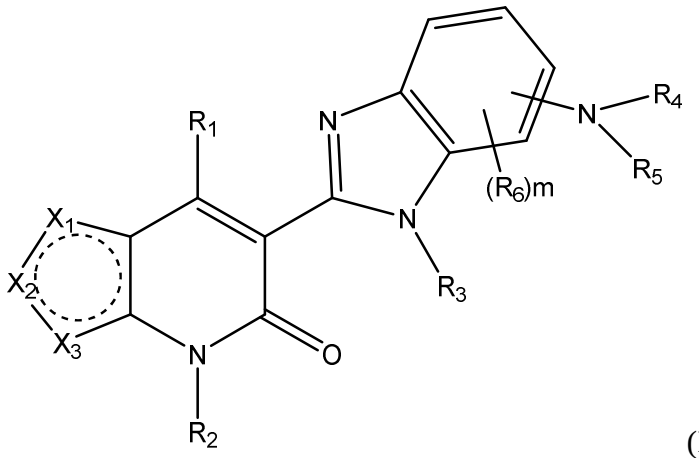
CLAIMS

~~What is claimed is:~~

1. Use of ~~A method of treating a subject with aberrant cytokine release from a disease or condition or at risk of developing aberrant cytokine release from a disease or condition, comprising administering to the subject an effective amount of~~ a compound represented by the following structural formula or a pharmaceutically acceptable salt thereof in the preparation of medicament for treating a subject with aberrant cytokine release from a disease or condition or at risk of developing aberrant cytokine release from a disease or condition:



(I),

~~or a pharmaceutically acceptable salt thereof,~~ wherein:

one of X_1, X_2, and X_3 is S, the other two are each independently CR;

R is H, -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylene-OH or 4-7 membered monocyclic heterocyclyl optionally substituted with 1-3 groups selected from -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)alkoxy, or -CO_2-(C_1-C_4)alkyl;

R_1 is $-NR^aR^b$ or $-OR^{a1}$;

R^a for each occurrence is independently -H, -(C_1-C_6)alkyl, -$(CH_2)_n$-(C_3-C_7)cycloalkyl, -$(CH_2)_n$-3-7 membered monocyclic heterocyclyl, -$(CH_2)_n$-bridged (C_6-C_{12})cycloalkyl,

optionally substituted -$(CH_2)_n$-5-10 membered heteroaryl; or -$(CH_2)_n$-6-12 membered bridged heterocyclyl, wherein -$(C_1$-$C_6)$alkyl, -$(CH_2)_n$-$(C_3$-$C_7)$cycloalkyl, -$(CH_2)_n$-3-7 membered monocyclic heterocyclyl, -$(CH_2)_n$-bridged $(C_6$-$C_{12})$cycloalkyl, -$(CH_2)_n$-5-10 membered heteroaryl, or -$(CH_2)_n$-6-12 membered bridged heterocyclyl, is optionally substituted with 1-3 groups selected from -F, -Cl, -Br, -CN, -NH_2, -OH, oxo, -$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$haloalkyl, -$(C_1$-$C_4)$alkoxy, -$(C_1$-$C_4)$haloalkoxy, -$(C_1$-$C_4)$alkylene-OH, or -$(C_1$-$C_4)$alkylene-NH_2;

R^b for each occurrence is independently –H or -$(C_1$-$C_6)$alkyl; or,

R^a and R^b, together with the nitrogen to which they are attached, form -$(C_3$-$C_{10})$heterocyclyl;

R^{a1} for each occurrence is independently –H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_{10})$cycloalkyl, 3-10 membered heterocyclyl, $(C_6$-$C_{10})$aryl, or 3-10 membered heteroaryl;

R_2 and R_3 are independently H or –$(C_1$-$C_4)$alkyl;

R_4 and R_5, together with the nitrogen to which they are attached, form 4-7 membered monocyclic heterocyclyl or 6-12 membered bridged heterocyclyl, wherein the 4-7 membered monocyclic heterocyclyl or 6-12 membered bridged heterocyclyl is optionally substituted with 1-3 groups selected from -F, -Cl, -Br, -CN, -NH_2, -OH, oxo, -$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$haloalkyl, -$(C_1$-$C_4)$alkoxy, -$(C_1$-$C_4)$haloalkoxy, -$(C_1$-$C_4)$alkylene-OH, or -$(C_1$-$C_4)$alkylene-NH_2;

R_6 for each occurrence is independently -F, -Cl, -Br, -CN, -NH_2, -OH, -$(C_1$-$C_6)$alkyl; -$(C_1$-$C_6)$haloalkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_6)$alkoxy, -$(C_1$-$C_6)$haloalkoxy, -$(C_1$-$C_6)$alkylene-OH, or -$(C_1$-$C_6)$alkylene-NH_2;

m is 0, 1, 2, or 3; and

n is 0, 1, or 2.

