~~We claim~~CLAIMS:

1. Use of an IRAK4 inhibitor in the manufacture of a medicament for ~~A method of~~ treating a disease or disorder, wherein the medicament is for administration to a subject with increased expression of a phosphorylated NF-κB ~~in a subject, comprising:~~

~~obtaining a biological sample from the subject;~~

~~measuring an expression level of a phosphorylated NF-κB in the biological sample;~~

~~comparing the level of expression of the phosphorylated NF-κB to a reference level of expression of phosphorylated NF-κB; and~~

~~administering an IRAK4-modifying compound selected from an IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression of a phosphorylated NF-κB is elevated in the sample as compared to the reference level of expression of phosphorylated NF-κB~~.

~~2. A method of treating an IRAK4-mediated disease or disorder in a subject, comprising:~~
~~obtaining a biological sample from the subject;~~
~~measuring an expression level of a phosphorylated NF-κB in the biological sample;~~
~~comparing the level of expression of the phosphorylated NF-κB to a reference level of expression of phosphorylated NF-κB; and~~
~~administering an IRAK4-modifying compound selected from an IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression of a phosphorylated NF-κB is elevated as compared to the reference level of expression of phosphorylated NF-κB.~~

~~3. The method of claim 1 or 2, wherein the reference level is a value obtained from a subject or a plurality of subjects that does not suffer from the disease or disorder.~~

~~4. The method of claim 3, wherein the value is obtained from the same biological source (e.g., tissue, blood, or other bodily fluid) as the biological sample.~~

~~5. The method of claim 3 or 4, wherein the value is obtained from tissue or blood.~~

2~~6~~. The ~~method~~ use of ~~any one of claims 1-5~~claim 1, wherein the phosphorylated NF-κB is NF-κB p-p50.

3~~7~~. ~~The method of claim 6, wherein the method comprises administering the IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression level of NF-κB p-p50 is elevated in the sample.~~

~~8~~. The ~~method~~ use of claim 2~~any one of claims 1-7~~, wherein the expression of NF-κB p-p50 is nuclear expression.

~~9. The method of any one of claims 1-7, wherein the expression of NF-κB p-p50 is cytoplasmic expression.~~

~~10. The method of any one of claims 1-7, wherein the expression of NF-κB p-p50 is the combination of nuclear expression and cytoplasmic expression.~~

4~~11~~. The ~~method~~ use of any one of claims 1-3~~5~~, wherein the phosphorylated NF-κB is NF-κB p-p65.

~~12. The method of claim 11, wherein the method comprises administering the IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression level of NF-κB p-p65 is elevated in the sample.~~

5~~13~~. The ~~method~~ use of claim ~~11 or 12~~4, wherein the expression of NF-κB p-p65 is nuclear expression.

~~14. The method of claim 11 or 12, wherein the expression of NF-κB p-p65 is cytoplasmic expression.~~

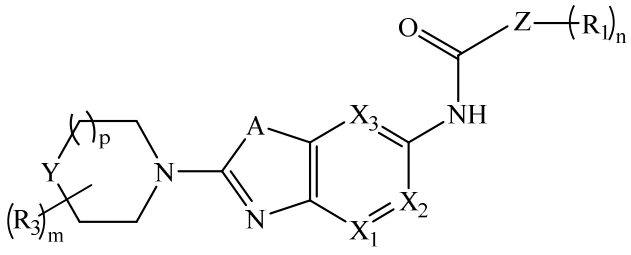
~~15. The method of any one of claims 1-5, wherein the expression of NF-κB p-p65 is the combination of nuclear expression and cytoplasmic expression.~~

~~16. The method of any one of claims 1-15, wherein the IRAK4-modifying compound is an IRAK4 inhibitor.~~

6. The use of any one of claims 1-5, wherein the disease or disorder is cancer.

7. The use of claim 6, wherein the cancer is a hematological malignancy, a relapsed hematological malignancy, a refractory hematological malignancy, leukemia, lymphoma, myelogenous leukemia, myeloid leukemia, acute myeloid leukemia (AML), primary AML, secondary AML, treatment-related AML, myelodysplastic syndrome (MDS), high grade MDS, low grade MDS, high risk MDS, lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), activated B cell like DLBCL, germinal center B cell like DLBCL, extranodal DLBCL, mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, marginal zone lymphoma (MZL), Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, extranodal marginal zone B cell lymphoma, transformed high grade B-cell lymphoma (HGBL), lymphoplasmacytic lymphoma (LPL), central nervous system lymphoma (CNSL), MALT lymphoma, brain cancer, kidney cancer, liver cancer, stomach cancer, penile cancer, vaginal cancer, ovarian cancer, gastric cancer, breast cancer, bladder cancer, colon cancer, prostate cancer, pancreatic cancer, lung cancer, cervical cancer, epidermal cancer, prostate cancer, head or neck cancer, or a solid tumor.

