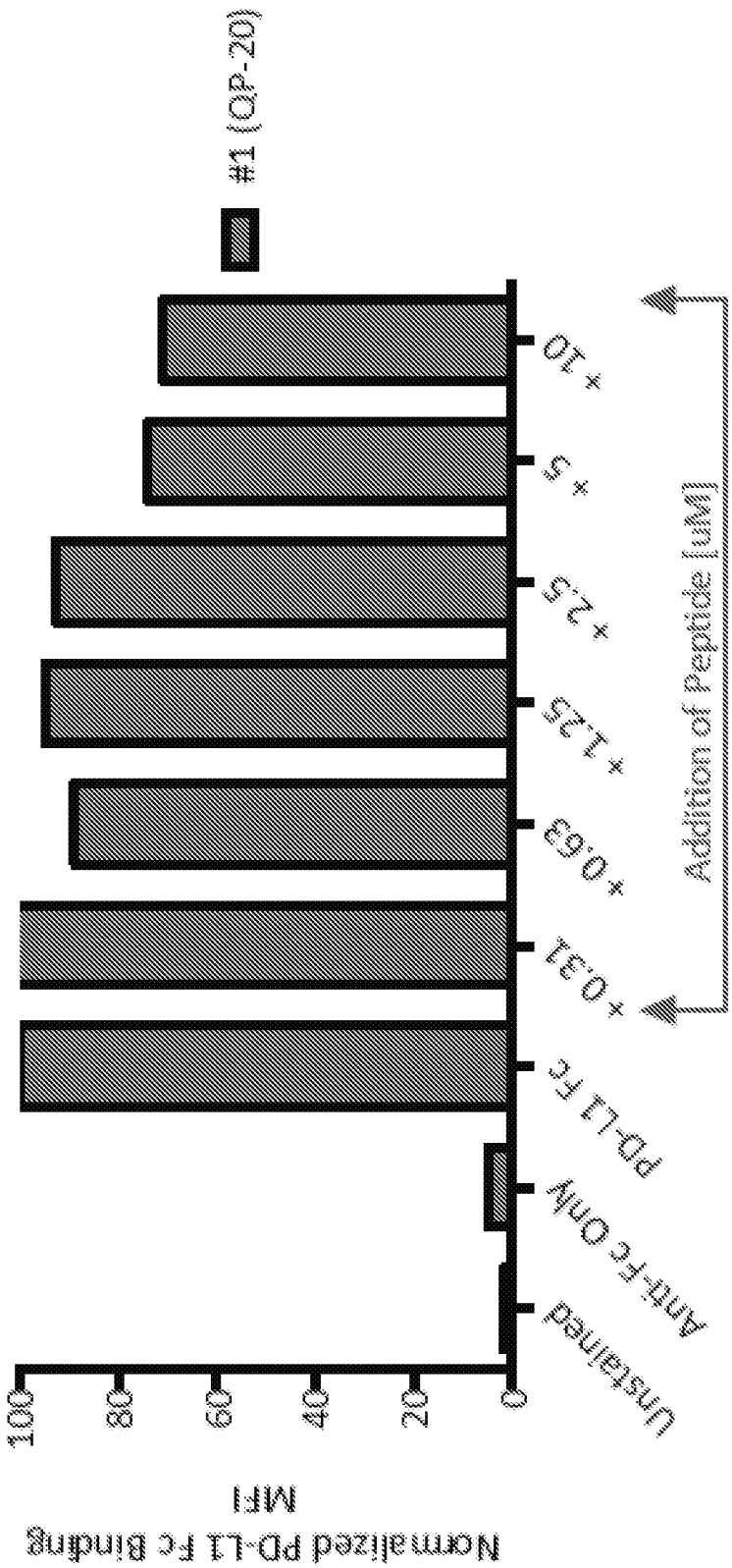

#1 (OP-20)
Addition of Peptide [uM]
10
5
2.5
1.25
0.63
0.31
PD-L1 Fc
Anti-Fc Only
Unstained
0
20
40
60
80
100
MFI
Normalized PD-L1 Fc Binding

FIG. 3B

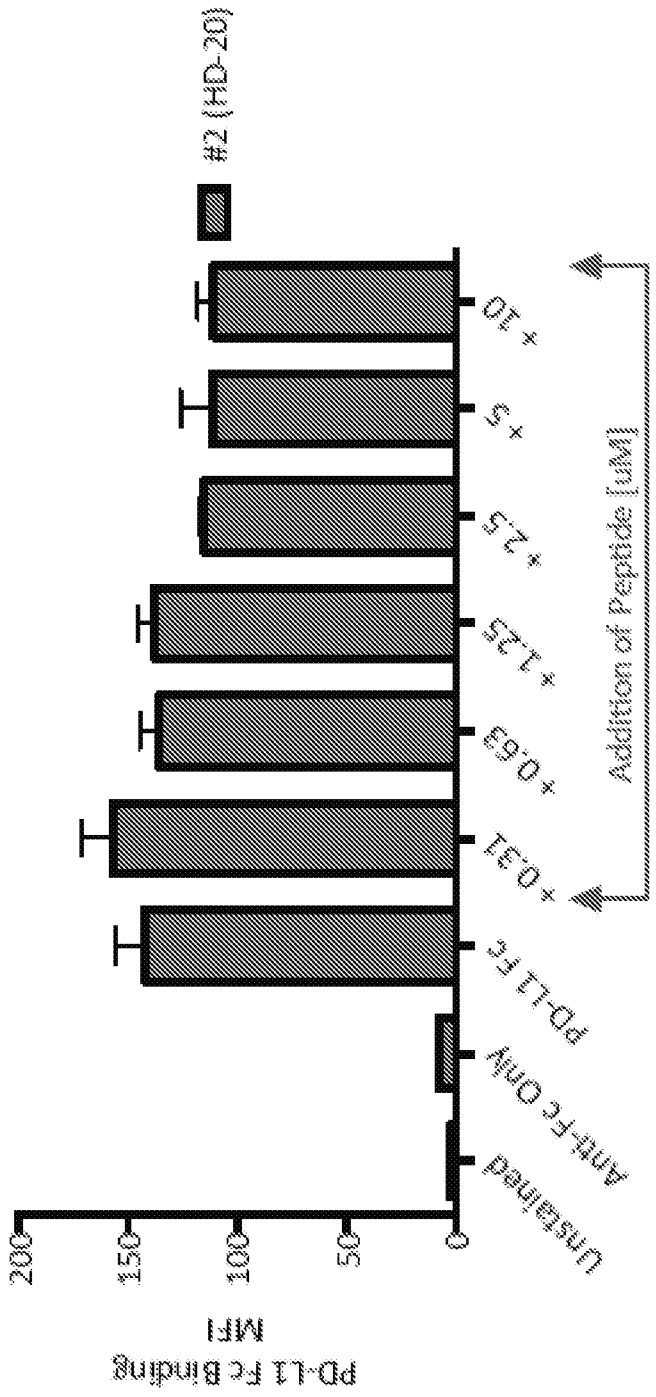

PD-L1 Fc Binding
MFI
200
150
100
50
0
Unstained
Anti-Fc Only
PD-L1 Fc
+0.31
+0.63
+1.25
+2.5
+5
+10
Addition of Peptide [uM]
#2 (HD-20)

FIG. 4A

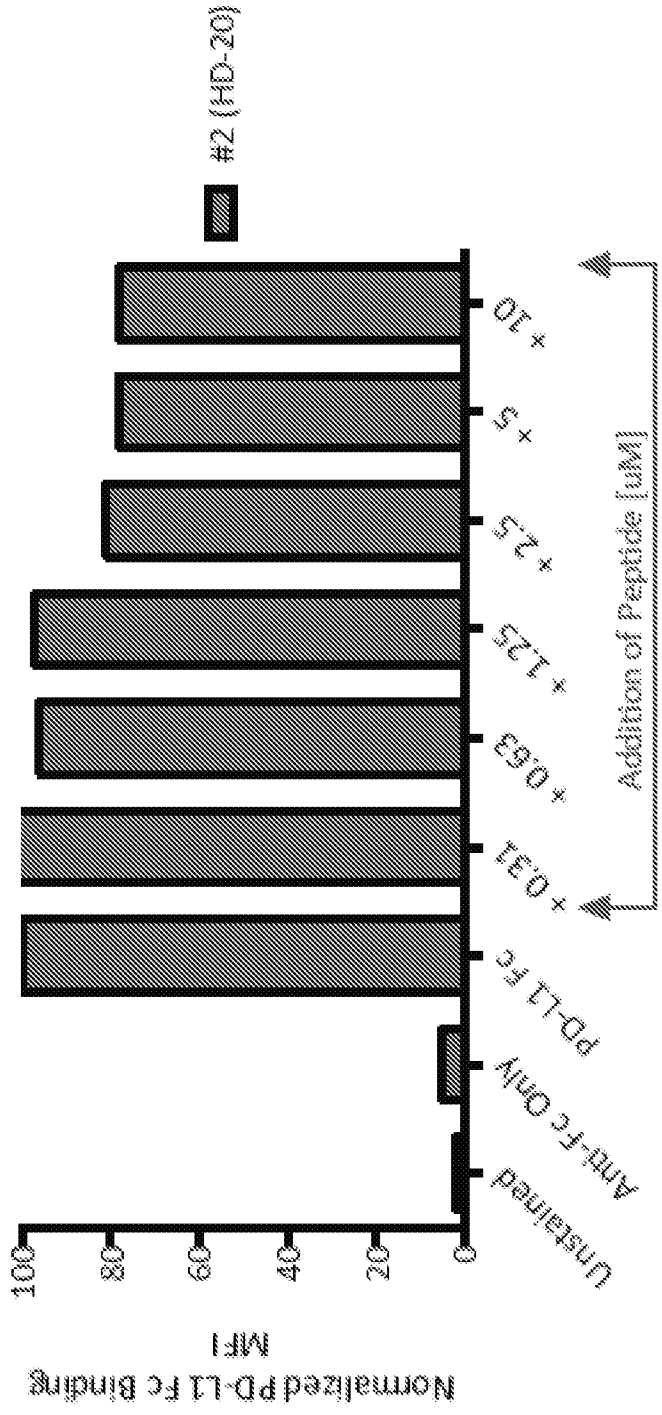

#2 (HD-20)
Addition of Peptide [uM]
10
5
2.5
1.25
0.63
0.31
PD-L1 Fc
Anti-Fc Only
Unstained
0
20
40
60
80
100
MFI
Normalized PD-L1 Fc Binding

FIG. 4B

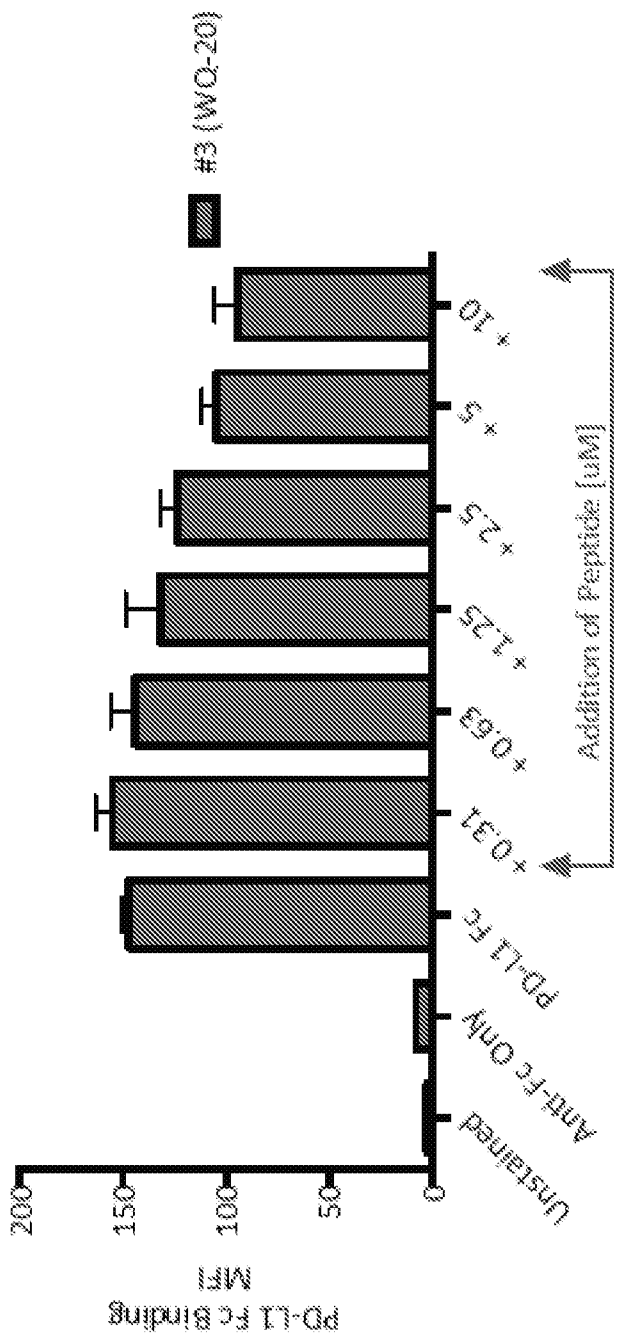

#3 (WO-20)
PD-L1 Fc Binding
MFI
200
150
100
50
0
Unstained
Anti-Fc Only
PD-L1 Fc
+0.31
+0.63
+1.25
+2.5
+5
+10
Addition of Peptide [uM]

