

WHAT IS CLAIMED IS:

1. Use of a tumor microenvironment (TME) phenotype class-specific therapy in the manufacture of a medicament for treating a human subject afflicted with a cancer, wherein a TME phenotype class is determined by applying an Artificial Neural Network (ANN) classifier to a plurality of RNA expression levels obtained from a gene panel from a cancer tumor sample obtained from the human subject, wherein the cancer tumor sample is assigned the TME phenotype class selected from the group consisting of IS (immune suppressed), A (angiogenic), IA (immune active), ID (immune desert), and combinations thereof.
2. A method for identifying a cancer suitable for treatment with a TME phenotype class-specific therapy, the method comprising applying an ANN classifier to a plurality of RNA expression levels obtained from a gene panel from a cancer tumor sample, wherein the cancer tumor is assigned a TME phenotype class selected from the group consisting of IS, A, IA, ID, and combinations thereof, and wherein the assigned TME phenotype class indicates a TME phenotype class-specific therapy to be administered to treat the cancer.
3. The use of claim 1 or method of claim 2, wherein the ANN classifier comprises:
 - (a) an input layer comprising between 2 and 100 nodes, wherein each node in the input layer corresponds to a gene in a gene panel selected from the genes presented in TABLE 1 and TABLE 2, wherein the gene panel comprises (i) between 1 and 63 genes selected from TABLE 1, and between 1 and 61 genes selected from TABLE 2, (ii) a gene panel comprising genes selected from TABLE 3 and TABLE 4, (iii) a gene panel of TABLE 5, or (iv) any of the gene panels (Genesets) disclosed in FIG. 9A-G;
 - (b) a hidden layer comprising 2 nodes; and
 - (c) an output layer comprising 4 output nodes, wherein each one of the 4 output nodes in the output layer corresponds to a TME phenotype class, wherein the 4 TME phenotype classes are IA, IS, ID, and A,and optionally further comprising applying a logistic regression classifier comprising a Softmax function to the output of the ANN, wherein the Softmax function assigns probabilities to each TME phenotype class.

4. The use of claim 1 or the method of any one of claims 2 to 3, wherein the TME phenotype class-specific therapy is an IA TME phenotype class-specific therapy comprising a checkpoint modulator therapy comprising:
 - (a) an activator of a stimulatory immune checkpoint molecule such as an antibody molecule against GITR, OX-40, ICOS, 4-1BB, or a combination thereof;
 - (b) a ROR γ agonist;
 - (c) an inhibitor of an inhibitory immune checkpoint molecule such as an antibody against PD-1 (such as nivolumab, pembrolizumab, cemiplimab, PDR001, CBT-501, CX-188, sintilimab, tislelizumab, TSR-042 or an antigen-binding portion thereof), an antibody against PD-L1 (such as avelumab, atezolizumab, durvalumab, CX-072, LY3300054, or an antigen-binding portion thereof), an antibody against PD-L2, or an antibody against CTLA-4, alone or a combination thereof, or in combination with an inhibitor of TIM-3, LAG-3, BTLA, TIGIT, VISTA, TGF- β , LAIR1, CD160, 2B4, GITR, OX40, 4-1BB, CD2, CD27, CDS, ICAM-1, LFA-1, ICOS, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, or CD86; or
 - (d) as combination thereof.
5. The use of claim 1 or the method of any one of claims 2 to 3, wherein the TME phenotype class-specific therapy is an IS-class TME therapy comprising:
 - (a) a checkpoint modulator therapy and an anti-immunosuppression therapy; and/or
 - (b) an antiangiogenic therapy;wherein the checkpoint modulator therapy comprises an inhibitor of an inhibitory immune checkpoint molecule comprising:
 - (i) an antibody against PD-1 selected from the group consisting of pembrolizumab, nivolumab, cemiplimab, PDR001, CBT-501, CX-188, sintilimab, tislelizumab, TSR-042, an antigen-binding portion thereof, and a combination thereof;
 - (ii) an antibody against PD-L1 selected from the group consisting of avelumab, atezolizumab, CX-072, LY3300054, durvalumab, an antigen-binding portion thereof, and a combination thereof;
 - (iii) an antibody against PD-L2 or an antigen binding portion thereof;
 - (iv) an antibody against CTLA-4 selected from ipilimumab and the bispecific antibody XmAb20717 (anti PD-1/anti-CTLA-4); or