8~~17~~. The ~~method~~use of any one of claims 1-7~~16~~, wherein the IRAK4 inhibitor is represented by formula I:



(I)

or a pharmaceutically acceptable salt thereof;

wherein

X_1 and X_3 independently are CH or N; X_2 is CR_2 or N; provided one and not more than one of X_1, X_2 or X_3 is N;

A is O or S;

Y is $-CH_2-$ or O;

Z is aryl or heterocyclyl;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$;

R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or $-NR_aR_b$; wherein the substituent is alkyl, amino, halo or hydroxyl;

R_3, at each occurrence, is alkyl or hydroxyl;

R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

'm' and 'n' are independently 0, 1 or 2; and

'p' is 0 or 1.

~~18. The method of claim 17, wherein~~

~~A is O or S;~~

~~Y is $-CH_2-$ or O;~~

~~Z is aryl or heterocyclyl;~~

~~R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;~~

~~R_2 is hydrogen, cycloalkyl, heterocyclyl or $-NR_aR_b$;~~

~~'m' is 0; and~~

~~'n' is 1.~~

~~1~~9. The ~~method~~use of claim ~~17~~8, wherein

A is O or S;

Y is $-CH_2-$ or O;

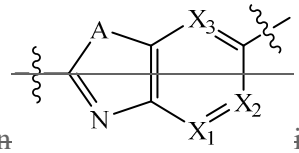
Z is aryl or heterocyclyl;

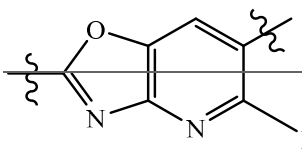
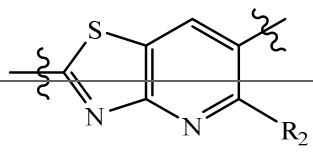
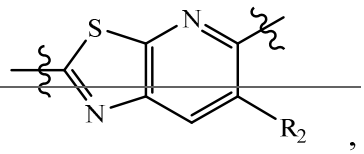
R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

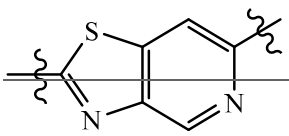
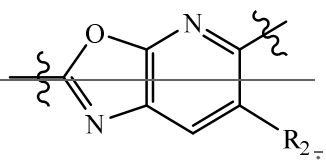
R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $-NR_aR_b$, where the substituent is selected from amino, halo or hydroxyl;

'm' and 'n' are independently 0, 1 or 2; and

'p' is 0 or 1.

~~20. The method of any one of claims 17-19, wherein~~  ~~is~~

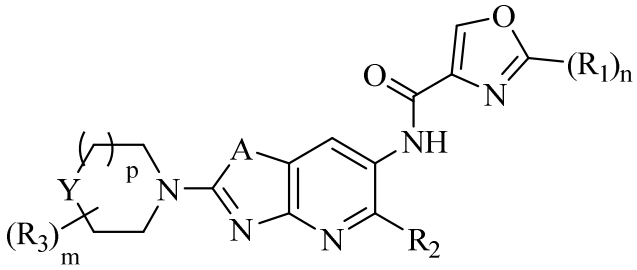
 ,  ,  ,

 or  .

10~~21~~. The ~~method~~use of ~~any one of claims 17-20~~claim 8 or 9, wherein Z is aryl or 5- or 6-membered heterocyclyl.

~~22. The method of any one of claims 17-21, wherein Z is an optionally substituted heterocyclyl selected from phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl and azabicyclo[3.2.1]octanyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or NR_aR_b; and R_a and R_b are independently hydrogen, alkyl or acyl.~~

~~23~~11. The ~~method~~use of claim ~~17~~8, wherein the IRAK4 inhibitor is represented by formula (IA):



(IA)

or a pharmaceutically acceptable salt thereof..

~~24. The method of claim 23, wherein~~

~~A is O or S;~~

~~Y is $-CH_2-$ or O;~~

~~R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;~~

~~R_2 is hydrogen, cycloalkyl, heterocyclyl or NR_aR_b;~~

~~'m' is 0; and~~

~~'n' is 1.~~

~~25~~12. The ~~method~~use of claim ~~23~~11, wherein

A is O or S;

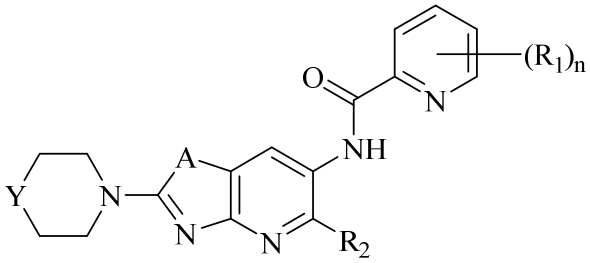
Y is -CH_2- or O;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

'm' and 'n' are independently 0, 1 or 2.

~~26~~13. The ~~method~~use of claim ~~17~~8, wherein the IRAK4 inhibitor is represented by formula (IB):



(IB)

or a pharmaceutically acceptable salt thereof.

~~27. The method of claim 26, wherein~~

~~A is O or S;~~

~~Y is -CH_2- or O;~~

~~R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;~~

~~R_2 is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; and~~

~~'n' is 1.~~

~~28~~14. The ~~method~~use of claim ~~26~~13, wherein

A is O or S;

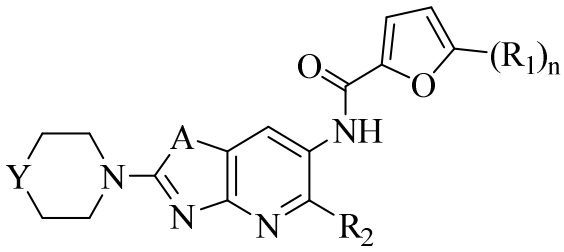
Y is -CH_2- or O;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

'm' and 'n' are independently 0, 1 or 2.

