CLAIMS

1. **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

2. The method according to claim 1, 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.

3. The method according to claim 1 or 2, 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.

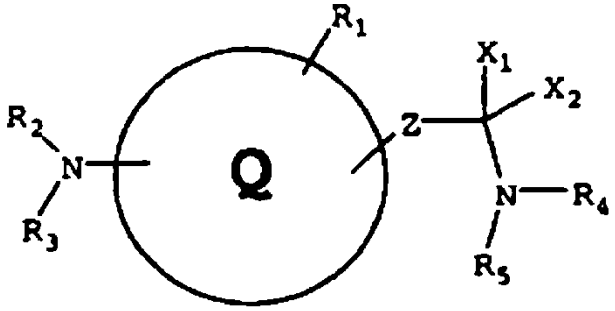
4. The method according to any one of claims 1 to 3, wherein the applicable biomarker further includes: (i) one or more class II or I la HDACs, or HDAC4, in particular the presence of, or an amount of, or expression and/or activity of such HDAC, preferably increased amount or activity of such HDAC or 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.

5. **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.

6. The method of claim 5, wherein the candidate compound is a SIK3 inhibitor, in particular 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;

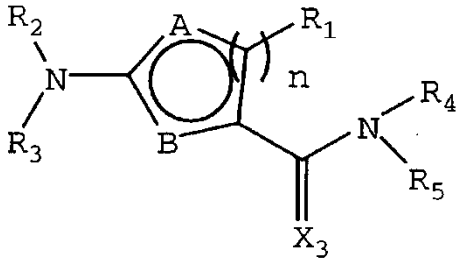
Z_{11} and Z_{12} are each independently:

(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:

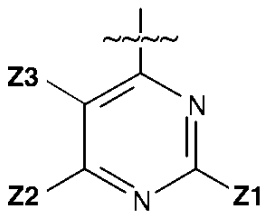


formula II

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:

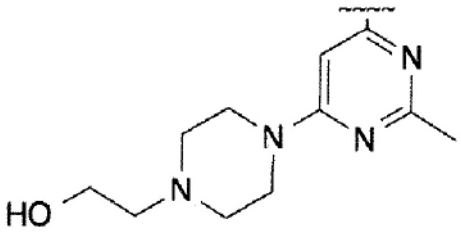


formula X,

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

7. The method of claim 6, 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 $-Z13-NR_7R_5$.

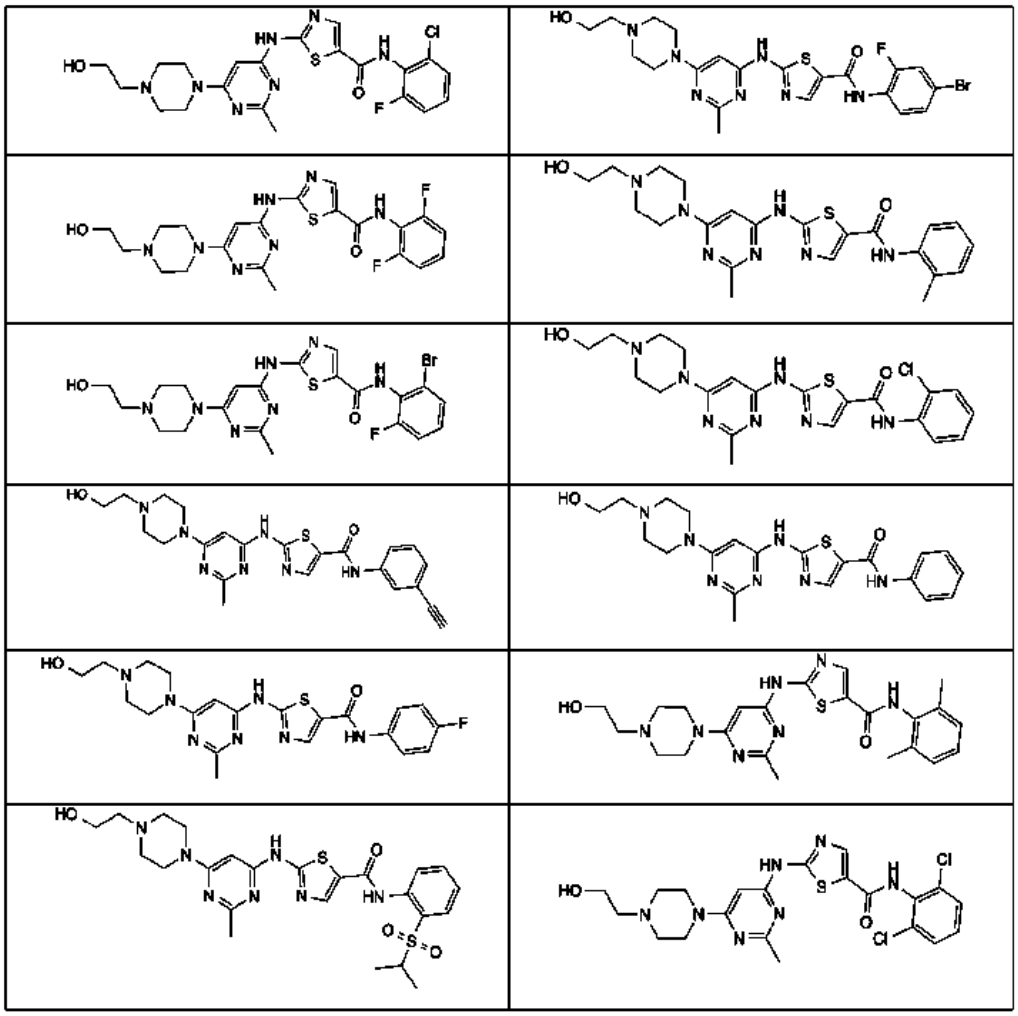
8. The method of claim 6 or 7, wherein R_2 is a hydrogen and R_3 has the following formula Y:



formula Y.

9. The method of any one of claims 6 to 8, wherein the SIK3 inhibitor is dasatinib.

10. The method of any one of claims 6 to 8, 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.

11. The method of any one of claims 5 to 10, wherein the disease, disorder or condition is a proliferative disorder.

12. The method of any one of claims 1 to 4 and 11, wherein the proliferative disorder is a cancer or tumour.