CLAIMS

**1. A SIK3 inhibitor for use in the treatment of a proliferative disorder, which is a cancer or tumour,** in a subject, by inhibiting SIK3 and sensitising cells involved with the proliferative disorder to a cell-mediated immune response, the treatment comprising administering the SIK3 inhibitor to the subject; wherein: (i) the subject has a plasma concentration of TNF greater than 2 pg/mL; and/or (ii) the proliferative disorder is a solid tumour that, in the subject, has an intratumoural concentration of TNF greater than 0.5 pg/mL.

2. The SIK3 inhibitor for use of claim 1, wherein said cells are **characterised by** activated TNFR2- and/or TNFR1 signalling.

3. **A SIK3 inhibitor for use in the treatment of a proliferative disorder, which is a cancer or tumour,** in a subject, the treatment comprising exposing cells involved with the proliferative disorder in the subject to: (i) TNF, and/or an agonist of TNFR1-signalling; and (ii) a SIK3 inhibitor, wherein the SIK3 inhibitor is administered to the subject; and wherein: (a) the TNF or the agonist of TNFR1-signalling is administered to the subject; (b) an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to the TNF or the agonist of TNFR1-signalling, is administered to the subject; or (c) the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

**4. A SIK3 inhibitor for use in a treatment for the reduction in risk of developing an iatrogenic immunodeficiency-associated lymphoproliferative disease** in a subject being treated with an anti-TNF agent, the treatment comprising administering the inhibitor of SIK3 to the subject.

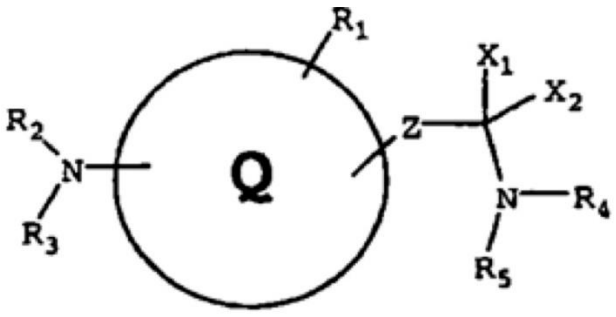
5. The SIK3 inhibitor for use of claim 4, wherein the anti-TNF agent is one selected from a list consisting of: infliximab, adalimumab, golimumab, humicade, etanercept, onercept and certolizumab pegol, in particular infliximab or humicade.

6. The SIK3 inhibitor for use of any one of claims 1 to 5, wherein the SIK3 inhibitor inhibits SIK3 more potently than it inhibits SIK2.

7. The SIK3 inhibitor for use of any one of claims 1 to 6, wherein the SIK3 inhibitor inhibits SIK3 preferentially to inhibiting Abl and/or Bcr-Abl.

8. The SIK3 inhibitor for use of any one of claims 1 to 7, wherein the SIK3 inhibitor is a small molecule, in particular, a small molecule ligand or a small cell-permeable molecule.

9. The SIK3 inhibitor for use of any one of claims 1 to 8, wherein the SIK3 inhibitor is a cyclic compound of the following formula I and salts thereof




**formula I**

where

Q is:

(1) a 5-membered heteroaryl ring;
(2) a 6-membered heteroaryl ring; or
(3) an aryl ring;

optionally substituted with one or more groups $R_1$;
Z is:

(1) a single bond;
(2) $-R_{16}C=CH-$; or
(3) $-(CH_2)_m-$, where m is 1 to 2;

$X_1$ and $X_2$ are each hydrogen, or together form =O or =S;
$R_1$ is:

(1) hydrogen or $R_6$,
where $R_6$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with $Z_1$, $Z_2$ and one or more (preferably, one or two) groups $Z_3$;
(2) -OH or $-OR_6$;
(3) -SH or $-SR_6$;
(4) $-C(O)_2H$, $-C(O)_qR_6$, or $-O-C(O)_qR_6$, where q is 1 or 2;
(5) $-SO_3H$ or $-S(O)_qR_6$;
(6) halo;
(7) cyano;
(8) nitro;
(9) $-Z_4-NR_7R_8$;
(10) $-Z_4-N(R_9)-Z_rNR_{10}R_{11}$;
(11) $-Z_4-N(R_{12})-Z_5-R_6$;
(12) $-P(O)(OR_6)_z$;