~~29~~15. The ~~method~~use ~~according to~~of claim ~~1~~78, wherein the compound of formula (I) is a compound of formula (IC)



(IC)

or a pharmaceutically acceptable salt thereof.

~~30. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or NR_aR_b; and R_a and R_b are independently hydrogen or acyl.~~

~~31. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, aminoalkyl, halo, or NR_aR_b; and R_a and R_b are independently hydrogen or acyl.~~

~~32. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; and the substituent is alkyl, aminoalkyl, halo, or NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.~~

33. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; and the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.

34. The method of any one of claims 17-33, wherein R_1 is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl.

35. The method of any one of claims 17-29, wherein R_1 is optionally substituted pyrazolyl, wherein the substituent is alkyl, hydroxyl or $-NR_aR_b$.

36. The method of any one of claims 35-29, wherein R_1 is halo.

37. The method of any one of claims 17-36, wherein R_2 is hydrogen, cycloalkyl, heterocyclyl or $-NR_aR_b$.

38. The method of any one of claims 17-36, wherein R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $-NR_aR_b$, where the substituent is selected from amino, halo or hydroxyl.

39. The method of any one of claims 17-36, wherein R_2 is optionally substituted heterocyclyl selected from piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidinyl, pyrazolyl, furanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is hydroxyl, halo, alkyl or amino.

40. The method of any one of claims 17-39, wherein R_2 is piperidinyl, pyrrolidinyl, morpholinyl, or piperazinyl.

41. The method of any one of claims 17-36, wherein R_2 is hydrogen.

42. The method of any one of claims 17-36, wherein R_2 is cycloalkyl.

43. The method of claim 42, wherein R_2 is cyclopropyl.

44. The method of any one of claims 17-43, wherein R_3 is alkyl.

~~45. The method of any one of claims 17-44, wherein m is 0 and p is 1.~~

~~46. The method of any one of claims 17-44, wherein m is 0 or 2, and p is 0 or 1.~~

~~47~~16. The ~~method~~use of any one of claims ~~17~~8-15~~46~~, wherein the IRAK4 inhibitor is selected from:

6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide hydrochloride;

N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-chloro-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide;

2-(2-chloropyridin-4-yl)-N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(2-morpholinothiazolo[4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;

2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-dimorpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(3-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methylpyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide hydrochloride;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide hydrochloride;

N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methoxypyridin-4-yl)oxazole-4-carboxamide;

2-(6-methoxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;

N-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-aminopyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;

N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-acetamidopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

5-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)furan-3-carboxamide hydrochloride;

2-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

2-(2-aminopyridin-4-yl)-N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

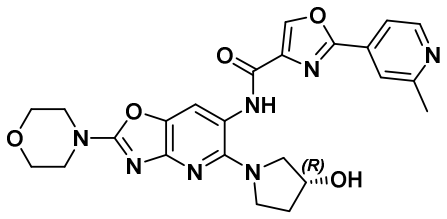
N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride; and

N-(5-(2-hydroxypyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

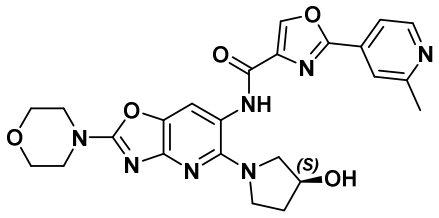
or a pharmaceutically acceptable salt or a stereoisomer thereof.

~~48~~17. The ~~method~~ use of any one of claims 1-16, wherein the IRAK4 inhibitor is



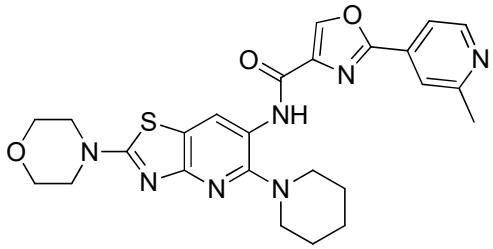
or a pharmaceutically acceptable salt thereof.

18. The use of any one of claims 1-16, wherein the IRAK4 inhibitor is



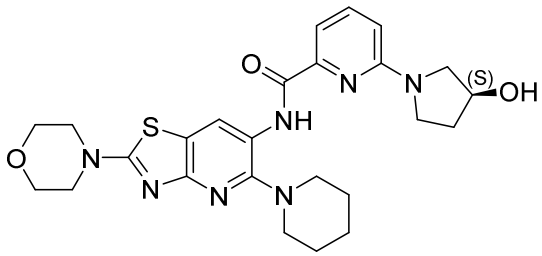
or a pharmaceutically acceptable salt thereof.