2. The ~~method~~ use of claim 1, wherein the subject has aberrant cytokine release from the disease or condition~~.~~

~~3. The method of claim 1, wherein~~ or the subject is at risk of developing aberrant cytokine release from the disease or condition.

~~4~~3. The ~~method~~ use of ~~any one of claims 1-3~~ claim 1 or 2, wherein the aberrant cytokine release is cytokine release syndrome or cytokine storm syndrome.

~~5~~4. The ~~method~~ use of any one of claims 1-~~4~~3, wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from activated T-cells, activated natural killer (NK) cells, activated dendritic cells, activated macrophages, activated B-cells, or antitumor cell therapy~~.~~, or

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~~6. The method of any one of claims 1-4,~~ wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from adoptive cell therapy using tumor-infiltrating lymphocyte (TIL) therapy, engineered T cell receptor (TCR) therapy, chimeric antigen receptor (CAR) T cell therapy and therapies that incorporate other immune cells, such as NK cells~~.~~, or

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~~7. The method of any one of claims 1-4,~~ wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from chimeric antigen receptor (CAR) T cell therapy~~.~~

~~8. The method of claim 7, wherein~~, optionally, the CAR T cell therapy is tisagenlecleucel or axicabtagene ciloleucel~~.~~, or

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~~9. The method of any one of claims 1-4,~~ wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from therapy with an antibody~~.~~, or

wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from therapy with a non-protein-based cancer drug, such as oxaliplatin and lenalidomide, or

wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from haploidentical donor stem cell transplantation.

~~10~~5. The ~~method~~ use of claim ~~9~~4, wherein the antibody is a monoclonal antibody, an antibody fragment, a Fc-fusion protein or a bispecific antibody (e.g., bispecific T cell engager or BiTE)~~.~~, or

~~11. The method of claim 9,~~ wherein the antibody is a monoclonal antibody~~.~~, or

~~12. The method of claim 9,~~ wherein the antibody is a monoclonal antibody selected from an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-1 antibody, anti-CD3 antibody, anti-CD20 antibody, anti-CD28 antibody, anti-CD52 antibody and anti-thymocyte globulin (ATG)~~.~~, or

~~13. The method of claim 9,~~ wherein the antibody is a monoclonal antibody selected from Nivolumab, Muromonab, Rituximab, Brentuximab, Theralizumab, Alemtuzumab, Obinutuzumab, Dacetuzumab, Pembrolizumab, Cemiplimab, Atezolizumab, Avelumab, Durvalumab and Ipilimumab; or the antibody is a bispecific T cell engager selected from Blinatumomab (Blincyto).

~~14. The method of any one of claims 1-4, wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from therapy with a non-protein-based cancer drug, such as oxaliplatin and lenalidomide.~~

~~15~~6. The ~~method~~ use of any one of claims 1-~~4~~3, wherein the disease or condition is an infectious disease~~.~~, or

wherein the disease or condition is an auto-inflammatory disease or an autoimmune disease, or

wherein the disease or condition is selected from hemophagocytic lymphohistiocytosis (HLH), familial (primary) hemophagocytic lymphohistiocytosis (FHL), sporadic HLH, macrophage activation syndrome (MAS), chronic arthritis, systemic Juvenile Idiopathic Arthritis (sJIA), Still's Disease, a Cryopyrin-associated Periodic Syndrome (CAPS), Familial Cold Auto-inflammatory Syndrome (FCAS), Familial Cold Urticaria (FCU), Muckle-Well Syndrome (MWS), Chronic Infantile Neurological Cutaneous and Articular (CINCA) Syndrome, a cryopyrinopathy comprising inherited or de novo gain of function mutations in the NLRP3 gene, a hereditary auto-inflammatory disorder, acute pancreatitis, severe burn injury, acute radiation syndrome, trauma, acute respiratory distress syndrome, systemic inflammatory response syndrome, and tumor lysis syndrome, or

wherein the disease or condition is selected from cachexia, a chronic inflammatory response, sepsis, septic shock syndrome, traumatic brain injury, cerebral cytokine storm, graft versus host disease (GVHD), autoimmune diseases, multiple sclerosis, acute pancreatitis, or hepatitis, or

wherein the disease or condition is selected from myocarditis, Type 1 diabetes, Type 2 diabetes, thyroiditis, uveitis, encephalomyelitis, arthritis (e.g., rheumatoid), lupus erythematosus, myositis, systemic sclerosis, Sjogren's syndrome and heart failure.

