

CLAIMS

1. A method of determining how an individual responds to immunotherapy for cancer comprising detecting the presence or absence in the individual of:

- all of the chromosome interactions shown in Table 8 to thereby determine whether the individual will

be responsive to immunotherapy; and/or

- all of the chromosome interactions shown in Table 2 to thereby determine whether the individual is a hyper-progressor in whom immunotherapy will accelerate disease.

2. A method according to claim 1 further comprising detecting the presence or absence in the individual of all of the chromosome interactions shown in Table 1 to thereby determine whether the individual will be responsive to immunotherapy.

3. A method according to claim 1 or 2 wherein the presence or absence of the chromosome interactions is determined:

- in a sample from the individual, and/or

- in DNA from the individual, and/or

- by detecting the presence or absence of a DNA loop at the site of the chromosome interactions, and/or

- detecting the presence or absence of distal regions of a chromosome being brought together in a chromosome conformation, and/or

- by detecting the presence of a ligated nucleic acid which is generated during said typing and whose sequence comprises two regions each corresponding to the regions of the chromosome which come together in the chromosome interaction, and/or

- by a process which detects the proximity of the chromosome regions which have come together in the chromosome interaction.

4. A method according to any one of the preceding claims wherein said detecting of the presence or absence of the chromosome interactions is by a process comprising:

(i) in vitro crosslinking of epigenetic chromosomal interactions which are present;

(ii) optionally isolating the cross-linked DNA;

(iii) subjecting said cross-linked DNA to cleaving;

(iv) ligating said cross-linked cleaved DNA ends to form ligated DNA; and

(v) identifying the presence or absence in said ligated DNA of a DNA sequence that corresponds to each chromosome interaction;

to thereby determine the presence or absence of each chromosome interaction.

5 5. A method according to claim 3 or 4 wherein said ligated DNA is detected by PCR or by use of a probe.

6. A method according to claim 5 wherein:

(i) detection is by use of a probe, wherein said probe preferably has at least 70% identity to any of the probes shown in Table 1, 2, or 8; or

10 (ii) detection is by use of PCR, wherein the PCR preferably uses a primer pair that has at least 70% identity to any of the primer pairs shown in Table 1, 2 or 8.

7. A method according to any one of the preceding claims wherein:

(i) the method is carried out prior to the individual receiving immunotherapy and/or is carried out to select which therapy the individual should receive for cancer, and/or

(ii) the method is carried out on an individual that has cancer or is suspected of having cancer, and/or

15 (iii) the method is carried out on individual that has been preselected based on a physical characteristic, risk factor or the presence of a symptom for cancer.

8. A method according to any one of the preceding claims in which the individual:

- is at an early stage of cancer; and/or

- is undergoing, or is about to undergo, cancer therapy, for example cancer immunotherapy.

20 9. A method according to any one of the preceding claims wherein the cancer is:

(i) one in which immune-checkpoint inhibitors PD-1/PD-L1 are used for therapy; and/or

(ii) melanoma, lung cancer, hepatocellular carcinoma (liver cancer), bladder, prostate, nasal cancer, parotid gland cancer (salivary gland cancer), alveolar soft part sarcoma (soft tissue cancer); and/or

25 (iii) breast cancer, cervical cancer, colon cancer, head and neck cancer, Hodgkin lymphoma, kidney cancer, stomach cancer, rectal cancer or a solid tumour.

10. A method according to any one of the preceding claims in which the immunotherapy:

(i) comprises an antibody or immune cell, preferably a T cell or dendritic cell; and/or

(ii) comprises a vaccine, preferably against the cancer; and/or

(iii) modulates, blocks or stimulates an immune checkpoint, and preferably targets or modulates PD-L1, PD-L2 or CTLA4 or any other immune checkpoint molecule disclosed in Table 3; and/or

5 (iv) comprises a therapy shown in any one of tables 4 to 6; and/or

(v) increases the killing of cancer cells by the immune system, preferably wherein such killing is by a T cell.

11. A method according to any one of the preceding claims wherein the immunotherapy is:

(i) a PD-1 inhibitor or PD-L1 inhibitor, and is preferably an antibody specific for PD-1 or PD-L1; and/or

10 (ii) a PD-2 inhibitor or PD-L2 inhibitor, and is preferably an antibody specific for PD-2 or PD-L2.

12. A method according to any one of the preceding claims, wherein the typing of chromosome interactions comprises specific detection of the ligated product by quantitative PCR (qPCR) which uses primers capable of amplifying the ligated product and a probe which binds the ligation site during the PCR reaction, wherein said probe comprises sequence which is complementary to sequence from each
15 of the chromosome regions that have come together in the chromosome interaction, wherein preferably said probe comprises:

- an oligonucleotide which specifically binds to said ligated product, and/or

- a fluorophore covalently attached to the 5' end of the oligonucleotide, and/or

- a quencher covalently attached to the 3' end of the oligonucleotide, and

20 optionally

- said fluorophore is selected from HEX, Texas Red and FAM; and/or

- said probe comprises a nucleic acid sequence of length 10 to 40 nucleotide bases, preferably a length of 20 to 30 nucleotide bases.

25 13. ~~An Use of an immunotherapy for cancer in the manufacture of a medicament for use in a method of~~
~~treatment~~ menting of a cancer in an individual, wherein ~~said method of treating comprises:~~

- ~~the individual has been identified~~ identifying whether the individual is being responsive to immunotherapy by the method of any one of the preceding claims, and

- the immunotherapy is to be administered to an individual that has been identified as being responsive to immunotherapy~~-said immunotherapy.~~

14. Use of a combination therapy for cancer in the manufacture of a medicament for use in a method of treating of a cancer in an individual, wherein said method of treating comprises:

5 - the individual has been identifying identified whether the individual is being non-responsive to immunotherapy by the method of any one of the preceding claims 1 to 12, and

- the combination therapy is to be administered to an individual that has been identified as being non-responsive to immunotherapy~~-said combination therapy,~~ wherein said combination therapy comprises a therapeutic agent disclosed in any of tables 4 to 6 or a combination therapy disclosed in any
10 of tables 4 to 6.

15. Use of aAn anti-cancer therapy which is not an immunotherapy in the manufacture of a medicament for use in a method of treating of a cancer in an individual, wherein said method of treating comprises:

15 - the individual has been identifying identified whether the individual is being a hyper-progressor for immunotherapy by the method of any one of the preceding claims 1 to 12, and

- the anti-cancer therapy is to be administering administered to an individual that has been identified as being a hyper-progressor for immunotherapy~~-said anti-cancer therapy.~~