19. The use of any one of claims 1-16, wherein the IRAK4 inhibitor is



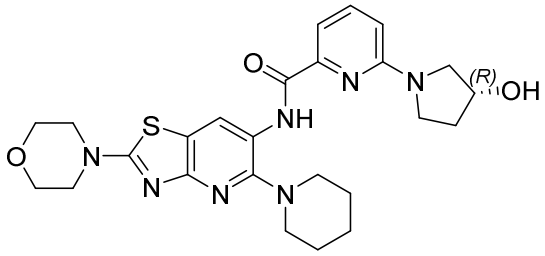
or a pharmaceutically acceptable salt thereof.

20. The use of any one of claims 1-16, wherein the IRAK4 inhibitor is



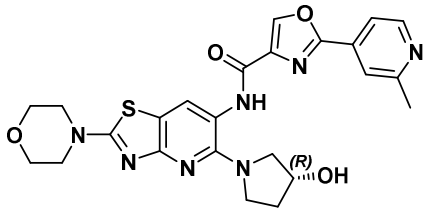
or a pharmaceutically acceptable salt thereof.

21. The use of any one of claims 1-16, wherein the IRAK4 inhibitor is



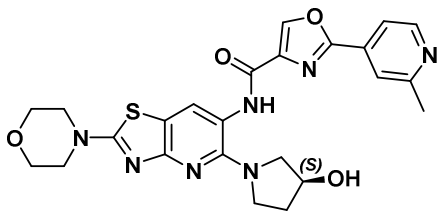
or a pharmaceutically acceptable salt thereof.

22. The use of any one of claims 1-16, wherein the IRAK4 inhibitor is

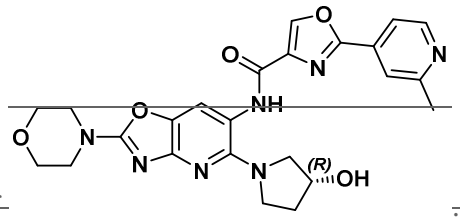


or a pharmaceutically acceptable salt thereof.

23. The use of any one of claims 1-16, wherein the IRAK4 inhibitor is



or a pharmaceutically acceptable salt thereof.

49. The method of any one of claims 1-16, wherein the IRAK4 inhibitor is a pharmaceutically acceptable salt of  .

50. The method of claim 48 or 49, comprising administering 100 – 400 mg of the IRAK4 inhibitor to the subject twice per day.

51. The method of claim 48 or 49, comprising administering 200 – 400 mg of the IRAK4 inhibitor to the subject twice per day.

52. The method of claim 48 or 49, comprising administering 250 – 350 mg of the IRAK4 inhibitor to the subject twice per day.

53. The method of claim 48 or 49, comprising administering about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor to the subject twice per day.

54. The method of claim 48 or 49, comprising administering about 50 mg, about 75 mg, about 100 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, or about 400 mg of the IRAK4 inhibitor to the subject twice per day.

55. The method of claim 48 or 49, comprising administering about 50 mg, about 100 mg, about 200 mg, or about 300 mg of the IRAK4 inhibitor to the subject twice per day.

56. The method of claim 48 or 49, comprising administering about 200 mg of the IRAK4 inhibitor to the subject twice per day.

~~57. The method of claim 48 or 49, comprising administering about 225 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~58. The method of claim 48 or 49, comprising administering about 250 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~59. The method of claim 48 or 49, comprising administering about 275 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~60. The method of claim 48 or 49, comprising administering about 300 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~61. The method of claim 48 or 49, comprising administering about 325 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~62. The method of claim 48 or 49, comprising administering about 350 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~63. The method of claim 48 or 49, comprising administering about 375 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~64. The method of claim 48 or 49, comprising administering about 400 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~65. The method of claim 48 or 49, comprising administering about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor to the subject once per day.~~

~~66. The method of claim 48 or 49, comprising administering about 50 mg of the IRAK4 inhibitor to the subject once per day.~~

~~67. The method of claim 48 or 49, comprising administering about 75 mg of the IRAK4 inhibitor to the subject once per day.~~

~~68. The method of claim 48 or 49, comprising administering about 100 mg of the IRAK4 inhibitor to the subject once per day.~~

~~69. The method of claim 48 or 49, comprising administering about 125 mg of the IRAK4 inhibitor to the subject once per day.~~

~~70. The method of claim 48 or 49, comprising administering about 150 mg of the IRAK4 inhibitor to the subject once per day.~~

~~71. The method of any one of claims 1-70, wherein the IRAK4 inhibitor or IRAK4 degrader is orally administered to the subject.~~

~~72. The method of claim 48 or 49, comprising orally administering about 200 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~73. The method of claim 48 or 49, comprising orally administering about 225 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~74. The method of claim 48 or 49, comprising orally administering about 250 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~75. The method of claim 48 or 49, comprising orally administering about 275 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~76. The method of claim 48 or 49, comprising orally administering about 300 mg of the IRAK4 inhibitor to the subject twice per day.~~

~~77. The method of claim 48 or 49, comprising orally administering about 325 mg of the IRAK4 inhibitor to the subject twice per day.~~

78. The method of claim 48 or 49, comprising orally administering about 350 mg of the IRAK4 inhibitor to the subject twice per day.

79. The method of claim 48 or 49, comprising orally administering about 375 mg of the IRAK4 inhibitor to the subject twice per day.

80. The method of claim 48 or 49, comprising orally administering about 400 mg of the IRAK4 inhibitor to the subject twice per day.