$R_2$ and $R_3$ are each independently:

(1) hydrogen or $R_6$;
(2)$-Z_4-R_6$; or
(3) $-Z_{13}-NR_7R_8$;

$R_4$ and $R_5$:

(1) are each independently hydrogen or $R_6$;
(2) $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$;
(3) $-N(R_9)Z_4R_6$; or
(4) together with the nitrogen atom to which they are attached complete a 3- to 8-membered saturated or unsaturated heterocyclic ring which is unsubstituted or substituted with $Z_1$, $Z_2$ and $Z_3$, which heterocyclic ring may optionally have fused to it a benzene ring itself unsubstituted or substituted with $Z_1$, $Z_2$ and $Z_3$;

$R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$ and $R_{12}$:

(1) are each independently hydrogen or $R_6$;
(2) $R_7$, and $R_8$ may together be alkylene, alkenylene or heteroalkyl, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with $Z_1$ $Z_2$ and $Z_3$; or
(3) any two of $R_9$, $R_{10}$ and $R_{11}$ may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with $Z_1$, $Z_2$ and $Z_3$;

$R_{13}$ is:

(1)cyano;
(2) nitro;
(3) $-NH_2$;
(4) -NHOalkyl;
(5) -OH;
(6) -NHOaryl;
(7) -NHCOOalkyl;
(8) -NHCOOaryl;
(9) $-NHSO_2$alkyl;
(10) $-NHSO_2$aryl;
(11) aryl;

(12) heteroaryl;
(13) -Oalkyl; or
(14) -Oaryl;

$R_{14}$ is:
(1) $-NO_2$;
(2) -COOalkyl; or
(3) -COOaryl;

$R_{15}$ is:

(1) hydrogen;
(2) alkyl;
(3) aryl;
(4) arylalkyl; or
(5) cycloalkyl;

$Z_1$, $Z_2$ and $Z_3$ are each independently:

(1) hydrogen or $Z_6$, where $Z_6$ is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of $Z_1$ $Z_2$ and $Z_3$;
(2) -OH or $-OZ_6$;
(3) -SH or $-SZ_6$;
(4) $-C(O)_qH$, $-C(O)_qZ_6$, or $-O-C(O)_qZ_6$;
(5) $-SO_3H$, $-S(O)_qZ_6$; or $S(O)_qN(Z_9)Z_6$;
(6) halo;
(7) cyano;
(8) nitro;
(9) $-Z_4-NZ_7Z_8$;
(10) $-Z_4-N(Z_9)-Z_5-NZ_7Z_8$;
(11) $-Z_4-N(Z_{10})-Z_5-Z_6$;
(12) $-Z_4-N(Z_{10})-Z_5-H$;
(13) oxo;
(14) $-O-C(O)-Z_6$;
(15)any two of $Z_1$, $Z_2$, and $Z_3$ may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or
(16)any two of $Z_1$, $Z_2$, and $Z_3$ may together be $-O-(CH_2)_r-O-$ ,where r is 1 to 5, completing a 4- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

$Z_4$ and $Z_5$ are each independently:

(1) a single bond;
(2) $-Z_{11}-S(O)_q-Z_{12}$;
(3) $-Z_{11}-C(O)-Z_{12}$ ;
(4) $-Z_{11}-C(S)-Z_{12}-$;
(5) $-Z_{11}-O-Z_{12}-$;
(6) $-Z_{11}-S-Z_{12}-$;
(7) $-Z_{11}-O-C(O)-Z_{12}$ ; or
(8) $-Z_{11}-C(O)-O-Z_{12}-$;

$Z_7$, $Z_8$, $z_9$ and $Z_{10}$:

(1) are each independently hydrogen or $Z_6$;
(2) $Z_7$ and $Z_8$, or $Z_6$ and $Z_{10}$, may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with $Z_1$ $Z_2$ and $Z_3$; or
(3) $Z_7$ or $Z_8$, together with $Z_9$, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted
or substituted with $Z_1$, $Z_2$ and $Z_3$;

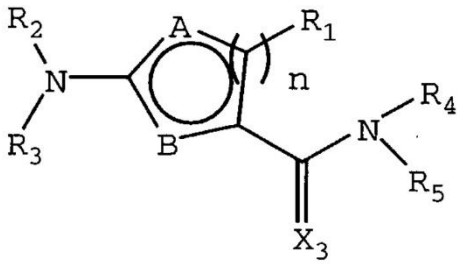
$Z_{11}$ and $Z_{12}$ are each independently:

(1) a single bond;
(2) alkylene;
(3) alkenylene; or
(4) alkynylene; and

$Z_{13}$ is:

(1) a single bond;
(2) $-Z_{11}-S(O)_q-Z_{12}-$;
($^3$) $-Z_{11}-C(O)-Z_{12}$;
(4) $-Z_{11}-C(S)-Z_{12}-$;
(5) $-Z_{11}-O-Z_{12}-$;
(6) $Z_{11}-S-Z_{12}-$;
(7) $-Z_{11}-O-C(O)-Z_{12}$;
(8) $-Z_{11}C(O)-O-Z_{12}$;
(9) $-C(NR_{13})-$;
(10)$-C(CHR_{14})-$; or
(11)$-C(C(R_{14})_2)-$;

wherein the cyclic compound of formula I has the following formula II:

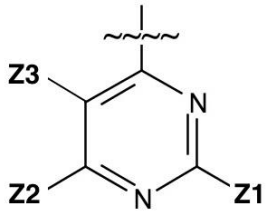



**formula II**

where

n is 1 or 2
A is selected from carbon and nitrogen;
B is selected from nitrogen, oxygen and sulphur;
$X_3$ is oxygen or sulphur; and
$R_1$, $P_2$, $R_3$, $R_4$ and $R_5$ are as described above; and

wherein the R2 of formula II is hydrogen, and R3 of formula II is Rx, wherein Rx has the following formula X:

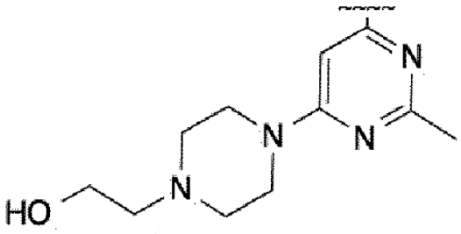



**formula X,**

wherein Z1, Z2 and Z3 of formula X are as defined above.

10. The SIK3 inhibitor for use of claim 9, wherein A is nitrogen; B is sulphur; n is 1; X3 is oxygen; $R_1$, $R_2$ and $R_4$ are hydrogen; and $R_5$ is selected from aryl groups or heteroaryl groups which are substituted with Z1, Z2 and one or more groups Z3, preferably substituted with one or two groups Z3, and R3 is selected from $-Z4-R_6$ or $-Z13-NR_7R_5$.