FIG. 5A

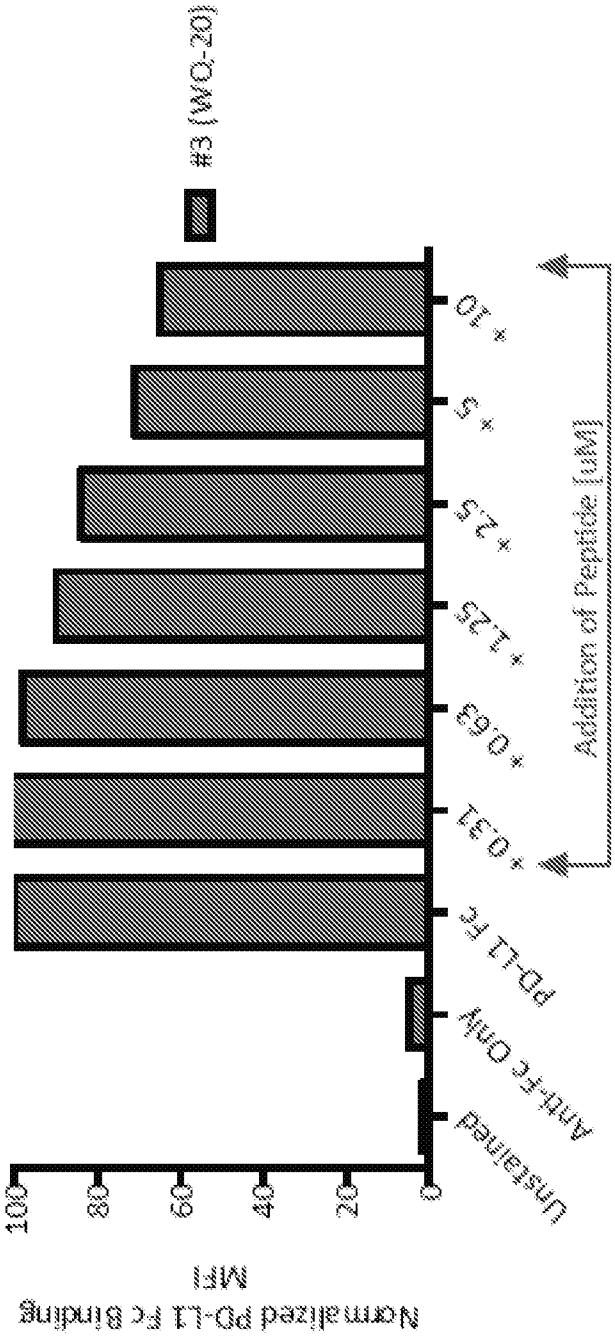

#3 (WO-20)
Addition of Peptide [uM]
+10
+5
+2.5
+1.25
+0.63
+0.31
PD-L1 Fc
Anti-Fc Only
Unstained
0
20
40
60
80
100
Normalized PD-L1 Fc Binding
MFI

FIG. 5B

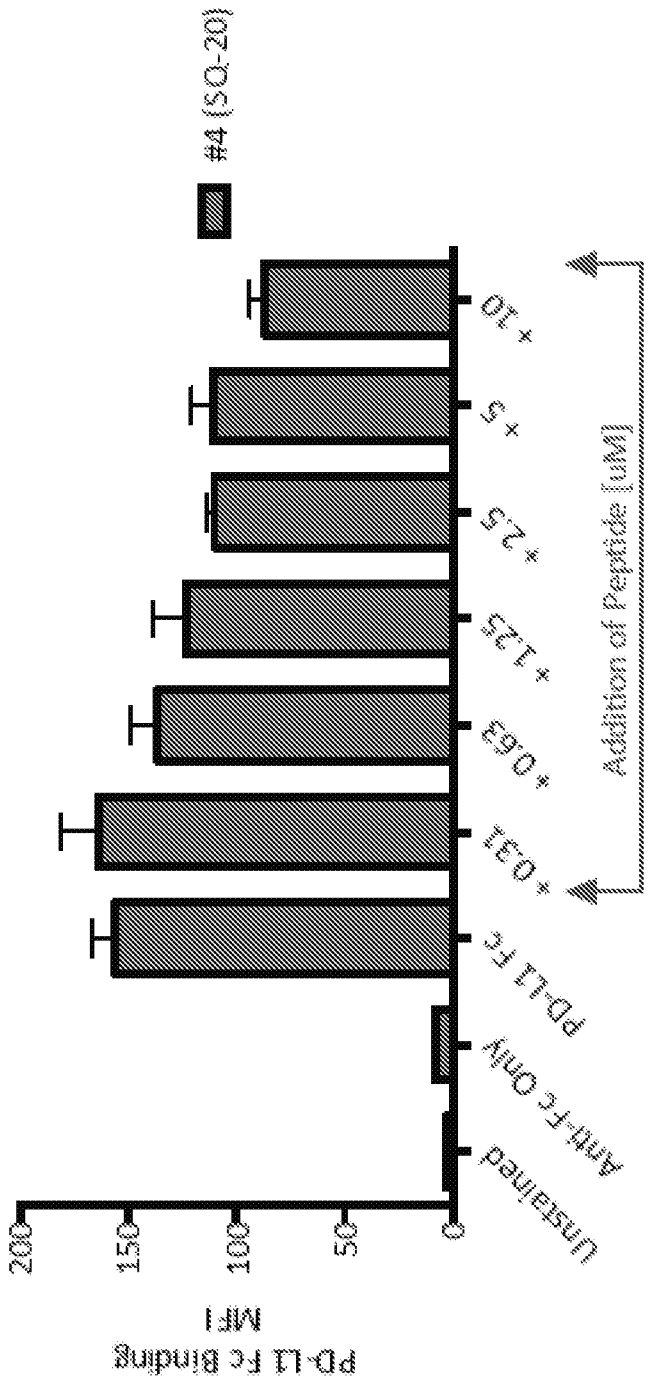

#4 (SO-20)
PD-L1 Fc Binding
MFI
200
150
100
50
0
Addition of Peptide [uM]
+10
+5
+2.5
+1.25
+.063
+.031
PD-L1 Fc
Anti-Fc Only
Unstained

FIG. 6A

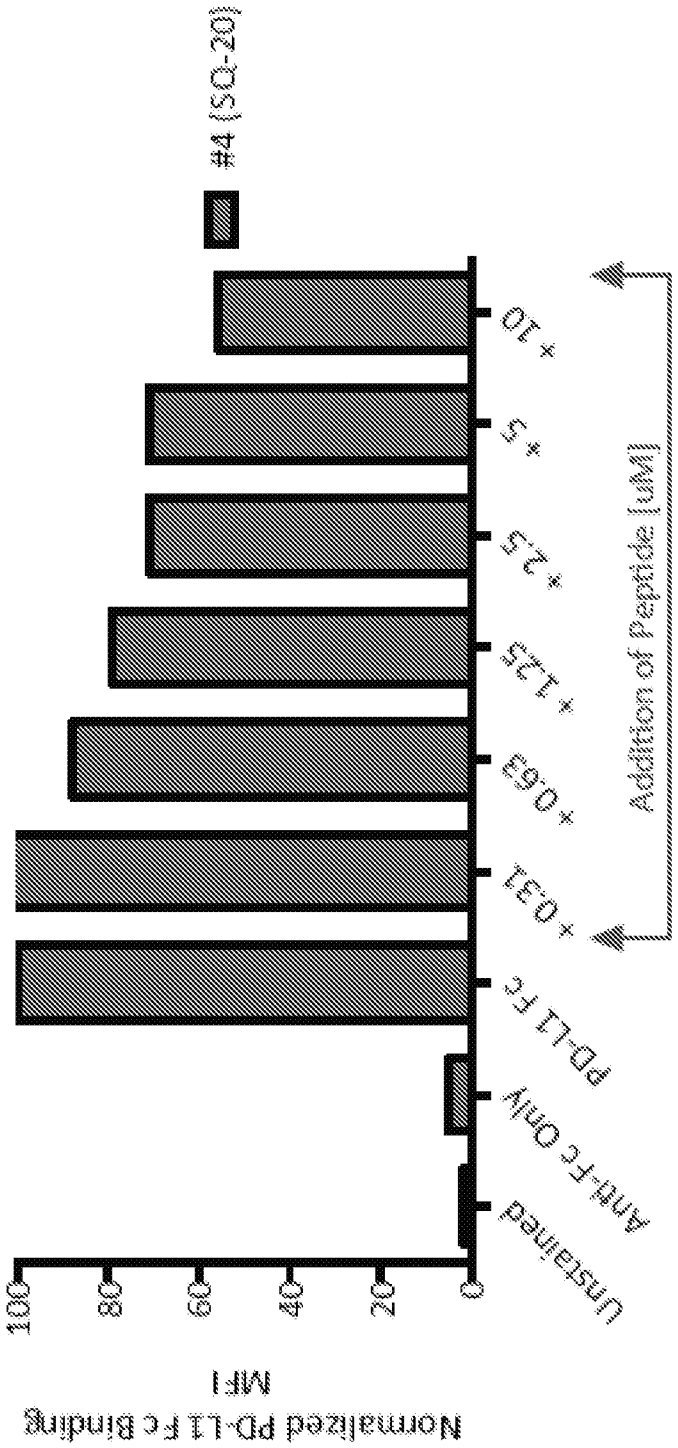

#4 (SO-30)
Addition of Peptide [uM]
+10
+5
+2.5
+1.25
+0.63
+0.31
PD-L1 Fc
Anti-Fc Only
Unstained
0
20
40
60
80
100
MFI
Normalized PD-L1 Fc Binding

FIG. 6B

FIG. 7A

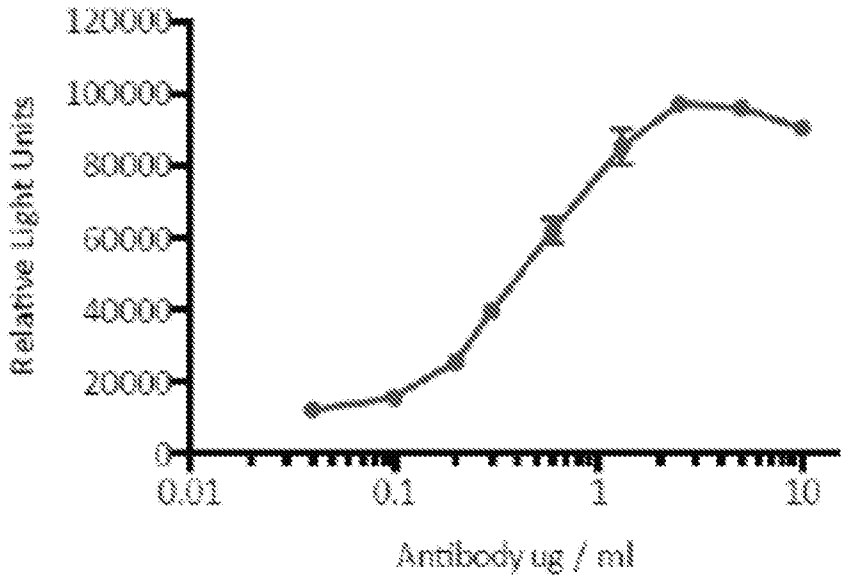

120000
100000
80000
60000
40000
20000
0
Relative Light Units
0.01
0.1
1
10
Antibody ug / ml