81. The method of claim 48 or 49, comprising administering about 50 mg of the IRAK4 inhibitor to the subject once per day.

82. The method of claim 48 or 49, comprising administering about 75 mg of the IRAK4 inhibitor to the subject once per day.

83. The method of claim 48 or 49, comprising administering about 100 mg of the IRAK4 inhibitor to the subject once per day.

84. The method of claim 48 or 49, comprising administering about 125 mg of the IRAK4 inhibitor to the subject once per day.

85. The method of claim 48 or 49, comprising administering about 150 mg of the IRAK4 inhibitor to the subject once per day.

86. The method of any one of claims 1-16, wherein the IRAK4-modifying compound is PF-06650833 or BAY-1830839.

87. The method of any one of claims 1-16, wherein the IRAK4-modifying compound is an IRAK4 degrader.

88. The method of claim 87, wherein the IRAK4 degrader is KT-474.

~~89. The method of any one of claims 1-88, wherein the method further comprises conjointly administering a BCL-2 inhibitor to the subject.~~

~~90. The method of claim 89, wherein the BCL-2 inhibitor is venetoclax.~~

~~91. The method of claim 89, comprising administering 400 mg of venetoclax daily.~~

~~92. The method of claim any one of claims 90, wherein the venetoclax is administered orally.~~

~~93. The method of claim 89, comprising orally administering 400 mg of venetoclax daily.~~

~~94. The method of any one of claims 1-88, wherein the method further comprises conjointly administering a BTK inhibitor to the subject.~~

~~95. The method of claim 94, wherein the BTK inhibitor is ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7-1224.~~

~~96. The method of claims 94, wherein the BTK inhibitor is acalabrutinib.~~

~~97. The method of claim 96, comprising administering 200 mg of acalabrutinib daily.~~

~~98. The method claim 96, wherein the acalabrutinib is administered orally.~~

~~99. The method of claim 96, comprising orally administering 200 mg of acalabrutinib daily.~~

~~100. The method of claim 94, wherein the BTK inhibitor is ibrutinib.~~

~~101. The method of claim 100, comprising administering 420 mg of ibrutinib daily.~~

~~102. The method of claim 100, comprising administering 560 mg of ibrutinib daily.~~

~~103. The method of claim 100, wherein the ibrutinib is administered orally.~~

~~104. The method of claim 11, comprising orally administering 420 mg of ibrutinib daily.~~

~~105. The method of claim 100, comprising orally administering 560 mg of ibrutinib daily.~~

~~106. The method of claims 96, wherein the BTK inhibitor is zanubrutinib.~~

~~107. The method of claim 106, comprising administering 160 mg of zanubrutinib twice daily.~~

~~108. The method of claim 106, comprising administering 320 mg of zanubrutinib once daily.~~

~~109. The method of claim 96, wherein the zanubrutinib is administered orally.~~

~~110. The method of claim 106, comprising orally administering 160 mg of zanubrutinib twice daily.~~

~~111. The method of claim 106, comprising orally administering 320 mg of zanubrutinib once daily.~~

~~112. The method of any one of claims 1-111, wherein the disease or disorder is a cancer.~~

~~113. The method of any one of claims 1-112, wherein the disease or disorder is a hematological malignancy.~~

~~114. The method of claim 113, wherein the hematological malignancy is a non-Hodgkin's lymphoma.~~

~~115. The method of claim 113, wherein the hematological malignancy is a leukemia or lymphoma.~~

~~116. The method of any one of claims 113-115, wherein the is hematological malignancy is myelogenous leukemia, myeloid leukemia (e.g., acute myeloid leukemia), myelodysplastic syndrome, lymphoblastic leukemia (e.g., acute lymphoblastic leukemia), chronic lymphocytic~~

~~leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) (e.g., DLBCL or ABC-DLBLC), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, marginal zone lymphoma (MZL), Burkitt's lymphoma, non-Burkitt high grade B-cell lymphoma, extranodal marginal zone B-cell lymphoma, transformed high-grade B-cell lymphoma (HGBL), lymphoplasmacytic lymphoma (LPL), central nervous system lymphoma (CNSL), or MALT lymphoma.~~

~~117. The method of claim 113, wherein the hematological malignancy is myelogenous leukemia.~~

~~118. The method of claim 113, wherein the hematological malignancy is myeloid leukemia (e.g., acute myeloid leukemia).~~

~~119. The method of claim 113, wherein the hematological malignancy is acute myeloid leukemia (e.g., AML).~~

~~120. The method of claim 119, wherein the AML is primary AML.~~

~~121. The method of claim 119, wherein the AML is secondary AML.~~

~~122. The method of any one of claims 119-121, wherein the AML is treatment related AML.~~

~~123. The method of claim 113, wherein the hematological malignancy is myelodysplastic syndrome.~~

~~124. The method of claim 123, wherein the myelodysplastic syndrome is high grade.~~

~~125. The method of claim 123, wherein the myelodysplastic syndrome is low grade.~~

~~126. The method of any one of claims 123-125, wherein the myelodysplastic syndrome is high risk.~~

~~127. The method of claim 113, wherein the hematological malignancy is lymphoblastic leukemia (e.g., acute lymphoblastic leukemia).~~