(v) a combination thereof;

wherein the antiangiogenic therapy comprises administering:

- (i) an anti-VEGF antibody selected from the group consisting of varisacumab, bevacizumab, navicixizumab (anti-DLL4/anti-VEGF bispecific), ABL101 (NOV1501) (anti-DLL4/anti-VEGF), ABT165 (anti-DLL4/anti-VEGF), and a combination thereof;
- (ii) an anti-VEGFR2 antibody, wherein the anti-VEGFR2 antibody comprises ramucirumab; or
- (iii) a combination thereof; and

wherein the anti-immunosuppression therapy comprises administering:

- (i) an anti-PS antibody, anti-PS targeting antibody, antibody that binds β 2-glycoprotein 1, inhibitor of PI3K γ , adenosine pathway inhibitor, inhibitor of IDO, inhibitor of TIM, inhibitor of LAG3, inhibitor of TGF- β , CD47 inhibitor, or a combination thereof, wherein the anti-PS targeting antibody is bavituximab, or an antibody that binds β 2-glycoprotein 1; the PI3K γ inhibitor is LY3023414 (samotolisib) or IPI-549; the adenosine pathway inhibitor is AB-928; the TGF β inhibitor is LY2157299 (galunisertib) or the TGF β R1 inhibitor is LY3200882; the CD47 inhibitor is magrolimab (5F9); and the CD47 inhibitor targets SIRP α ;
- (ii) an inhibitor of TIM-3, LAG-3, BTLA, TIGIT, VISTA, TGF- β or its receptors, an inhibitor of LAIR1, CD160, 2B4, GITR, OX40, 4-1BB, CD2, CD27, CDS, ICAM-1, LFA-1, ICOS, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, an agonist of CD86, or a combination thereof; or
- (iii) a combination thereof.

6. The use of claim 1 or the method of any one of claims 2 to 3, wherein the TME phenotype class-specific therapy is an A TME phenotype class-specific therapy comprising:
- (a) a VEGF-targeted therapy, an inhibitor of angiopoietin 1 (Ang1), an inhibitor of angiopoietin 2 (Ang2), an inhibitor of DLL4, a bispecific of anti-VEGF and anti-DLL4, a TKI inhibitor, an anti-FGF antibody, an anti-FGFR1 antibody, an anti-FGFR2 antibody, a small molecule that inhibits FGFR1, a small molecule that inhibits FGFR2, an anti-PLGF antibody, a small molecule against a PLGF receptor, an antibody against a PLGF receptor,

an anti-VEGFB antibody, an anti-VEGFC antibody, an anti-VEGFD antibody, an antibody to a VEGF/PLGF trap molecule such as aflibercept, or ziv-aflibercept, an anti-DLL4 antibody, an anti-Notch therapy such as an inhibitor of gamma-secretase, or any combination thereof, wherein the TKI inhibitor is selected from the group consisting of cabozantinib, vandetanib, tivozanib, axitinib, lenvatinib, sorafenib, regorafenib, sunitinib, fruquitinib, pazopanib, and any combination thereof; and

wherein the VEGF-targeted therapy comprises (i) an anti-VEGF antibody comprising varisacumab, bevacizumab, an antigen-binding portion thereof, or a combination thereof; (ii) an anti-VEGFR2 antibody comprising ramucirumab or an antigen-binding portion thereof; or (iii) a combination thereof;

(b) an angiopoietin/TIE2-targeted therapy comprising endoglin and/or angiopoietin; or

(c) a DLL4-targeted therapy comprising navicixizumab, ABL101 (NOV1501), ABT165, or a combination thereof.