FIG. 7B

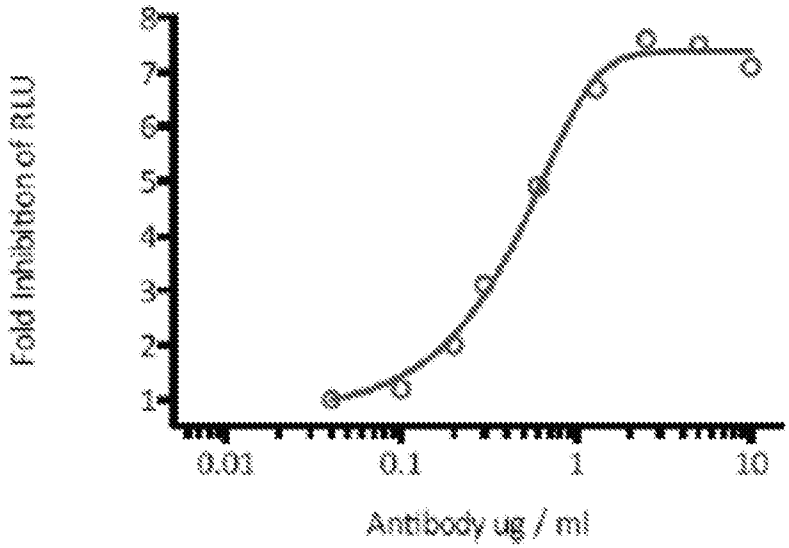
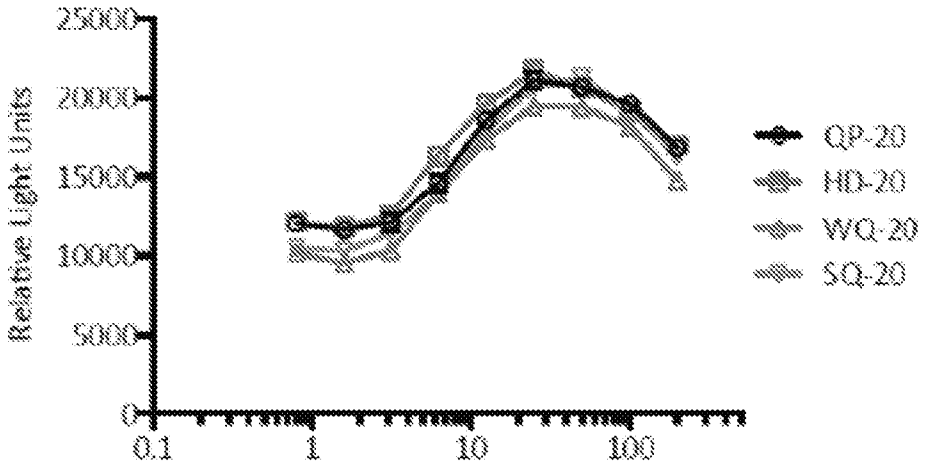
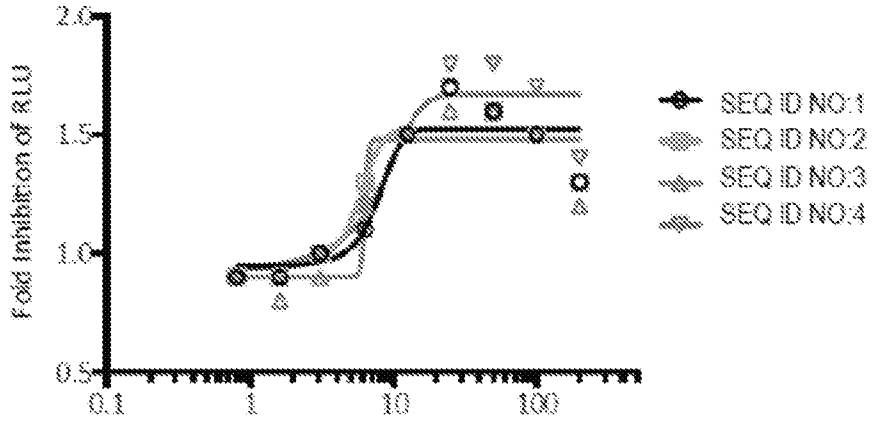

Fold Inhibition of RLU
0.01
0.1
1
10
Antibody ug / ml

FIG. 8A



Peptide (μM)

FIG. 8B



Peptide (μM)

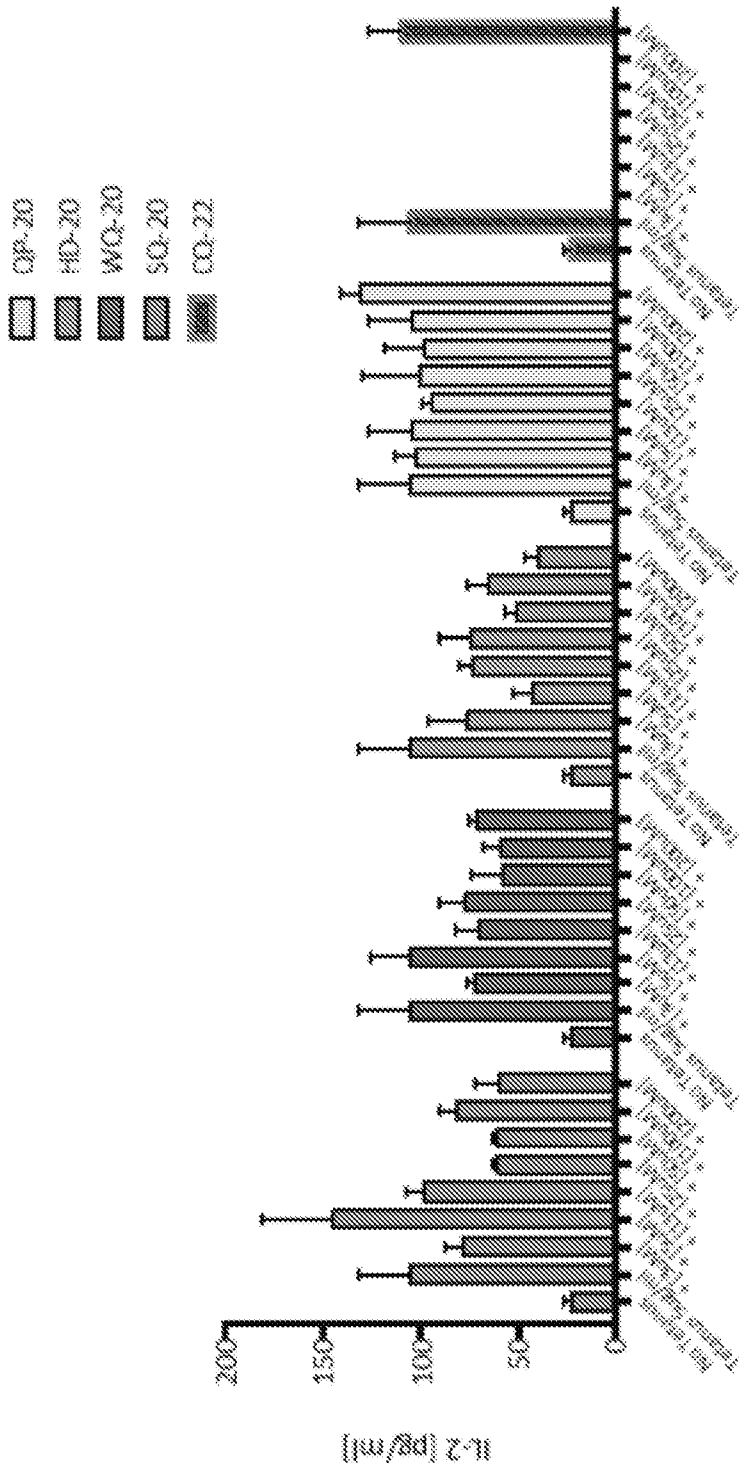


FIG. 9

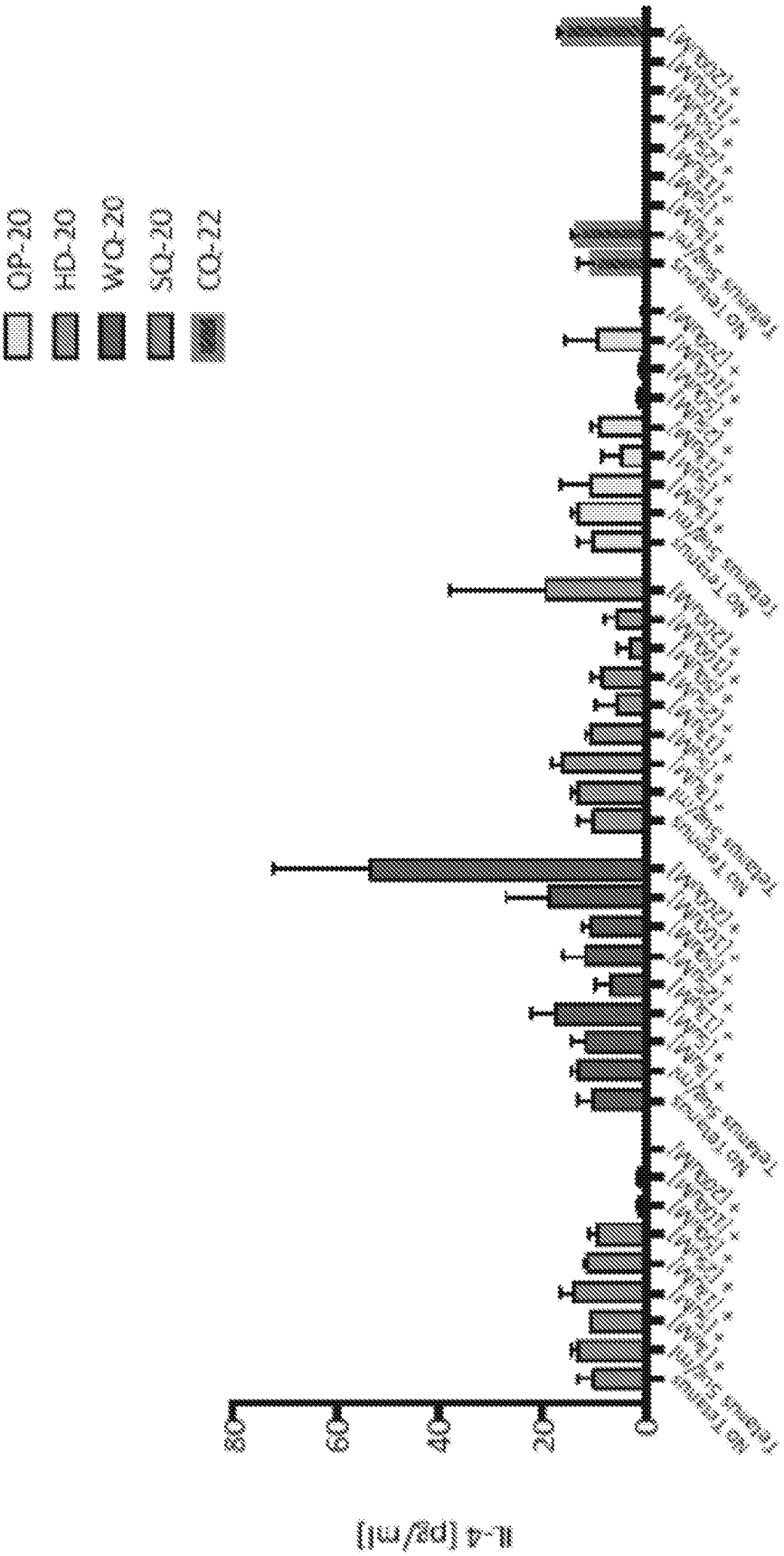
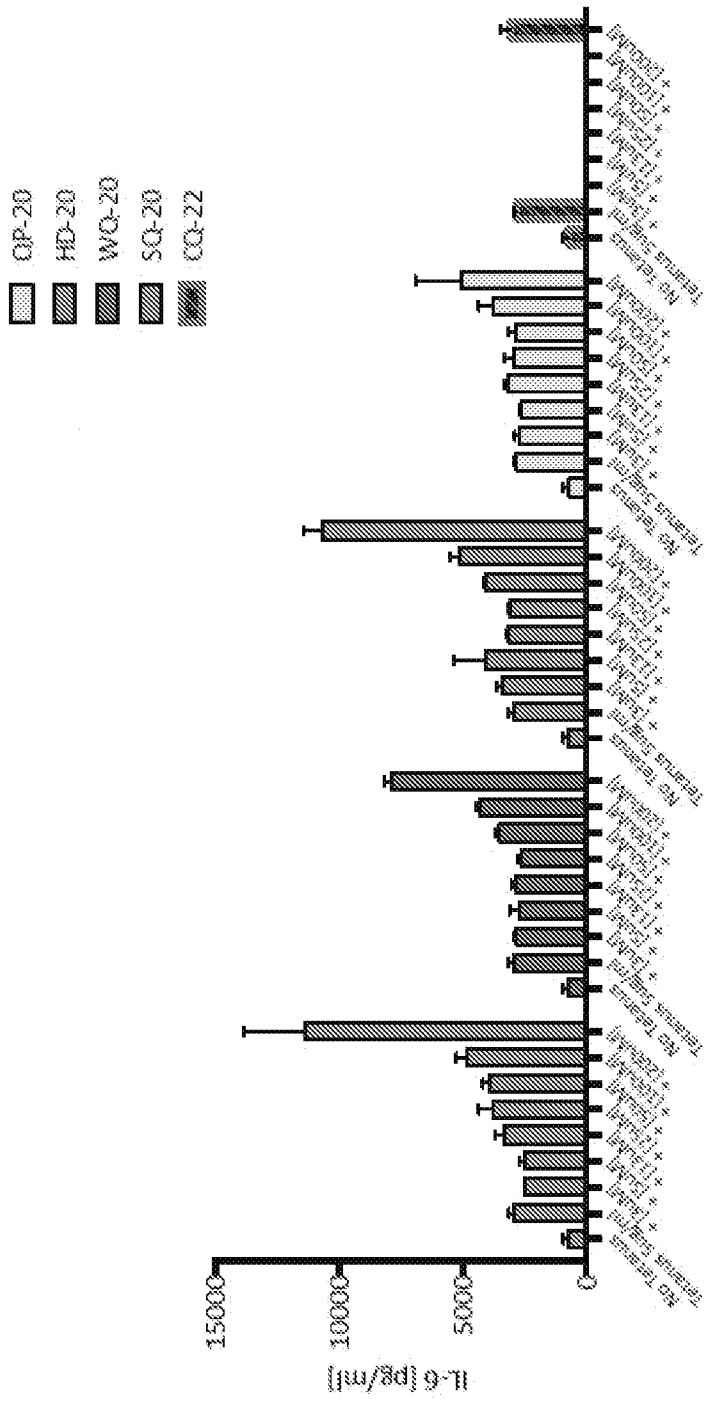