~~128. The method of claim 113, wherein the hematological malignancy is chronic lymphocytic leukemia (CLL).~~

~~129. The method of claim 128, wherein the CLL is high risk CLL.~~

~~130. The method of claim 113, wherein the hematological malignancy is small lymphocytic lymphoma (SLL).~~

~~131. The method of claim 113, wherein the hematological malignancy is follicular lymphoma.~~

~~132. The method of claim 113, wherein the hematological malignancy is diffuse large B-cell lymphoma (DLBCL).~~

~~133. The method of claim 113, wherein the hematological malignancy is activated B-cell-like (ABC) DLBCL.~~

~~134. The method of claim 113, wherein the hematological malignancy is germinal center B cell-like (GCB) DLBCL.~~

~~135. The method of any one of claims 132-134, wherein the DLBCL is extranodal.~~

~~136. The method of any one of claims 132-135, wherein the DLBCL is extranodal leg lymphoma, extranodal testicle lymphoma, or extra nodal not otherwise specified (NOS) type lymphoma.~~

~~137. The method of claim 113, wherein the hematological malignancy is mantle cell lymphoma.~~

~~138. The method of claim 113, wherein the hematological malignancy is Waldenstrom's macroglobulinemia.~~

~~139. The method of claim 113, wherein the hematological malignancy is multiple myeloma.~~

~~140. The method of claim 113, wherein the hematological malignancy is marginal zone lymphoma.~~

~~141. The method of claim 113, wherein the hematological malignancy is Burkitt's lymphoma.~~

~~142. The method of claim 113, wherein the hematological malignancy is non-Burkitt high grade B-cell lymphoma.~~

~~143. The method of claim 113, wherein the hematological malignancy is extranodal marginal zone B-cell lymphoma.~~

~~144. The method of claim 113, wherein the hematological malignancy is transformed high grade B-cell lymphoma (HGBL).~~

~~145. The method of claim 113, wherein the hematological malignancy is lymphoplasmacytic lymphoma (LPL).~~

~~146. The method of claim 113, wherein the hematological malignancy is CNS lymphoma.~~

~~147. The method of claim 146, wherein the CNS lymphoma is primary CNS lymphoma (PCNSL).~~

~~148. The method of claim 113, wherein the hematological malignancy is MALT lymphoma.~~

~~149. The method of any one of claims 113-148, wherein the hematological malignancy is relapsed.~~

~~150. The method of any one of claims 113-149, wherein the hematological malignancy is refractory.~~

~~151. The method of claim 112, wherein the cancer is selected from brain cancer, kidney cancer, liver cancer, stomach cancer, penile cancer, vaginal cancer, ovarian cancer, gastric cancer, breast cancer, bladder cancer, colon cancer, prostate cancer, pancreatic cancer, lung cancer, cervical cancer, epidermal cancer, prostate cancer, head or neck cancer.~~

~~152. The method of claim 112, wherein the cancer is pancreatic cancer.~~

~~153. The method of claim 112, wherein the cancer is colon cancer.~~

~~154. The method of any one of claims 151-153, wherein the cancer is a solid tumor.~~

~~155. The method of any one of claims 151-154, wherein the cancer is relapsed.~~

~~156. The method of any one of claims 151-155, wherein the cancer is refractory.~~

~~157. The method of any one of claims 1-156, wherein the disease or disorder is resistant to treatment with a BTK inhibitor.~~

~~158. The method of claim 157, wherein the disease or disorder is resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7-1224.~~

~~159. The method of claim 157, wherein the disease or disorder is resistant to treatment with ibrutinib.~~

~~160. The method of claim 157, wherein the disease or disorder is resistant to treatment with acalabrutinib.~~

~~161. The method of any one of claims 1-111, wherein the disease or disorder is an inflammatory disease or disorder.~~

~~162. The method of claim 161, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.~~

~~163. The method of claim 161, wherein the inflammatory disease or disorder is an ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, autoimmune hematological disorders, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven- Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior or posterior), Sjogren's syndrome, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis, idiopathic nephrotic syndrome, minimal change nephropathy, chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic urticarial dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma, acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, fibrositis, gastritis, gastroenteritis, nasal sinusitis, ocular allergy, silica induced diseases, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, juvenile rheumatoid arthritis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis,~~

~~mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, urticaria, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticarial, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute or chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS) and osteoarthritis.~~

~~164. The method of claim 161, wherein the inflammatory disease or disorder is hypercytokinemia.~~

~~165. The method of claim 164, wherein the hypercytokinemia is induced by an infectious agent.~~

~~166. The method of claim 165, wherein the infectious agent is a virus.~~

~~167. The method of claim 166, wherein the virus is a coronavirus (e.g., COVID-19).~~

~~168. The method of claim 165, wherein the infectious agent is a bacteria.~~

~~169. The method of claim 161, wherein the inflammatory disease or disorder is graft vs host disease (GVHD).~~

~~170. The method of claim 161, wherein the GVHD is chronic graft vs host disease (cGVHD).~~

~~171. The method of claim 161, wherein the GVHD is sclerodermatous GVHD, steroid resistant GVHD, cyclosporin-resistant GVHD, GVHD, oral GVHD, reticular oral GVHD, erosive GVHD, or ulcerative oral GVHD.~~