7. The use of claim 1 or the method of any one of claims 2 to 3, wherein the TME phenotype class-specific therapy is an ID TME phenotype class-specific therapy comprising:

a checkpoint modulator therapy to be administered concurrently or after the administration of a therapy that initiates an immune response, wherein the checkpoint modulator therapy comprises an inhibitor of an inhibitory immune checkpoint molecule such as an antibody against PD-1, PD-L1, PD-L2, CTLA-4, or a combination thereof, and wherein the therapy that initiates an immune response is a vaccine, a CAR-T, or a neo-epitope vaccine, wherein:

(a) the anti-PD-1 antibody comprises nivolumab, pembrolizumab, cemiplimab, PDR001, CBT-501, CX-188, sintilimab, tislelizumab, or TSR-042, or an antigen-binding portion thereof;

(b) the anti-PD-L1 antibody comprises avelumab, atezolizumab, CX-072, LY3300054, durvalumab, or an antigen-binding portion thereof; or

(c) the anti-CTLA-4 antibody comprises ipilimumab or the bispecific antibody XmAb20717 (anti PD-1/anti-CTLA-4), or an antigen-binding portion thereof.

8. The use of claim 1 or the method of any one of claims 2 to 7, wherein the cancer is relapsed, refractory, metastatic, dMMR, or a combination thereof.
9. The use of claim 1 or the method of any one of claims 2 to 7, wherein the cancer is selected from the group consisting of:
 - (a) gastric cancer, such as locally advanced, metastatic gastric cancer, or previously untreated gastric cancer;
 - (b) breast cancer, such as locally advanced, triple negative breast cancer, or metastatic Her2-negative breast cancer;
 - (c) prostate cancer, such as castration-resistant metastatic prostate cancer;
 - (d) liver cancer, such as advanced metastatic hepatocellular carcinoma;
 - (e) carcinoma of head and neck, such as recurrent or metastatic squamous cell carcinoma of head and neck;
 - (f) melanoma, such as metastatic melanoma;
 - (g) colorectal cancer, such as advanced colorectal cancer metastatic to liver;
 - (h) ovarian cancer, such as platinum-resistant ovarian cancer or platinum-sensitive recurrent ovarian cancer;
 - (i) glioma, such as metastatic glioma;
 - (j) lung cancer, such non-small cell lung cancer (NSCLC); and
 - (k) glioblastoma.
10. The use of claim 1 or the method of any one of claims 2 to 9, wherein the TME phenotype class-specific therapy results in:
 - (a) reduction of the cancer burden by at least about 10%, 20%, 30%, 40%, or 50% compared to the cancer burden prior to the therapy;
 - (b) progression-free survival of at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, or at least about 1, 2, 3, 4 or 5 years after the initial administration of the TME phenotype class-specific therapy;
 - (c) stable disease about one month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about one year, about eighteen months, about two years, about

three years, about four years, or about five years after the initial administration of the TME phenotype class-specific therapy;

(d) partial response about one month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about one year, about eighteen months, about two years, about three years, about four years, or about five years after the initial administration of the TME phenotype class-specific therapy;

(e) complete response about one month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about one year, about eighteen months, about two years, about three years, about four years, or about five years after the initial administration of the TME phenotype class-specific therapy;

(f) improved progression-free survival probability by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 110%, at least about 120%, at least about 130%, at least about 140%, or at least about 150%, compared to the progression-free survival probability of a subject who has not received a TME phenotype class-specific therapy assigned using an ANN classifier such as TME Panel-1;

(g) improved overall survival probability by at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 325%, at least about 350%, or at least about 375%, compared to the overall survival probability of a subject who has not received a TME phenotype class-specific therapy assigned using an ANN classifier such as TME Panel-1;
or

(h) a combination thereof.