FIG. 10

FIG. 11



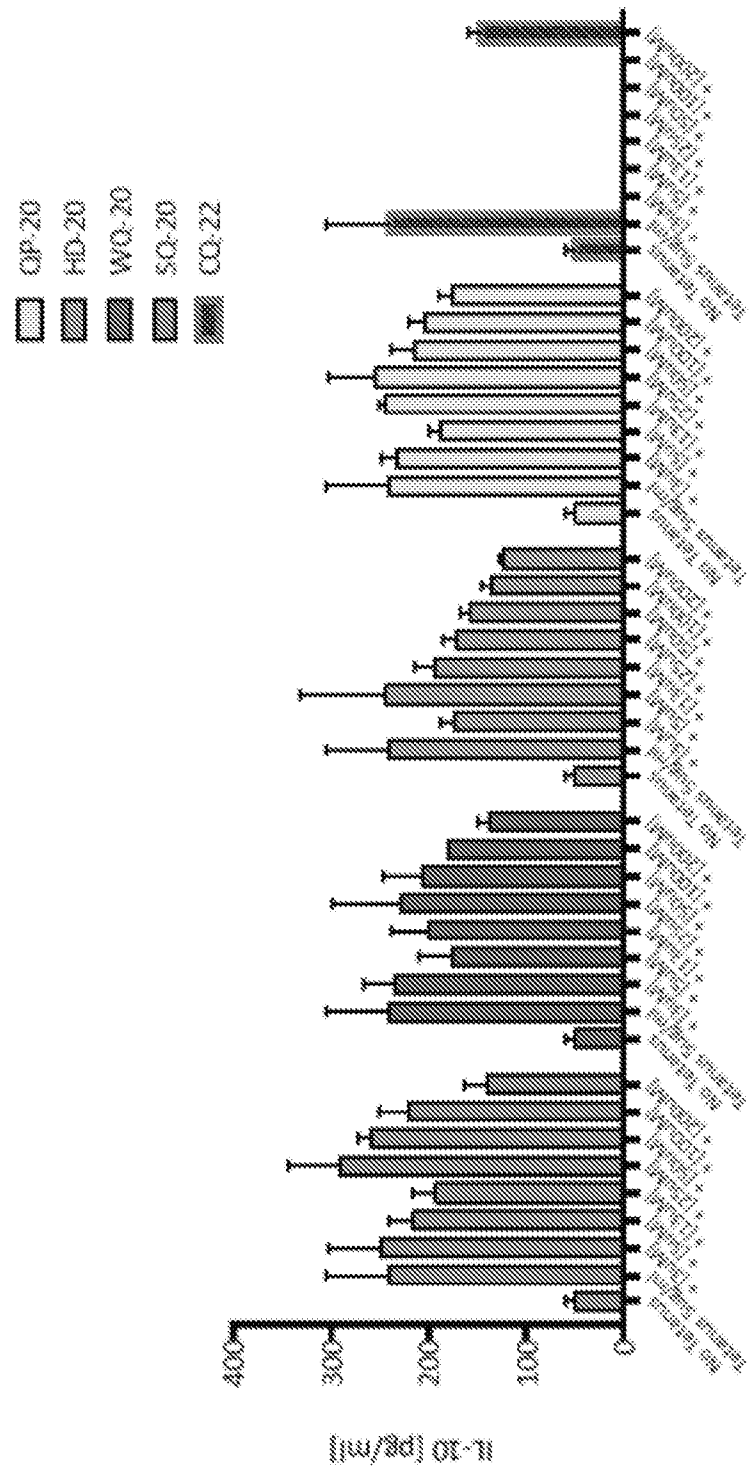


FIG. 12

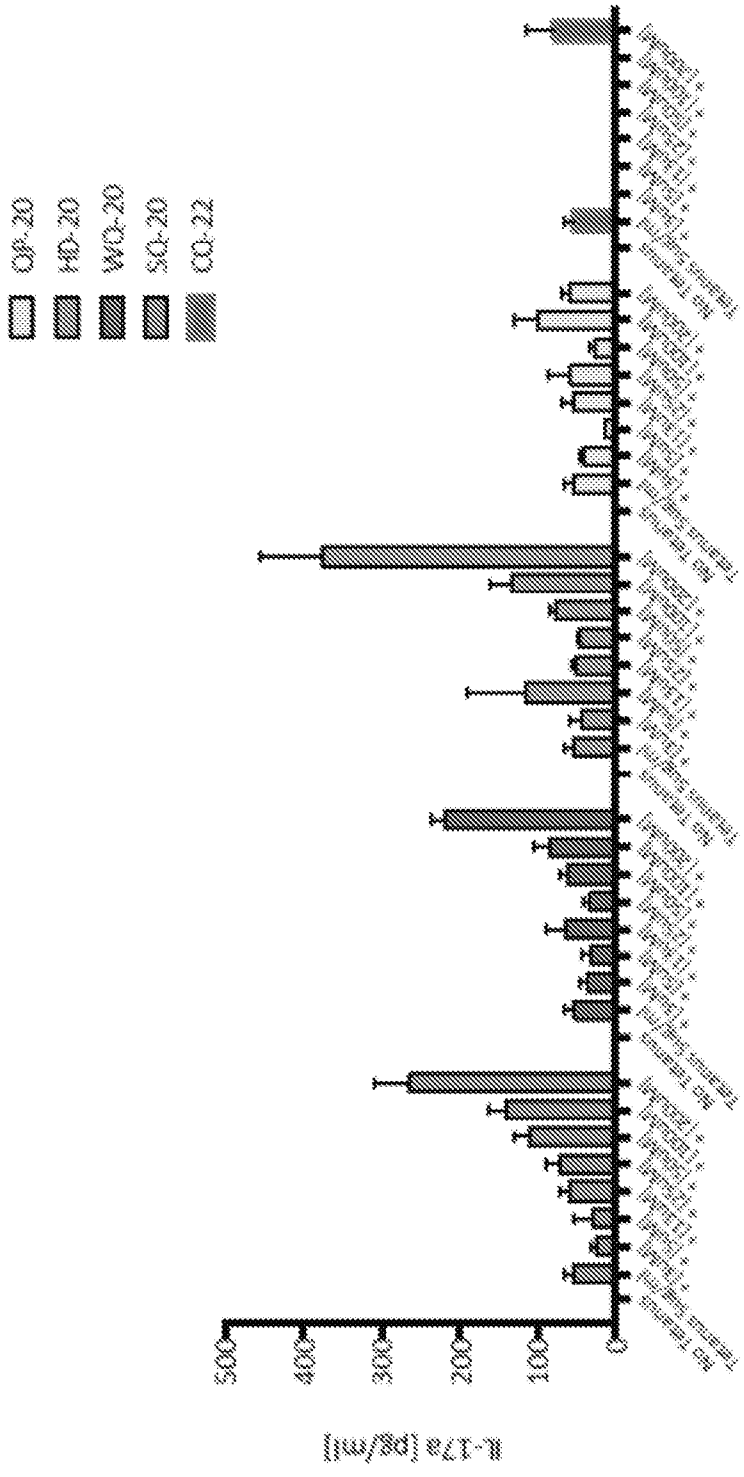


FIG. 13

FIG. 14

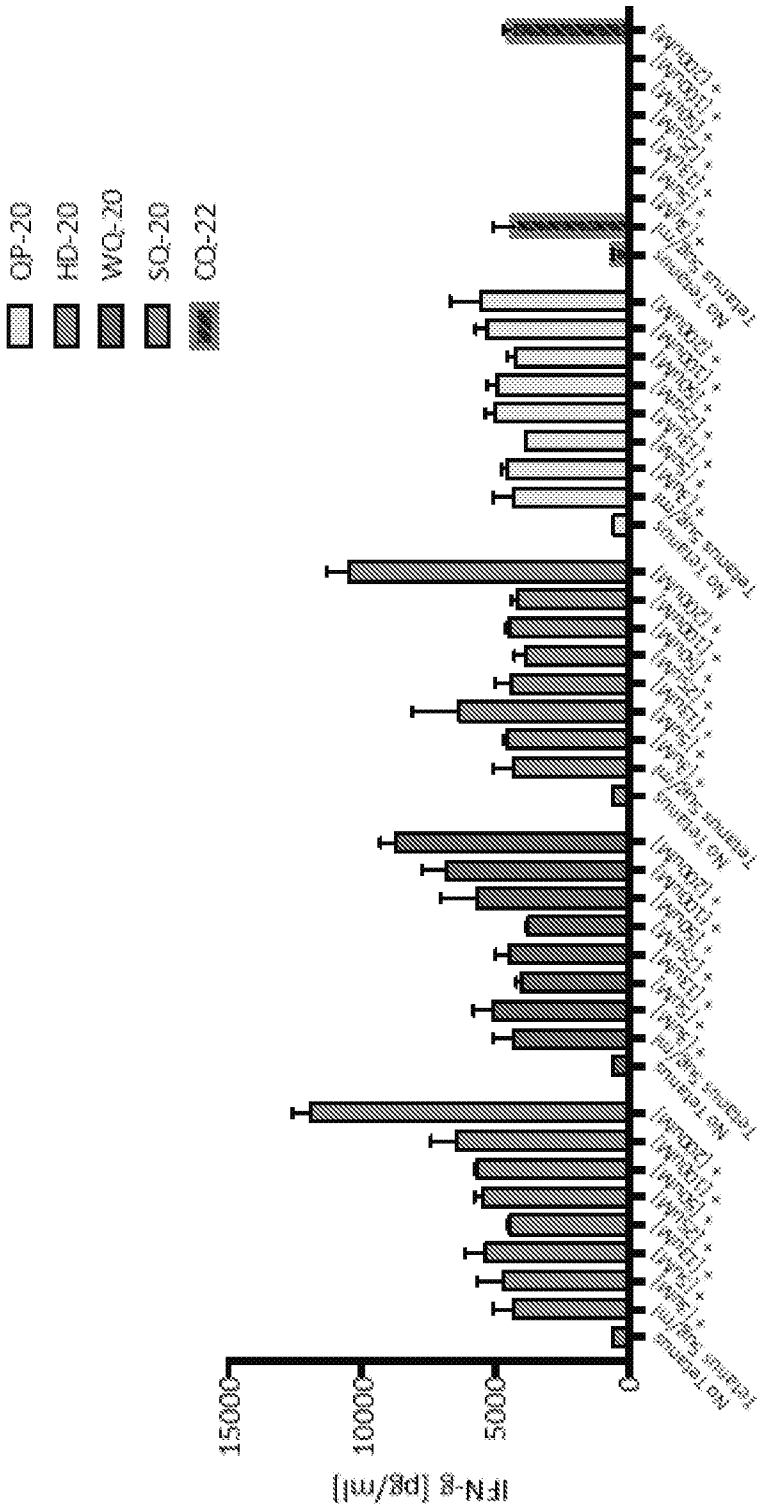


FIG. 15

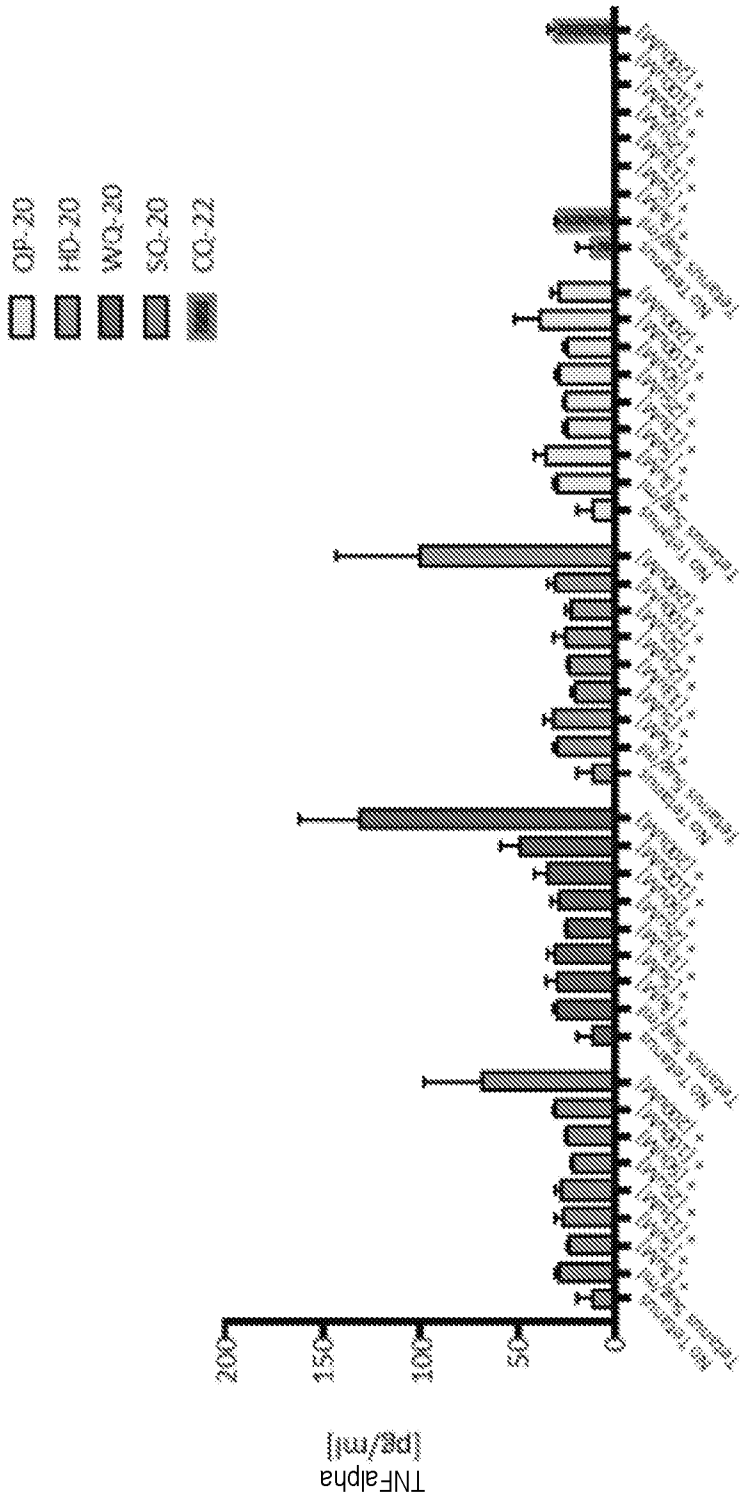


FIG. 16

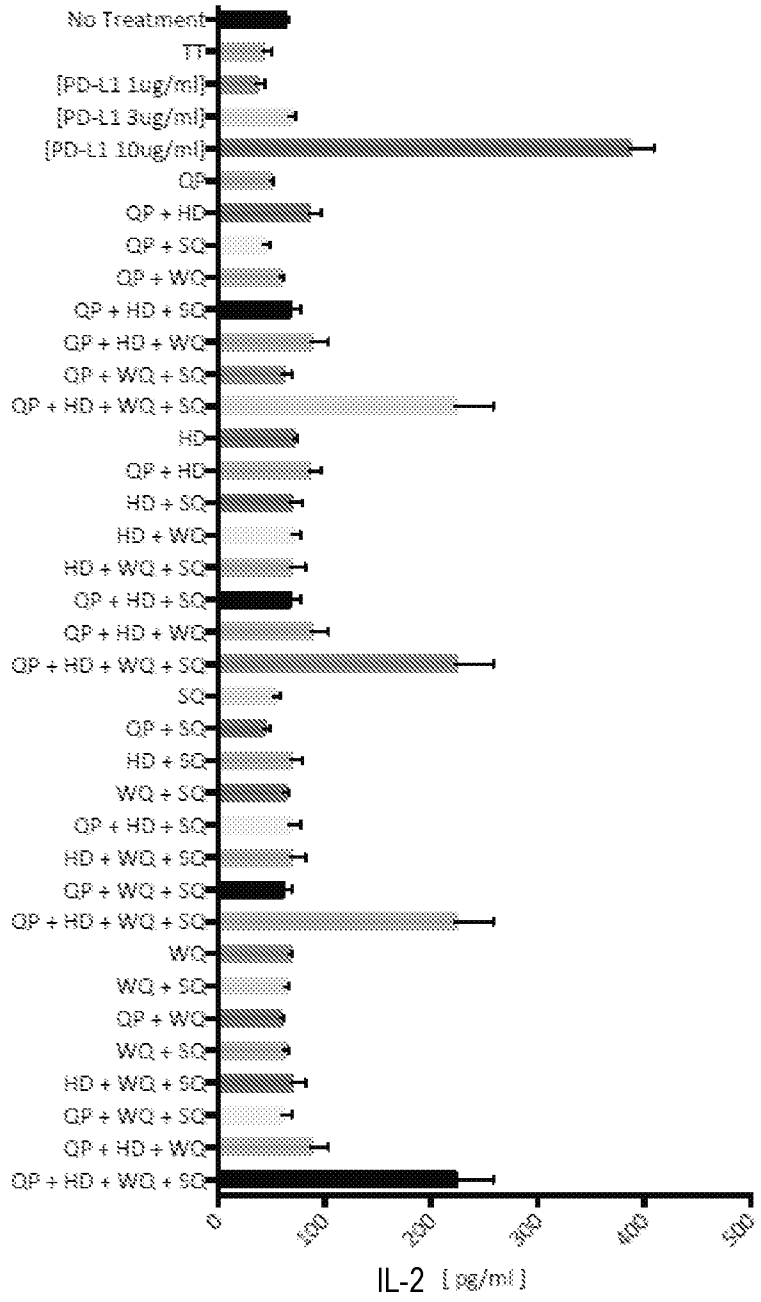

No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
QP
QP + HD
QP + SQ
QP + WQ
QP + HD + SQ
QP + HD + WQ
QP + WQ + SQ