~~172. The method of claim 170 or 171, wherein the GVHD is sclerodermatous GVHD.~~

~~173. The method of claim 170 or 171, wherein the GVHD is oral GVHD.~~

~~174. The method of claim 170 or 171, wherein the GVHD is reticular oral GVHD.~~

~~175. The method of claim 170 or 171, wherein the GVHD is erosive GVHD.~~

~~176. The method of claim 170 or 171, wherein the GVHD is ulcerative oral GVHD.~~

~~177. The method of any one of claims 170-176, wherein the GVHD is overlap chronic GVHD.~~

~~178. The method of any one of claims 170-176, wherein the GVHD is classic chronic GVHD.~~

~~179. The method of any one of claims 170-178, wherein the GVHD is steroid resistant GVHD.~~

~~180. The method of any one of claims 170-179, wherein the GVHD is cyclosporin resistant GVHD.~~

~~181. The method of any one of claims 170-180, wherein the GVHD is refractory.~~

~~182. The method of any one of claims 170-181, wherein the GVHD is relapsed.~~

~~183. The method of any one of claims 1-182, wherein the disease or disorder is associated with chronic anemia.~~

~~184. The method of any one of claims 1-111, wherein the disease or disorder is chronic anemia.~~

~~185. The method of any one of claims 1-184, wherein the disease or disorder is associated with transfusion dependency.~~

~~186. The method of any one of claims 1-185, wherein the subject is an adult human.~~

~~187. The method of any one of claims 1-186, wherein the subject has previously received at least one anti-cancer therapy (e.g., an anti-cancer therapy or an anti-inflammatory therapy).~~

~~188. The method of claim 187, wherein the subject has previously received one anti-cancer therapy.~~

~~189. The method of claim 187, wherein the subject has previously received two anti-cancer therapies.~~

~~190. The method of claim 187, wherein the subject has previously received three anti-cancer therapies.~~

~~191. The method of claim 187, wherein the subject has previously received four anti-cancer therapies.~~

~~192. The method of claim 187, wherein the subject has previously received five anti-cancer therapies.~~

~~193. The method of any one of claims 187-192, wherein the at least one anti-cancer therapy is selected from an anti-CD20 antibody, a nitrogen mustard, a steroid, a purine analog, a DNA a topoisomerase inhibitor, a DNA intercalator, a tubulin inhibitor, a BCL-2 inhibitor, a proteasome inhibitor, a toll-like receptor inhibitor, a kinase inhibitor, an SRC kinase inhibitor, a PI3K kinase inhibitor, BTK inhibitor, a glutaminase inhibitor, a steroid, a PD-1 inhibitor a PD-L1 inhibitor, and a methylating agent; or a combination thereof.~~

~~194. The method of any one of claims 187-193, wherein the anti-cancer therapy is selected from ibrutinib, rituximab, bendamustine, bortezomib, dexamethasone, chlorambucil, cladribine, cyclophosphamide, doxorubicin, vincristine, venetoclax, ifosfamide, prednisone, oprozomib, ixazomib, acalabrutinib, zanubrutinib, IMO-08400, idelalisib, umbrelasib, CB-839, fludarabine, and thalidomide; or a combination thereof.~~

~~195. The method of any one of claims 187-194, wherein the therapy is dexamethasone.~~

~~196. The method of any one of claims 187-194, wherein the anti-cancer therapy is ibrutinib.~~

~~197. The method of any one of claims 187-194, wherein the anti-cancer therapy is ibrutinib and rituximab.~~

~~198. The method of any one of claims 187-194, wherein the anti-cancer therapy is bendamustine.~~

~~199. The method of any one of claims 187-194, wherein the anti-cancer therapy is bendamustine and rituximab.~~

~~200. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib.~~

~~201. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib and dexamethasone.~~

~~202. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib and rituximab.~~

~~203. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib, rituximab, and dexamethasone.~~

~~204. The method of any one of claims 187-194, wherein the anti-cancer therapy is chlorambucil.~~

~~205. The method of any one of claims 187-194, wherein the anti-cancer therapy is cladribine.~~

~~206. The method of any one of claims 187-194, wherein the anti-cancer therapy is cladribine and rituximab.~~

~~207. The method of any one of claims 187-194, wherein the anti-cancer therapy is cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (i.e., CHOP-R).~~

~~208. The method of any one of claims 187-194, wherein the anti-cancer therapy is cyclophosphamide, prednisone, and rituximab (i.e., CPR).~~

~~209. The method of any one of claims 187-194, wherein the anti-cancer therapy is fludarabine.~~

~~210. The method of any one of claims 187-194, wherein the anti-cancer therapy is fludarabine and rituximab.~~

~~211. The method of any one of claims 187-194, wherein the anti-cancer therapy is fludarabine, cyclophosphamide, and rituximab.~~

~~212. The method of any one of claims 187-194, wherein the anti-cancer therapy is rituximab.~~

~~213. The method of any one of claims 187-194, wherein the anti-cancer therapy is rituximab, cyclophosphamide, and dexamethasone (i.e., RCD).~~