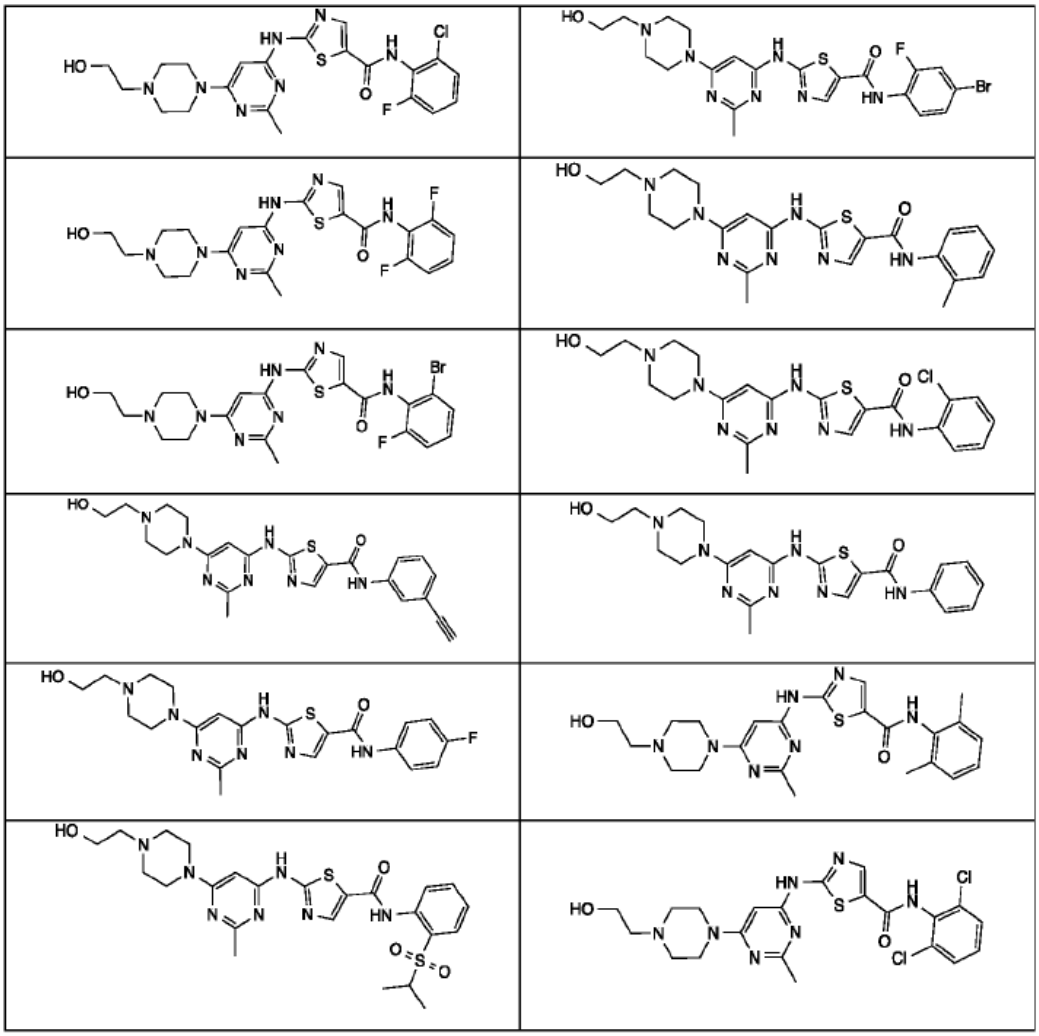
11. The SIK3 inhibitor for use of claim 9 or 10, wherein $R_2$ is a hydrogen and $R_3$ has the following formula Y:



**formula Y.**

12. The SIK3 inhibitor for use of any one of claims 1 to 11, wherein the SIK3 inhibitor is dasatinib.

13. The SI K3 inhibitor for use of any one of claims 1 to 11, wherein the SIK3 inhibitor is selected from the group consisting of:



and solvates, salts, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, isotopically labelled forms, and combinations thereof.

14. The SIK3 inhibitor for use of any one of claims 1 to 7, wherein the SIK3 inhibitor is an inhibitory nucleic acid.

15. The SIK3 inhibitor for use of any one of claims 1 to 3, or 6 to 14 when not referring to claim 4 or 5, wherein cells involved in the proliferative disorder are resistant against a cell-mediated immune response.

16. The SIK3 inhibitor for use of any one of claims 1 to 3, or 6 to 15 when not referring to claim 4 or 5, wherein cells involved in the proliferative disorder have been subjected to prior immunotherapy, in particular the subject has had prior immunotherapy by administration with an immune checkpoint molecule.

17. The SIK3 inhibitor for use of any one of claims 1 to 3, 15 or 16, or 6 to 14 when not referring to claim 4 or 5, wherein cells involved in the proliferative disorder are **characterised by** expression and/or activity of SIK3, in particular such cells express mRNA and/or protein of SIK3, and/or are positive for such SIK3 expression and/or activity.