~~16~~7. The ~~method~~ use of claim ~~15~~6, wherein the infectious disease is viral, bacterial, fungal, helminthic, protozoan or hemorrhagic~~.~~, or

~~17. The method of claim 15,~~ wherein the infectious disease is a viral infection selected from influenza, Arenaviridae, Filoviridae, Bunyaviridae, Flaviviridae, Rhabdoviridae and Cornaviridae~~.~~, optionally, the viral infection is Cornaviridae, or

~~18. The method of claim 15,~~ wherein the infectious disease is a viral infection selected from Epstein Barr virus, small pox, Ebola, Marburg, Crimean-Congo hemorrhagic fever (CCHF), South American hemorrhagic fever, dengue, yellow fever, Rift Valley fever, Omsk

hemorrhagic fever virus, Kyasanur Forest, Junin, Machupo, Sabia, Guanarito, Garissa, Ilesha and Lassa~~.~~, or

wherein the infectious disease is an influenza virus infection.

~~19. The method of claim 17, wherein the viral infection is Cornaviridae.~~

~~20~~8. The ~~method~~ use of claim ~~19~~7, wherein the infection by Coronaviridae is from a virus selected from SARS, SARS-CoV-2, MERS, 229E, NL63, OC43, and HKUl~~.~~, or

~~21. The method of claim 19,~~ wherein the Cornaviridae infection is a SARS virus infection~~.~~, or

~~22. The method of claim 19,~~ wherein the Cornaviridae infection is a SARS-CoV-2 virus infection~~.~~, or

~~23. The method of claim 19,~~ wherein the Cornaviridae infection is a MERS virus infection.

~~24. The method of claim 15, wherein the infectious disease is an influenza virus infection.~~

~~25. The method of any one of claims 1-4, wherein the disease or condition is an auto-inflammatory disease or an autoimmune disease.~~

~~26~~9. The ~~method~~ use of claim ~~25~~6, wherein the autoimmune disease or auto-inflammatory disease is selected from Type 1 diabetes, Type 2 diabetes, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (Crohn's disease and ulcerative colitis), psoriasis, asthma, familial Mediterranean fever (FMF), Tumor Necrosis Factor (TNF) receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS), Muckle-Wells syndrome (MWS), familial cold auto-inflammatory syndrome (FCAS), neonatal-onset multisystem inflammatory disease (NOMID), periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA syndrome), pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA),

deficiency of the interleukin-1 receptor antagonist (DIRA), Behcet's disease, Majeed Syndrome, Chronic recurrent multifocal osteomyelitis (CRMO), Schnitzler syndrome and Blau syndrome.

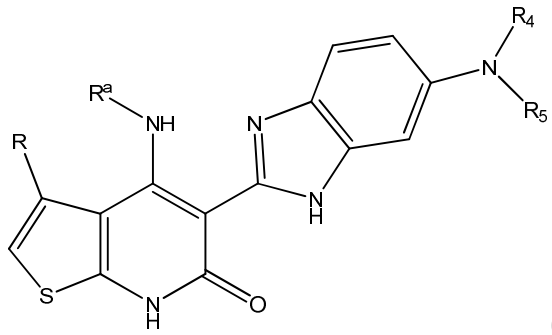
~~27. The method of any one of claims 1-4, wherein the disease or condition is selected from hemophagocytic lymphohistiocytosis (HLH), familial (primary) hemophagocytic lymphohistiocytosis (FHL), sporadic HLH, macrophage activation syndrome (MAS), chronic arthritis, systemic Juvenile Idiopathic Arthritis (sJIA), Still's Disease, a Cryopyrin-associated Periodic Syndrome (CAPS), Familial Cold Auto-inflammatory Syndrome (FCAS), Familial Cold Urticaria (FCU), Muckle-Well Syndrome (MWS), Chronic Infantile Neurological Cutaneous and Articular (CINCA) Syndrome, a cryopyrinopathy comprising inherited or de novo gain of function mutations in the NLRP3 gene, a hereditary auto-inflammatory disorder, acute pancreatitis, severe burn injury, acute radiation syndrome, trauma, acute respiratory distress syndrome, systemic inflammatory response syndrome, and tumor lysis syndrome.~~

~~28. The method of any one of claims 1-4, wherein the disease or condition is selected from cachexia, a chronic inflammatory response, sepsis, septic shock syndrome, traumatic brain injury, cerebral cytokine storm, graft versus host disease (GVHD), autoimmune diseases, multiple sclerosis, acute pancreatitis, or hepatitis.~~