QP + HD + WQ + SQ
HD
QP + HD
HD + SQ
HD + WQ
HD + WQ + SQ
QP + HD + SQ
QP + HD + WQ
QP + HD + WQ + SQ
SQ
QP + SQ
HD + SQ
WQ + SQ
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ + SQ
WQ
WQ + SQ
QP + WQ
WQ + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ
0
100
200
300
400
500
IL-2 [pg/ml]

FIG. 17

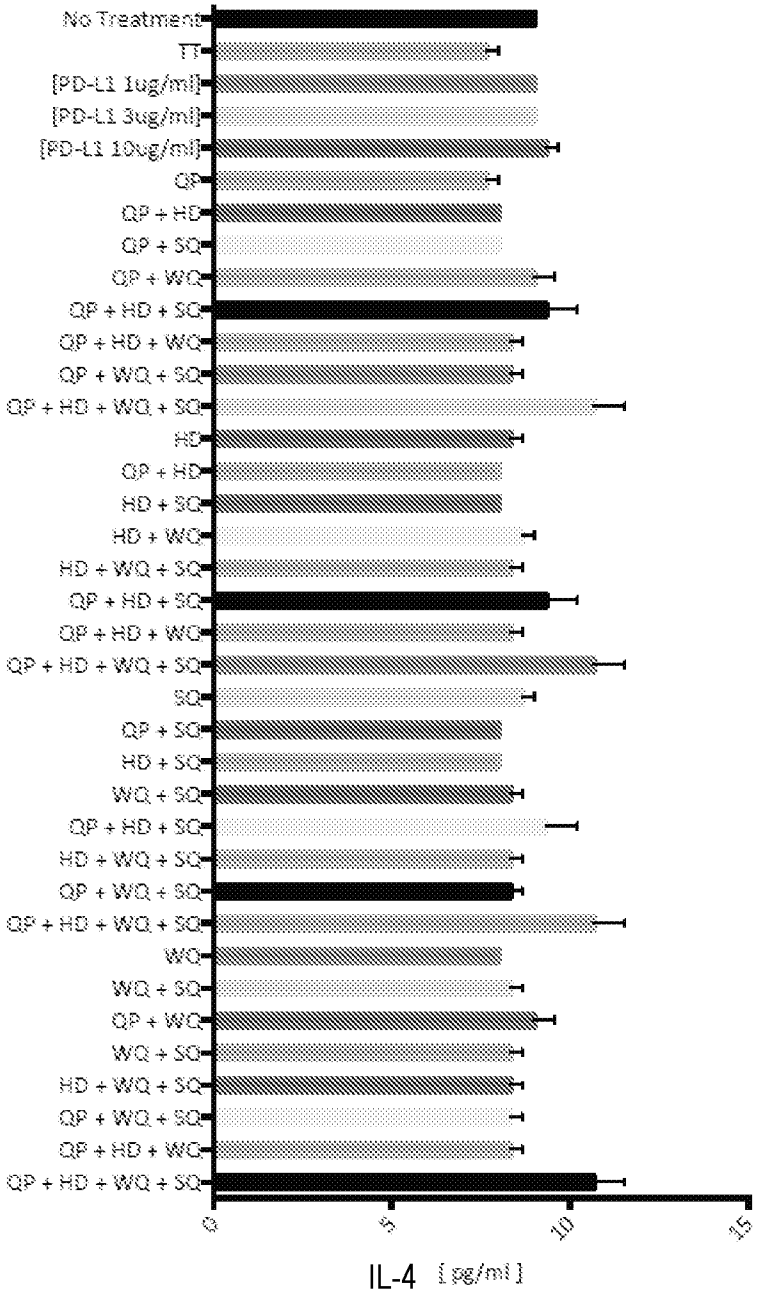
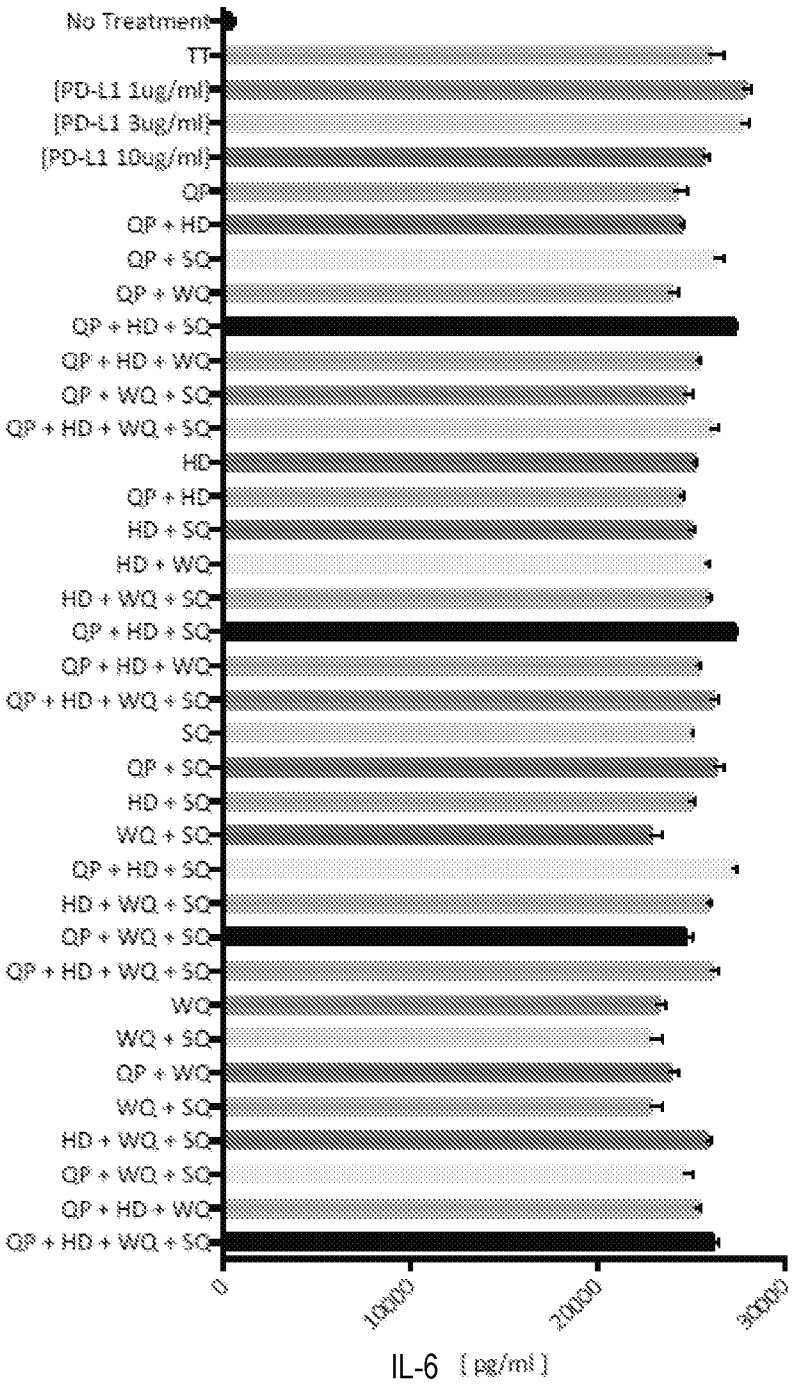

