

diagnosis, the main tools for post-treatment follow up or active surveillance also include only imaging studies. Surgery or ablation would result in tissue change and scar formation, causing the detection of local recurrence to be challenging. Lastly, there is also a lack of methods to assess the efficiency of systemic treatments in advanced clear cell renal cell carcinoma patients. In view of the above, there is an unmet need for a method of identifying clear cell renal cell carcinoma, differentiation of benign lesions from malignant tumours, for detection of recurrence after local treatments, and for assessment of systemic treatments.

SUMMARY OF INVENTION

[006] In one aspect, the present invention refers to a clear cell renal cell carcinoma (ccRCC) biomarker set, wherein the biomarker set comprises at least two biomarkers selected from the group consisting of ZNF395, SMPDL3A, SLC28A1, SLC6A3, VEGFA, EGLN3, wherein one of the at least two biomarkers is SMPDL3A or SLC28A1; wherein the biomarkers are proteins, or nucleic acids encoding the same, or variants thereof.

[007] In another aspect, the present invention refers to a detection system comprising a) a receiving section to receive a sample from a subject suspected to suffer from clear cell renal cell carcinoma, and wherein the sample is suspected to comprise the biomarker set as disclosed herein; and b) a detection section comprising a substance or substances capable of detecting the biomarker set as disclosed herein.

[008] In one aspect, the present invention refers to a method of determining whether a subject has or shows recurrence of clear cell renal cell carcinoma, wherein the method comprises obtaining a sample from the subject; detecting the presence of the biomarker set as disclosed herein in the sample using a detection system as disclosed herein, wherein the presence of the biomarker set determines that the subject has or shows recurrence of clear cell renal cell carcinoma.

[009] In a further aspect, the present invention refers to a method of detecting response of a subject to systemic treatment, the method comprising a) obtaining a sample from the subject; and b) determining the levels of the biomarker set as defined herein in the sample; wherein a decrease in levels or an absence of the biomarker set indicates that the subject is responsive to treatment.

[009a] In another aspect, the present invention refers to a method of detecting response of a subject to systemic treatment for clear cell renal cell carcinoma, the method comprising a) obtaining a sample from the subject; b) determining the levels of the biomarker set as defined herein in the sample; wherein a decrease in levels or an absence of the biomarker set indicates that the subject is responsive to treatment.

[0010] In yet another aspect, the present invention refers to a method of determining whether a renal mass sample is benign or malignant, the method comprising obtaining a sample from the

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renal mass of a subject; determining the levels or the presence or absence of the biomarker set as disclosed herein in the sample; wherein the increase in levels of the biomarker set compared to a benign sample indicates that the sample is malignant.

CLAIMS

1. A clear cell renal cell carcinoma (ccRCC) biomarker set, wherein the biomarker set comprises at least two biomarkers selected from the group consisting of ZNF395, SMPDL3A, SLC28A1, SLC6A3, VEGFA, EGLN3, wherein one of the at least two biomarkers is SMPDL3A or SLC28A1; wherein the biomarkers are proteins, or nucleic acids encoding the same, or variants thereof.
2. The clear cell renal cell carcinoma biomarker set of claim 1, wherein the biomarker set comprises at least three biomarkers.
3. The clear cell renal cell carcinoma biomarker set of claim 1 or 2, wherein the biomarker set consists of ZNF395, SMPDL3A and SLC28A1.
4. A detection system comprising a) a receiving section to receive a sample from a subject suspected to suffer from clear cell renal cell carcinoma, and wherein the sample is suspected to comprise the biomarker set according to claim 3 and b) a detection section comprising a substance or substances capable of detecting the biomarker set according to claim 3.
5. The detection system of claim 4, wherein the substance is a bio-specific capture reagent selected from the group consisting of antibodies, or antigen-binding fragments thereof, interacting fusion proteins, aptamers, and affibodies.
6. The detection system of claim 4, wherein the system is selected from the group consisting of a biochip, a test strip, a polymerase chain reaction (PCR) apparatus and a microtiter plate.
7. A method of determining whether a subject has or shows recurrence of clear cell renal cell carcinoma, wherein the method comprises:
 - a) obtaining a sample from the subject;
 - b) detecting the presence of the biomarker set according to any one of claims 1 to 3 in the sample using a detection system according to claims 4 to 6,
 wherein the presence of the biomarker set determines that the subject has or shows recurrence of clear cell renal cell carcinoma.
8. A method of detecting response of a subject to systemic treatment for clear cell renal cell carcinoma, the method comprising
 - a. obtaining a sample from the subject;
 - b. determining the levels of the biomarker set according to any one of claims 1 to 3 in the sample;
 wherein a decrease in levels or an absence of the biomarker set indicates that the subject is responsive to treatment.
9. A method of determining whether a renal mass sample is benign or malignant, the method comprising
 - a. obtaining a sample from the renal mass of a subject;

b. determining the levels or the presence or absence of the biomarker set according to any one of claims 1 to 3 in the sample;

wherein the increase in levels of the biomarker set compared to a benign sample indicates that the sample is malignant.

10. The method of any one of claims 7 to 9, wherein detection is carried out using, and/or the detection system uses, one or more molecular biological methods.

11. The method of claim 10, wherein the one or more molecular biological methods are selected from the group consisting of polymerase chain reaction (PCR), quantitative polymerase chain reaction (qPCR), Western Blot, dot blot, mass spectrometry, nucleic acid sequencing and immunological methods.

12. The method of any one of claims 7 to 11, wherein the determination as to whether the subject has or shows recurrence of clear cell renal cell carcinoma is made based on comparison of the same biomarker set with a control group.

13. The method of claim 12, wherein the control group comprises one or more samples obtained from disease-free subjects and/or samples from non-diseased areas of the same or different subjects suffering from clear cell renal cell carcinoma.

14. The detection system of claims 4 to 6, or the method of claims 7 to 13, wherein the sample is solid sample or fluid sample.

15. The detection system or the method of claim 14, wherein the solid sample is solid tumour biopsy.

16. The detection system or the method of claim 14, wherein the fluid sample is liquid tumour biopsy, urine sample, blood sample, sputum sample or cell culture medium.

17. The detection system of any one of claims 14 or 16, wherein the fluid sample contains exosomes suspected to comprise the biomarker set as defined in claim 3.

18. The method of any one of claims 14 or 16, wherein the fluid sample contains exosomes suspected to comprise the biomarker set as defined in claims 1 to 3.

19. The detection system or method of claim 17 or 18, wherein the exosomes are detected using quantitative polymerase chain reaction (qPCR).

20. A kit for carrying out the method of any one of claims 7 to 16, 18 or 19, wherein the kit comprises a detection buffer, a lysis buffer, and a substance or substances as defined in claim 5 suitable for the detection of the biomarker set according to any one of claims 1 to 3.

21. A kit according to claim 20 and a detection system according to any one of claims 4 to 6, 14 to 17 or 19 for detecting the biomarker set of claim 3.