~~214. The method of any one of claims 187-194, wherein the anti-cancer therapy is thalidomide.~~

~~215. The method of any one of claims 187-194, wherein the anti-cancer therapy is thalidomide and rituximab.~~

~~216. The method of any one of claims 187-194, wherein the anti-cancer therapy is venetoclax.~~

~~217. The method of any one of claims 187-194, wherein the anti-cancer therapy is cyclophosphamide, bortezomib, and dexamethasone (i.e., R-CyBorD).~~

~~218. The method of any one of claims 187-194, wherein the anti-cancer therapy a hypomethylating agent.~~

~~219. The method of any one of claims 1-218, wherein the subject has previously received at least 6 cycles of a hypomethylating agent.~~

~~220. The method of any one of claims 1-219, wherein the subject has previously received etoposide chemo-mobilization therapy.~~

~~221. The method of any one of claims 1-220, wherein the subject has previously received a bone marrow transplant.~~

~~222. The method of any one of claims 1-221, wherein the subject has previously received a hematopoietic cell transplantation.~~

~~223. The method of any one of claims 1-222, wherein the subject has previously received a stem cell transplant.~~

~~224. The method of any one of claims 1-223, wherein the subject has previously received an autologous stem cell transplant.~~

~~225. The method of any one of claims 1-224, wherein the subject has previously received an allogenic stem cell transplant.~~

~~226. The method of any one of claims 1-225, wherein the subject has previously received carmustine, etoposide, cytarabine, and melphalan (i.e., BEAM conditioning).~~

~~227. The method of any one of claims 1-226, wherein the subject has previously received re-induction therapy.~~

~~228. The method of any one of claims 187-227, wherein the subject has previously achieved a partial response.~~

~~229. The method of any one of claims 187-227, wherein the subject has previously achieved a good partial response.~~

~~230. The method of any one of claims 187-227, wherein the subject has previously achieved a complete response.~~

~~231. The method of any one of claims 1-230, wherein the subject has a mutation in RICTOR.~~

~~232. The method of any one of claims 1-231, wherein the subject has a N1065S mutation in RICTOR.~~

~~233. The method of any one of claims 1-232, wherein the subject has a mutation in MYD88.~~

~~234. The method of any one of claims 1-233, wherein the subject has a L265P mutation in MYD88.~~

~~235. The method of any one of claims 1-234, wherein the subject has a mutation in TET2.~~

~~236. The method of any one of claims 1-235, wherein the subject does not have a mutation in CXCR4.~~

~~237. The method of any one of claims 1-235, wherein the subject has a mutation in CXCR4.~~

~~238. The method of any one of claims 1-237, wherein the subject shows early progression.~~

~~239. The method of any one of claims 1-238, wherein the subject has not previously received a BTK inhibitor.~~

~~240. The method of any one of claims 1-239, wherein following administration of the IRAK4 inhibitor, the subject achieves a partial response.~~

~~241. The method of any one of claims 1-239, wherein following administration of the IRAK4 inhibitor, the subject achieves a good partial response.~~

~~242. The method of any one of claims 1-239, wherein following administration of the IRAK4 inhibitor, the subject achieves a complete response.~~

~~243. The method of any one of claims 1-242, wherein following administration of the IRAK4 inhibitor, the subjects IL-1 induced signaling decreases.~~

~~244. The method of any one of claims 1-243, wherein following administration of the IRAK4 inhibitor, the subject's cytokine production decreases.~~

~~245. The method of any one of clams 1-244, wherein the IRAK4 inhibitor is administered until disease progression or unacceptable toxicity.~~

~~246. A method for detecting elevated expression of NF-κB p-p50 in a biological sample comprising:~~

~~contacting the biological sample with a first antibody specific for NF-κB p-p50, thereby providing an antibody-NF-κB p-p50 conjugate;~~

~~contacting the antibody-NF-κB p-p50 conjugate with a second antibody thereby providing an antibody/antibody conjugate mixture, wherein the second antibody is specific for the first antibody and the second antibody has enzymatic activity;~~

~~treating the antibody/antibody conjugate mixture with a chromogenic substrate for the enzymatic activity, thereby providing a substrate/antibody/antibody conjugate mixture; and~~

~~counterstaining the substrate/antibody/antibody conjugate mixture.~~

~~247. The method of claim 246, wherein counterstaining the substrate/antibody/antibody conjugate mixture is performed for no more than 60 seconds.~~

~~248. The method of claim 246, wherein counterstaining the substrate/antibody/antibody conjugate mixture is performed for no more than 10 seconds.~~

~~249. The method of any one of claims 246-248, wherein the counterstain is hematoxylin.~~

~~250. The method of any one of claims 246-249, wherein the enzymatic activity is peroxidase activity.~~

~~251. The method of claim 2650, wherein the chromogenic substrate is a peroxidase substrate.~~

~~252. The method of any one of claims 246-249, wherein the enzymatic activity is alkaline phosphatase activity.~~

~~253. The method of claim 252, wherein the chromogenic substrate is a phosphatase substrate.~~

~~254. The method of any one of claims 246-253, wherein the first antibody is a monoclonal antibody.~~

~~255. The method of any one of claims 246-254, wherein the second antibody is a monoclonal antibody.~~