18. **An in-vitro method for determining** whether a subject has, or is at risk of developing, a proliferative disorder, such as a tumour, that is associated with cellular resistance against a cell-mediated immune response, the method comprising the step of:

(a) detecting an applicable biomarker in a biological sample from said subject; and
(b) determining the presence or amount of TNF in a biological sample from said subject; and

wherein the applicable biomarker is:

- SIK3, in particular the presence (or an amount) of or expression and/or activity of SIK3, preferably of phosphorylated SIK3 protein; and

wherein: (x) the detection of the applicable biomarker in the sample; and (y) the presence of or an amount of TNF in the sample indicates a proliferative disorder or a risk of developing a proliferative disorder that is associated with cellular resistance against the cell-mediated immune response in the subject

19. The method according to claim 18, wherein (i) the sample is a plasma sample and the plasma concentration of TNF greater than 2 pg/mL; and/or (ii) the sample is a sample of a solid tumour and the intratumoural concentration of TNF greater than 0.5 pg/mL.

20. The method according to claim 18 or 19, wherein the applicable biomarker further includes: (i) TNFR1 or TNFR2, in particular the presence of, or an amount of, or expression and/or activity of TNFR1 or TNFR2, in each case preferably TNFR1; and/or (ii) LKB1, preferably the presence of, or an amount of, or expression and/or activity of LKB1, preferably increased activity of LKB1 or pLKB1.

21. The method according to any one of claims 18 to 20, wherein the applicable biomarker further includes: (i) one or more class II or I la HDACs, or HDAC4, in particular the presence of, or an amount of, or expression and/or activity of such HDAC, preferably increased amount or activity of such HDAC or pHDAC, especially in the cytoplasm of cells of the tumour; and/or (ii) NF-kappa-B, in particular the presence of, or an amount of, or expression and/or activity of NF-kappa-B, preferably increased amount or activity of NF-kappa-B or acetylated NF-kappa-B, especially in the nucleus of cells of the tumour.

22. The SIK3 inhibitor for use of any one of claims 1 to 17, or the method of any one of claims 18 to 21, wherein the subject is a human subject.

23. **An in-vitro method for identifying and/or characterising** a compound suitable for the treatment of a disease, disorder or condition that is **characterised by** cellular resistance against a cell-mediated immune response the method comprising the steps of:

(a) bringing into contact a first cell expressing SIK3 and the candidate compound; and
(b) determining (i) the expression, activity, function and/or stability of SIK3, in particular, of phosphorylated SI K3, in the first cell; and (ii) the cytotoxicity of a cell-mediated immune response against the first cell,

wherein: (x) a reduced expression, activity function and/or stability of the SIK3, in said first cell contacted with the candidate compound compared to said first cell not contacted with said candidate compound; and (y) an enhanced cytotoxicity of the cell-mediated immune response against the first cell contacted with the candidate compound compared to the cytotoxicity of the cell-mediated immune response against the first cell not contacted with the candidate compound; indicate that the candidate compound is a compound suitable for the treatment of the disease, disorder or condition that is **characterised by** cellular resistance against a cell-mediated immune response; and wherein the cell-mediated immune response is TNF.

24. The method of claim 23, wherein the candidate compound is a SIK3 inhibitor, in particular a SIK3 inhibitor as defined in any one of claims 9 to 13.

25. The method of claim 23 or 24, wherein the disease, disorder or condition is a proliferative disorder.

26. The method of any one of claims 18 to 21 or 25, wherein the proliferative disorder is a cancer or tumour.

27. The SIK3 inhibitor for use of any one of claims 1 to 3, or 6 to 17 and 22, when not referring to claim 4 or 5, or the method of claim 26, wherein the proliferative disorder is a solid tumour.

28. The SIK3 inhibitor for use of any one of claims 1 to 3, 6 to 14, 17, or 22, when not referring to claim 4 or 5, or the method of claim 26, wherein the proliferative disorder is a haematological malignancy.