No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
QP
QP + HD
QP + SQ
QP + WQ
QP + HD + SQ
QP + HD + WQ
QP + WQ + SQ
QP + HD + WQ + SQ
HD
QP + HD
HD + SQ
HD + WQ
HD + WQ + SQ
QP + HD + SQ
QP + HD + WQ
QP + HD + WQ + SQ
SQ
QP + SQ
HD + SQ
WQ + SQ
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ + SQ
WQ
WQ + SQ
QP + WQ
WQ + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ
0
5
10
15
IL-4 [pg/ml]

FIG. 18


No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
QP
QP + HD
QP + SQ
QP + WQ
QP + HD + SQ
QP + HD + WQ
QP + WQ + SQ
QP + HD + WQ + SQ
HD
QP + HD
HD + SQ
HD + WQ
HD + WQ + SQ
QP + HD + SQ
QP + HD + WQ
QP + HD + WQ + SQ
SQ
QP + SQ
HD + SQ
WQ + SQ
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ + SQ
WQ
WQ + SQ
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HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ
0
10000
20000
30000
IL-6 [pg/ml]

FIG. 19

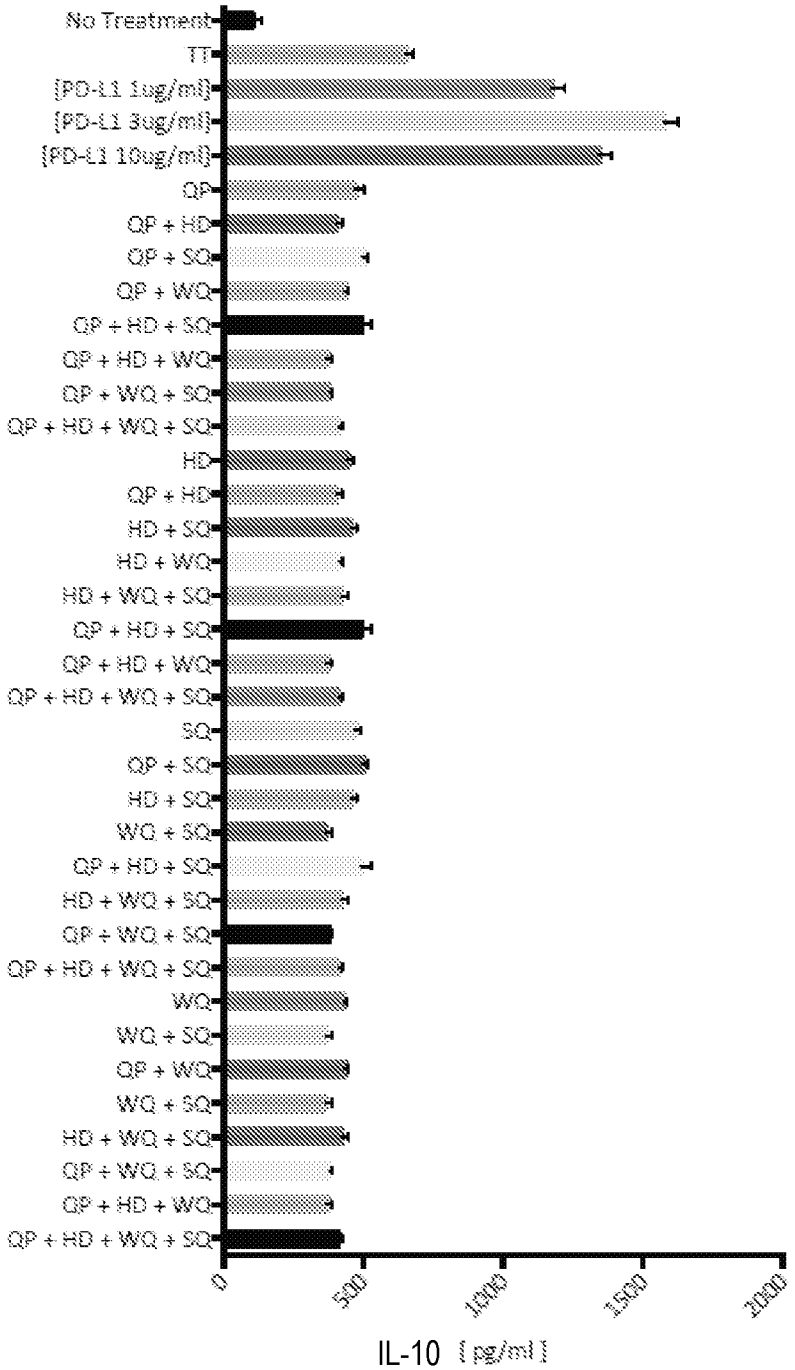
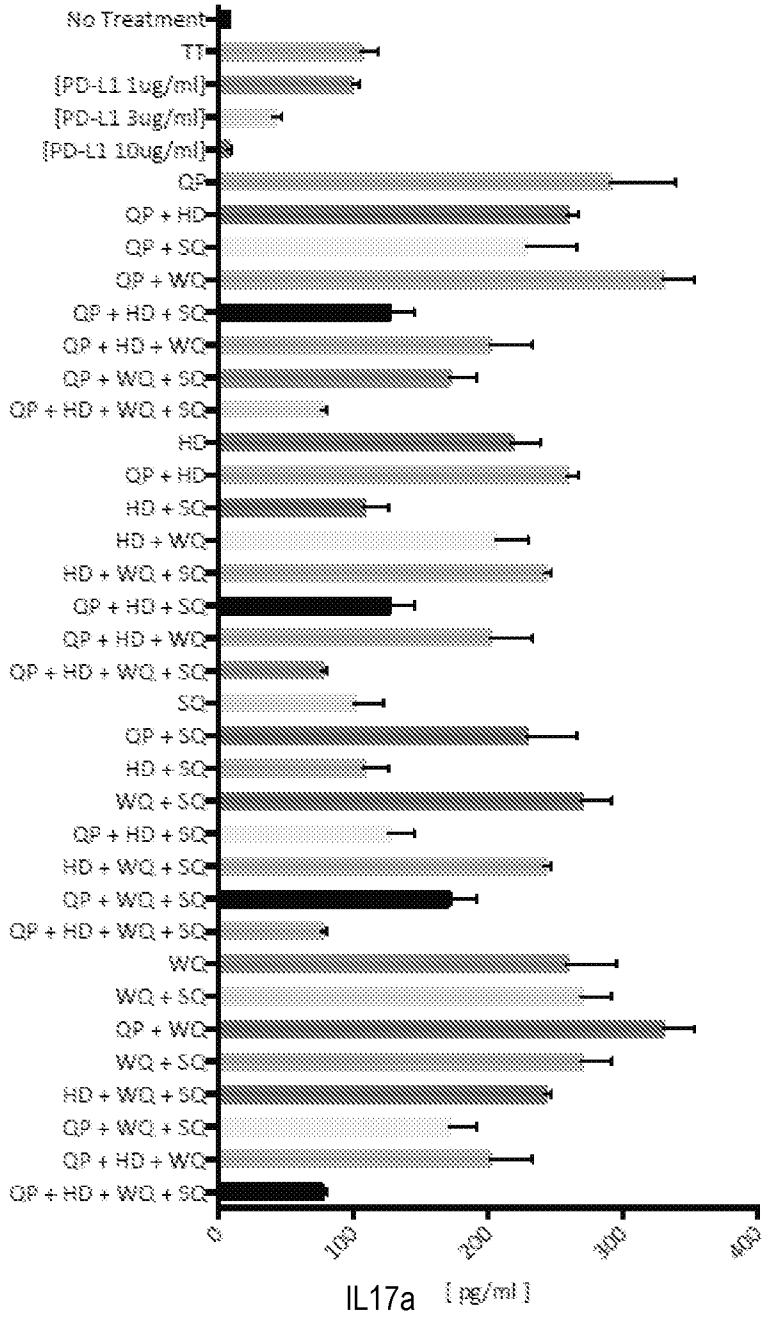

No Treatment
TT
(PD-L1 1ug/ml)
(PD-L1 3ug/ml)
(PD-L1 10ug/ml)
QP
QP + HD
QP + SQ
QP + WQ
QP + HD + SQ
QP + HD + WQ
QP + WQ + SQ
QP + HD + WQ + SQ
HD
QP + HD
HD + SQ
HD + WQ
HD + WQ + SQ
QP + HD + SQ
QP + HD + WQ
QP + HD + WQ + SQ
SQ
QP + SQ
HD + SQ
WQ + SQ
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ + SQ
WQ
WQ + SQ
QP + WQ
WQ + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ
0
500
1000
1500
2000
IL-10 [pg/ml]

FIG. 20


No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
QP
QP + HD
QP + SQ
QP + WQ
QP + HD + SQ
QP + HD + WQ
QP + WQ + SQ
QP + HD + WQ + SQ
HD
QP + HD
HD + SQ
HD + WQ
HD + WQ + SQ
QP + HD + SQ
QP + HD + WQ
QP + HD + WQ + SQ
SQ
QP + SQ
HD + SQ
WQ + SQ
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ + SQ
WQ
WQ + SQ
QP + WQ
WQ + SQ
HD + WQ + SQ
QP + WQ + SQ
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0
100
200
300
400
IL17a [pg/ml]