11. A method of assigning a TME phenotype class to a cancer, the method comprising:

(a) generating an ANN classifier by training an ANN with a training set comprising RNA expression levels for each gene in a gene panel in a plurality of samples, wherein each sample is assigned a TME phenotype classification; and

assigning, using the ANN classifier, a TME phenotype class to the cancer, wherein the input to the ANN classifier comprises RNA expression levels for each gene in the gene panel in a test sample;

(b) generating an ANN classifier by training an ANN with a training set comprising RNA expression levels for each gene in a gene panel in a plurality of samples, wherein each sample is assigned a TME phenotype classification; wherein the ANN classifier assigns a TME phenotype class to the cancer using as input RNA expression levels for each gene in the gene panel in a test sample; or

(c) using an ANN classifier to predict the TME phenotype class of the cancer in the subject, wherein the ANN classifier is generated by training an ANN with a training set comprising RNA expression levels for each gene in a gene panel in a plurality of samples, wherein each sample is assigned a TME phenotype class or combination thereof.

12. The method of claim 11, where the method is implemented in a computer system comprising at least one processor and at least one memory, the at least one memory comprising instructions executed by the at least one processor to cause the at least one processor to implement the machine-learning model.
13. The method of claim 12, further comprising (a) inputting, into the memory of the computer system, the ANN classifier code; (b) inputting, into the memory of the computer system, the gene panel input data, wherein the input data comprises RNA expression levels; (c) executing the ANN classifier code; or (d) any combination thereof.
14. Use of a TME phenotype class-specific therapy in the manufacture of a medicament for treating a subject having a cancer with a specific TME phenotype wherein:
 - (a) the cancer is locally advanced, metastatic gastric cancer and the TME phenotype is IA, A, or IS;
 - (b) the cancer is untreated gastric cancer and the TME phenotype is IS or A;
 - (c) the cancer is advanced/metastatic HER2-negative breast Cancer and the TME phenotype is A or IS;
 - (d) the cancer is castration-resistant metastatic prostate cancer and the TME phenotype is A or IS;

- (e) the cancer is advanced metastatic hepatocellular carcinoma and the TME phenotype is IA or IS;
- (f) the cancer is recurrent/metastatic squamous cell carcinoma of head and neck and the TME phenotype is IA or IS;
- (g) the cancer is melanoma and the TME phenotype is IA or IS;
- (h) the cancer is advanced colorectal cancer metastatic to liver and the TME phenotype is ID;
- (i) the cancer is platinum resistant or platinum-sensitive recurrent ovarian cancer and the TME phenotype is IA, IS or A;
- (j) the cancer is platinum-resistant or platinum-sensitive recurrent triple negative breast cancer and the TME phenotype is IA, IS or A;
- (k) the cancer is metastatic colorectal cancer and the TME phenotype is A or IS;
- (l) the cancer is glioma or glioblastoma and the TME phenotype is IS or IA; or
- (m) the cancer is non-small cell lung cancer and the TME phenotype is IS or IA;

wherein the TME phenotype class has been assigned by applying an ANN classifier to a plurality of RNA expression levels obtained from a gene panel from a cancer tumor sample obtained from the subject, wherein the ANN classifier comprises:

- (i) an input layer comprising between 2 and 100 nodes, wherein each node in the input layer corresponds to a gene in a gene panel selected from the genes presented in TABLE 1 and TABLE 2, wherein the gene panel comprises (1) between 1 and 63 genes selected from TABLE 1, and between 1 and 61 genes selected from TABLE 2, (2) a gene panel comprising genes selected from TABLE 3 and TABLE 4, (3) a gene panel of TABLE 5, or (4) any of the gene panels (Genesets) disclosed in FIG. 9A-G;
 - (ii) a hidden layer comprising 2 nodes; and
 - (iii) an output layer comprising 4 output nodes, wherein each one of the 4 output nodes in the output layer corresponds to a TME phenotype class, wherein the 4 TME phenotype classes are IA, IS, ID, and A,
- and optionally further comprises a logistic regression classifier comprising a Softmax function to the output of the ANN, wherein the Softmax function assigns probabilities to each TME phenotype class.

15. A kit or article of manufacture comprising (a) a plurality of oligonucleotide probes capable of specifically detecting an RNA encoding a gene biomarker from TABLE 1 (or FIG. 9A-9G) and (b) a plurality of oligonucleotide probes capable of specifically detecting an RNA encoding a gene biomarker from TABLE 2 (or FIG. 9A-9G), wherein the article of manufacture comprises a microarray.