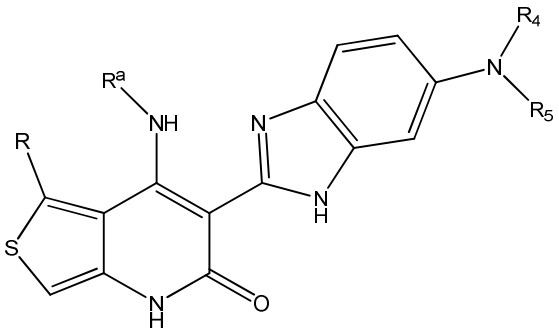
~~29. The method of any one of claims 1-4, wherein the disease or condition is selected from myocarditis, Type 1 diabetes, Type 2 diabetes, thyroiditis, uveitis, encephalomyelitis, arthritis (e.g., rheumatoid), lupus erythematosus, myositis, systemic sclerosis, Sjogren's syndrome and heart failure.~~

~~30. The method of any one of claims 1-4, wherein the subject has aberrant cytokine release or is at risk of developing aberrant cytokine release from haploidentical donor stem cell transplantation.~~

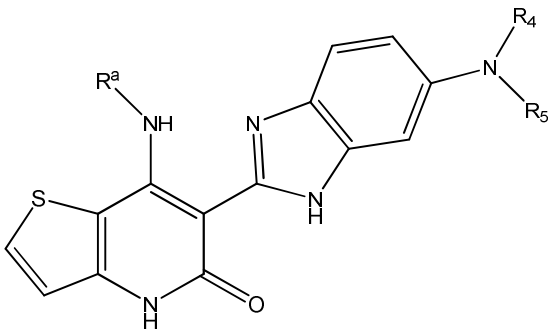
~~31~~10. The ~~method~~ use of any one of claims 1-~~30~~9, wherein the compound is represented by a structural formula selected from:



(II-A),



(II-B), and



(II-C);

or a pharmaceutically acceptable salt thereof.

~~32~~11. The ~~method~~ use of any one of claims 1-~~31~~10, wherein;

R is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, N-piperazinyl optionally substituted with –CO_2-(C_1-C_4)alkyl;

R_4 and R_5, together with the nitrogen to which they are attached, form –N-alkyl-piperazinyl or morpholinyl, wherein the piperazinyl or morpholinyl is optionally substituted with 1-2 groups selected from -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, or -(C_1-C_4)alkoxy;

R^a for each occurrence is independently -H, -$(CH_2)_n$-(C_3-C_6)cycloalkyl, -$(CH_2)_n$-3-6 membered monocyclic heterocyclyl, wherein the -$(CH_2)_n$-(C_3-C_6)cycloalkyl or -$(CH_2)_n$-3-6 membered monocyclic heterocyclyl is optionally substituted with 1-3 groups selected from -F, -Cl, -Br, -CN, -NH_2, -OH, -(C_1-C_4)alkyl, or -(C_1-C_4)alkoxy; and

n is 0 or 1.

~~33~~12. The ~~method~~ use of any one of claims 1-~~32~~11, wherein:

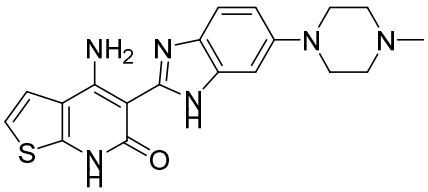
R is H;

R_4 and R_5, together with the nitrogen to which they are attached, form –N-methyl-piperazinyl or morpholinyl, both of which are optionally substituted with one or two methyl;

R^a for each occurrence is independently –H; -(C_3-C_6)cycloalkyl optionally substituted with –OH; -$(CH_2)_n$-tetrahydro-2H-pyran; morpholinyl; piperidinyl optionally substituted with –F, –OH or methyl; or tetrahydrofuranyl; and

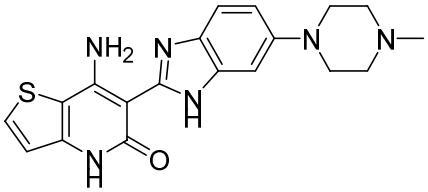
n is 0 or 1.

~~34~~13. The ~~method~~ use of any one of claims 1-~~30~~9, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

~~35~~14. The ~~method~~ use of any one of claims 1-~~30~~9, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

~~36~~15. Use of ~~A method of treating a subject with a systemic inflammatory response from a disease or condition or a subject at risk of developing systemic inflammatory response from a disease or condition, comprising administering to the subject~~ a compound from any one of claims 1 or ~~31-35~~ 10-14 or a pharmaceutically acceptable salt thereof in the preparation of medicament for treating a subject with a systemic inflammatory response from a disease or condition or a subject at risk of developing systemic inflammatory response from a disease or condition, wherein the disease or condition is as recited in any one of claims 4-9.

~~37. The method of claim 36, wherein the disease or condition is as recited in any one of claims 5-30.~~