FIG. 21

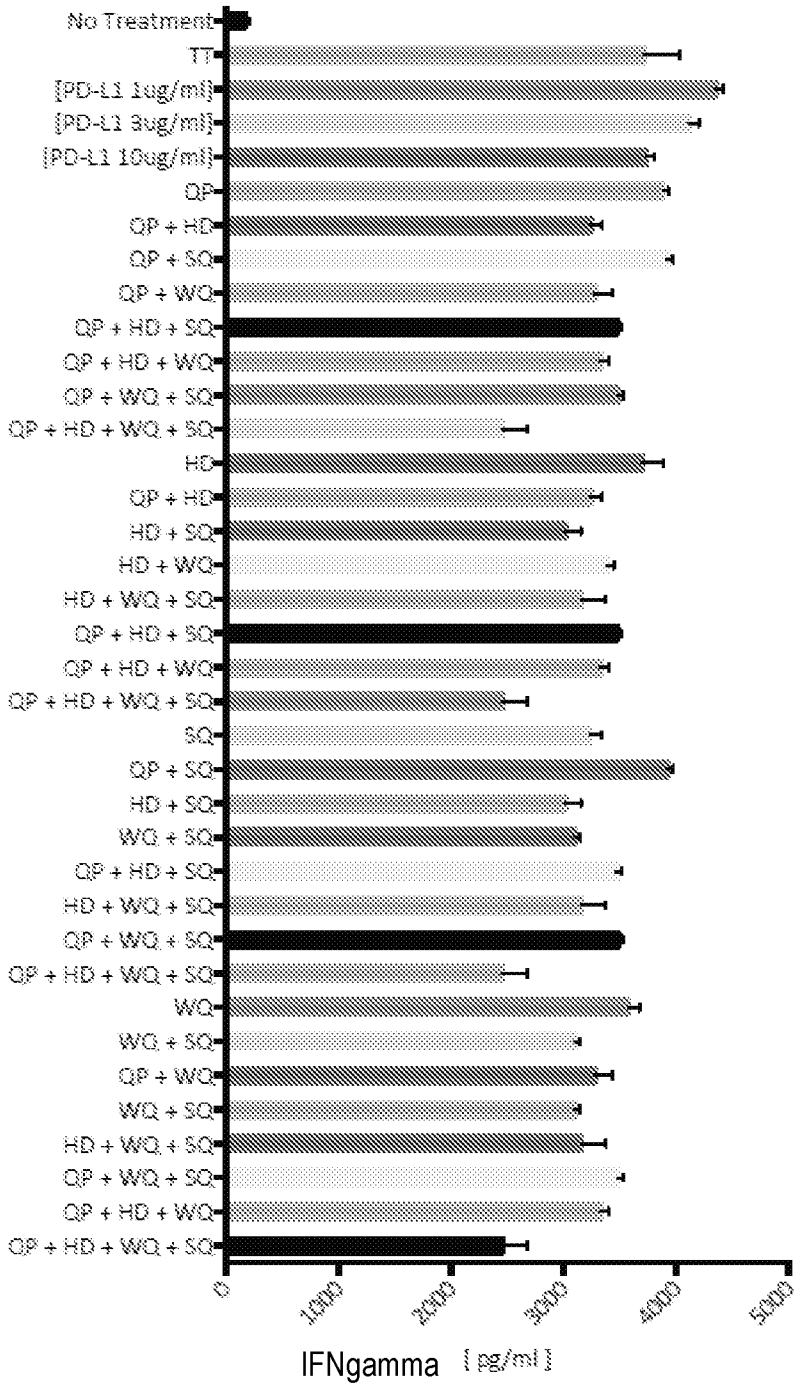
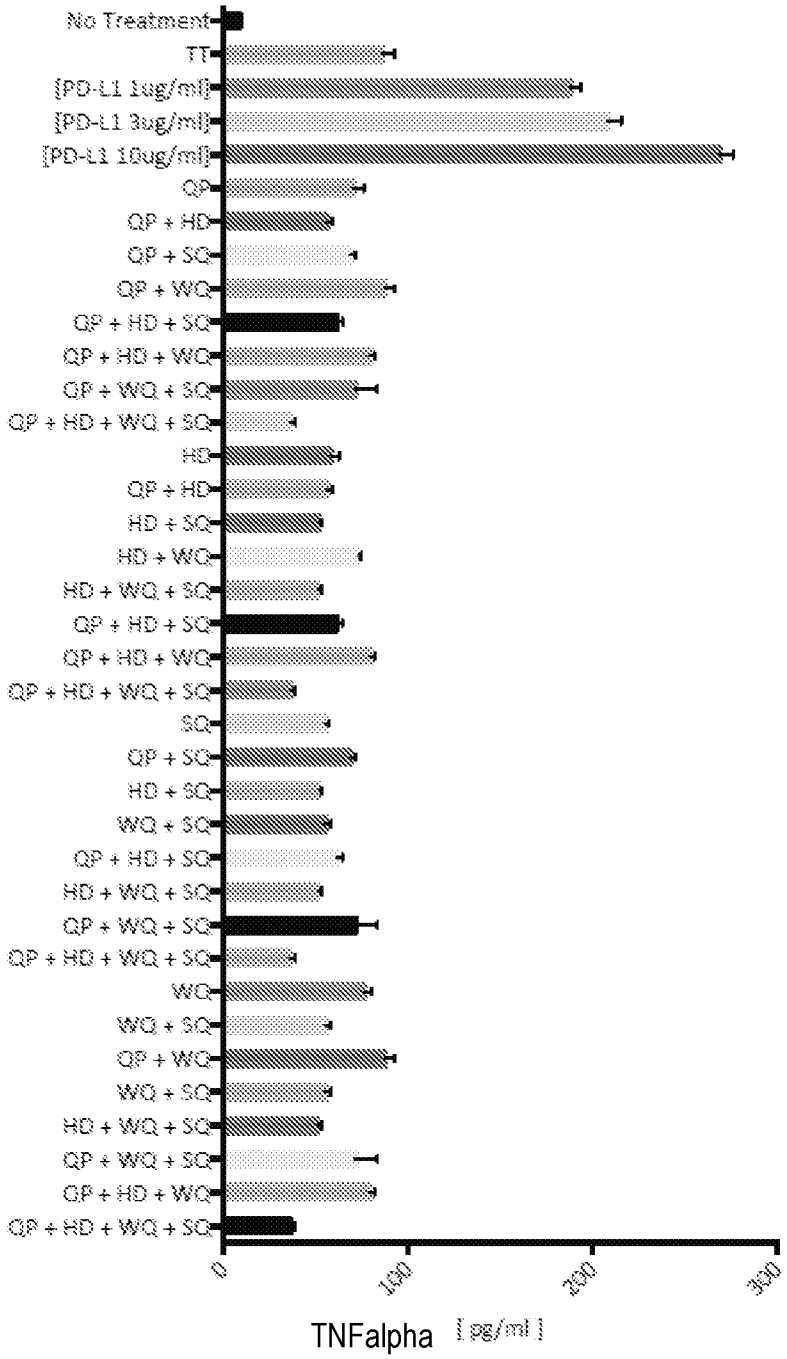

No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
QP
QP + HD
QP + SQ
QP + WQ
QP + HD + SQ
QP + HD + WQ
QP + WQ + SQ
QP + HD + WQ + SQ
HD
QP + HD
HD + SQ
HD + WQ
HD + WQ + SQ
QP + HD + SQ
QP + HD + WQ
QP + HD + WQ + SQ
SQ
QP + SQ
HD + SQ
WQ + SQ
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ + SQ
WQ
WQ + SQ
QP + WQ
WQ + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ
0
1000
2000
3000
4000
5000
IFNgamma [pg/ml]

FIG. 22


No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
QP
QP + HD
QP + SQ
QP + WQ
QP + HD + SQ
QP + HD + WQ
QP + WQ + SQ
QP + HD + WQ + SQ
HD
QP + HD
HD + SQ
HD + WQ
HD + WQ + SQ
QP + HD + SQ
QP + HD + WQ
QP + HD + WQ + SQ
SQ
QP + SQ
HD + SQ
WQ + SQ
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ + SQ
WQ
WQ + SQ
QP + WQ
WQ + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ
0
100
200
300
TNFalpha [pg/ml]

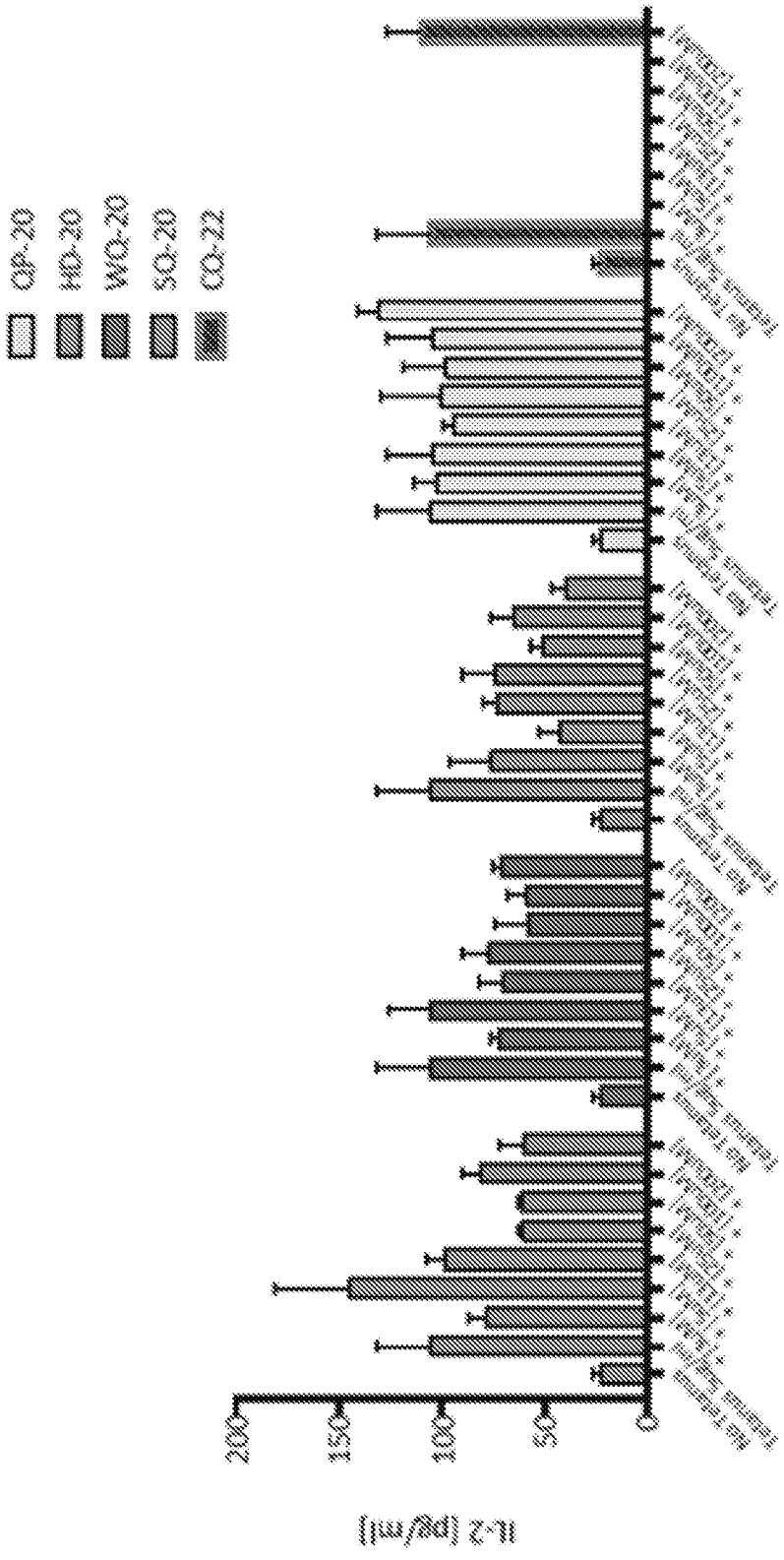


FIG. 23A

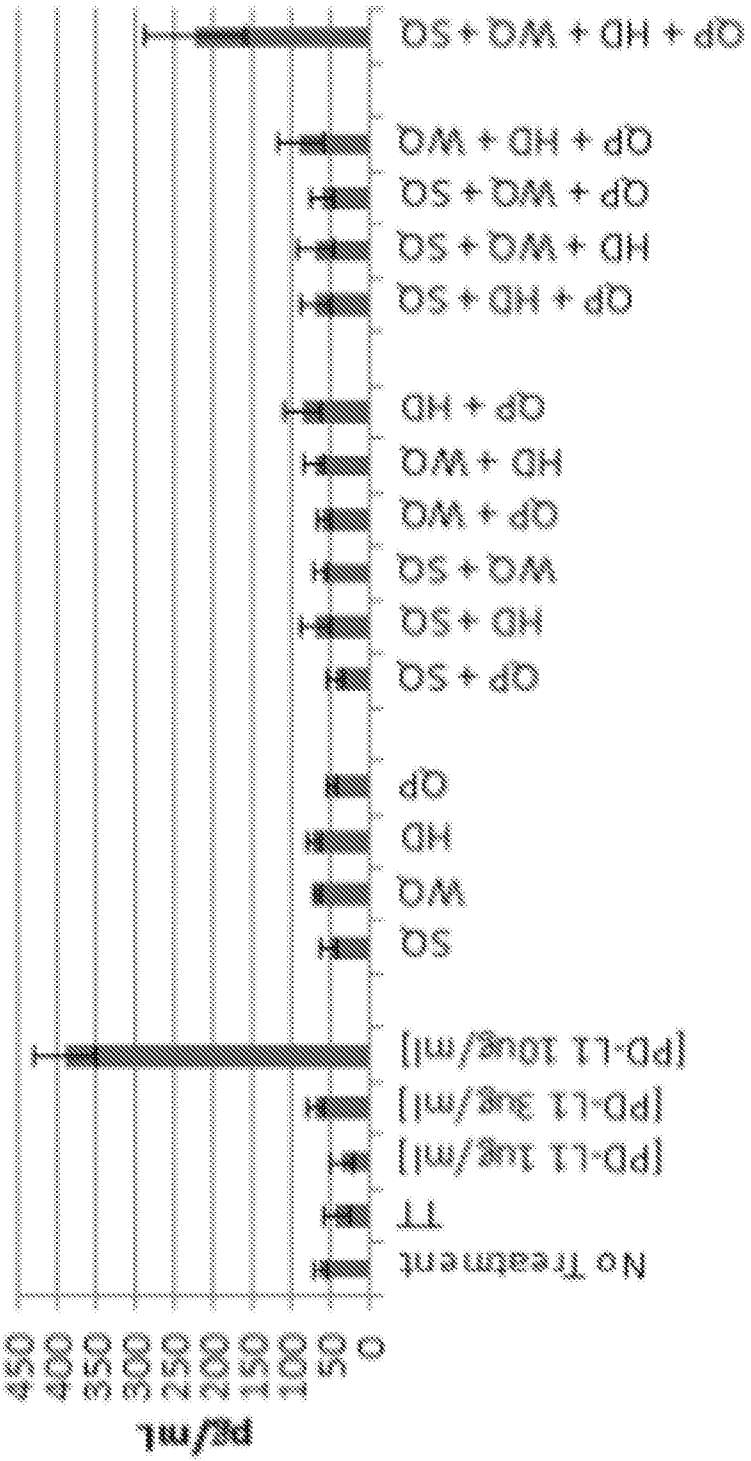

No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
SQ
WQ
HD
QP
QP + SQ
HD + SQ
WQ + SQ
QP + WQ
HD + WQ
QP + HD
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ
0
65
1000
2000
3000
4000
5000
6000
pg/mL

FIG. 23B

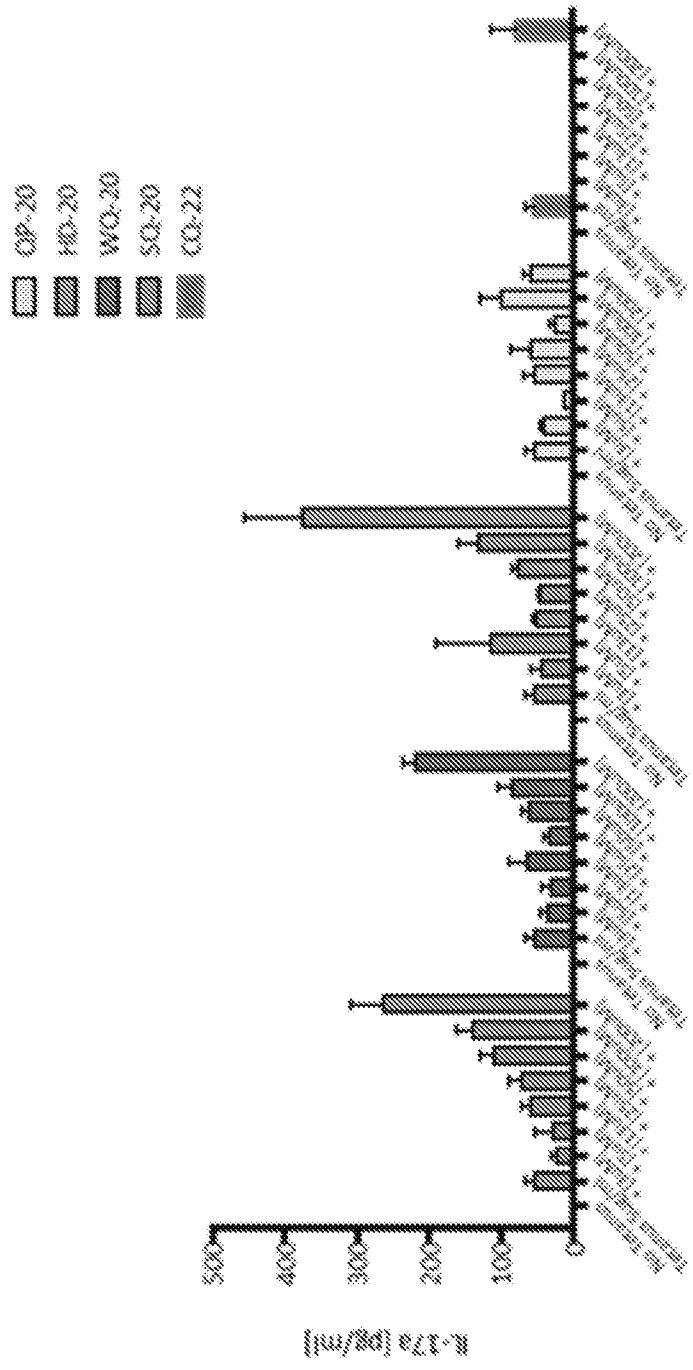


FIG. 24A

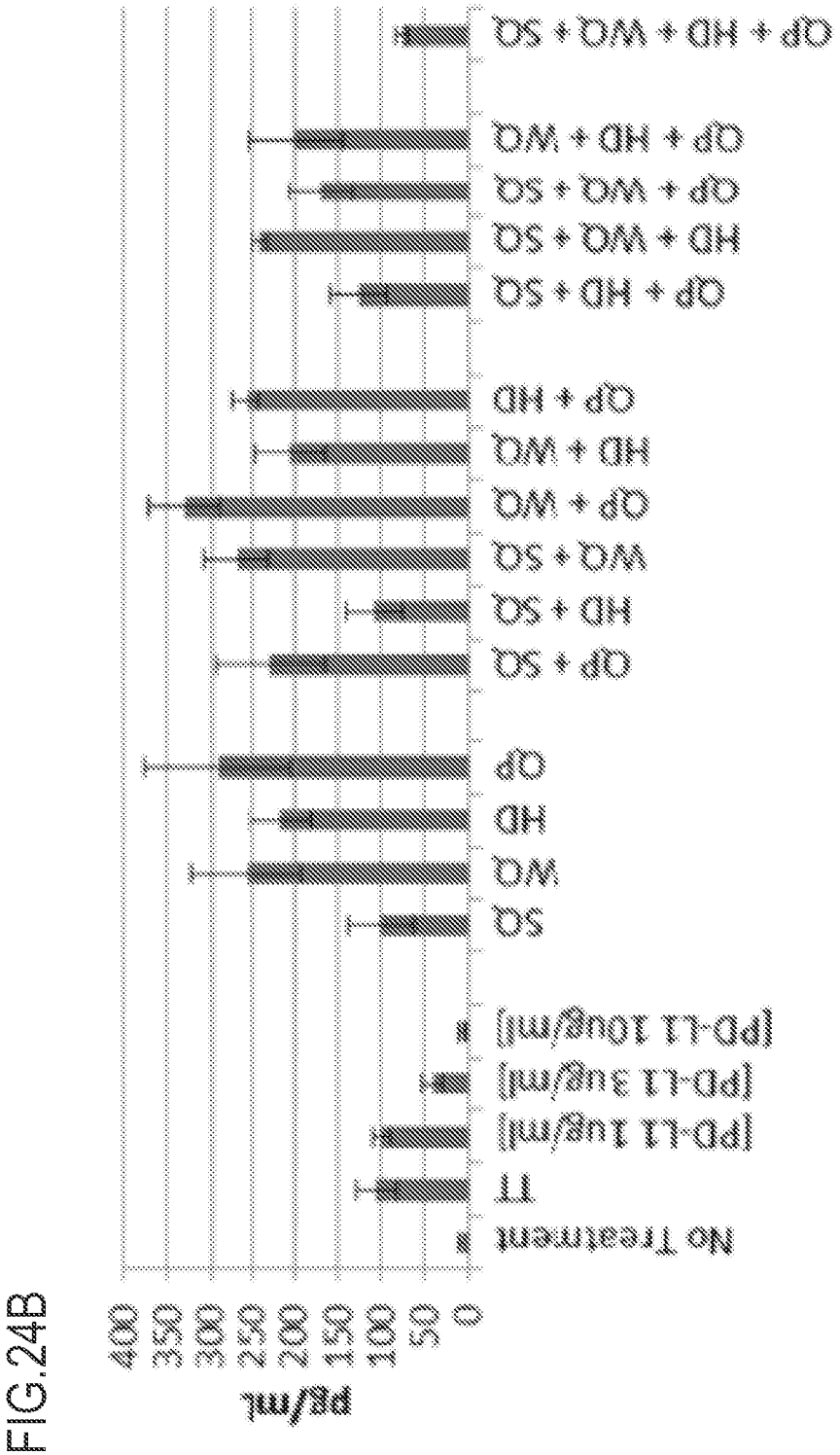

pg/mL
400
350
300
250
200
150
100
50
0
No Treatment
TT
[PD-L1 1ug/ml]
[PD-L1 3ug/ml]
[PD-L1 10ug/ml]
SQ
WQ
HD
QP
QP + SQ
HD + SQ
WQ + SQ
QP + WQ
HD + WQ
QP + HD
QP + HD + SQ
HD + WQ + SQ
QP + WQ + SQ
QP + HD + WQ
QP + HD + WQ + SQ

FIG.24B

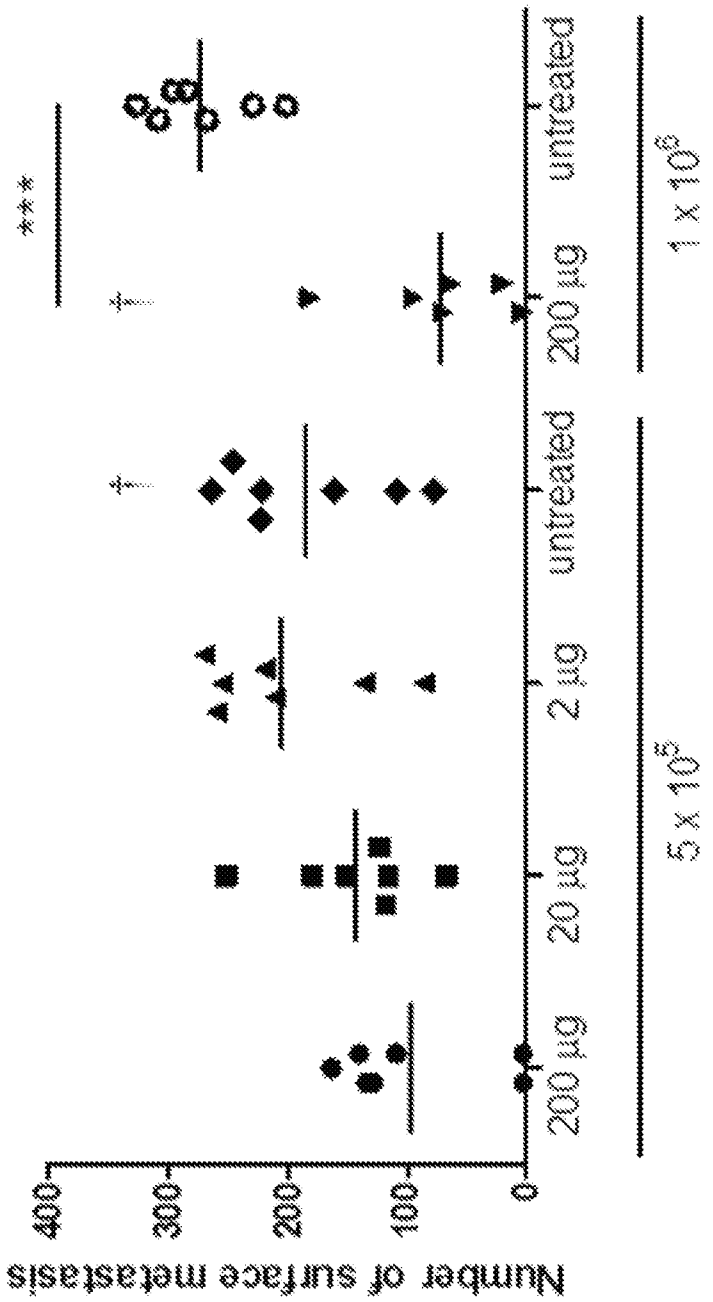

Number of surface metastasis
400
300
200
100
0
***
†
†
200 µg
20 µg
2 µg
untreated
200 µg
untreated
5 x 10^5
1 x 10^6

FIG. 25

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/051697

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/10 C07K7/08 A61P35/00 A61P31/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HAO-NAN CHANG ET AL: "-Peptide Antagonist for Cancer Immunotherapy", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 54, no. 40, 10 August 2015 (2015-08-10), pages 11760-11764, XP55247320, ISSN: 1433-7851, DOI: 10.1002/anie.201506225 abstract; figure 3; table 1	1-18
A	WO 2014/127917 A1 (CUREVAC GMBH [DE]) 28 August 2014 (2014-08-28) claims 1-28	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2017	01/12/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Habedanck, Robert

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/051697

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014127917 A1	28-08-2014	AU 2014220957 A1	30-07-2015
		CA 2897858 A1	28-08-2014
		CN 105073135 A	18-11-2015
		JP 2016514097 A	19-05-2016
		KR 20150121022 A	28-10-2015
		RU 2015139969 A	28-03-2017
		SG 11201506052P A	29-09-2015
		US 2016130345 A1	12-05-2016
		US 2016206719 A1	21-07-2016
		WO 2014127917 A1	28-08-2014