

WHAT IS CLAIMED IS:

1. An artificial neural network (ANN) for determining a presence of an angiogenic tumor microenvironment (TME) of a cancer in a subject in need thereof, wherein:
 - the ANN identifies the subject as exhibiting an angiogenic TME using as input RNA expression levels obtained from a gene panel from a tumor tissue sample from the subject;
 - the gene panel comprises (a) one or more genes selected from the group consisting of ABCC9, AFAP1L2, BACE1, BGN, BMP5, CAVIN2, COL4A2, COL8A1, COL8A2, CPXM2, CXCL12, EBF1, ECM2, EDNRA, ELN, EPHA3, FBLN5, GNAS, GNB4, GUCY1A1, HEY2, HSPB2, IL1B, ITGA9, ITPR1, JAM2, JAM3, KCNJ8, LAMB2, LHFPL6, LTBP4, MEOX1, MGP, MMP12, MMP13, NAALAD2, NFATC1, NOV, OLFML2A, PCDH17, PDE5A, PDGFRB, PEG3, PLSCR2, PLXDC2, RGS4, RGS5, RNF144A, RRAS, RUNX1T1, SELP, SERPINE2, SGIP1, SMARCA1, SPON1, STAB2, STEAP4, TBX2, TEK, TGFB2, TMEM204, TTC28, and UTRN, and (b) one or more genes selected from the group consisting of ADAMTS4, AGR2, C10orf54, C11orf9, CAPG, CCL2, CCL3, CCL4, CD19, CD274, CD3E, CD4, CD79A, CD8B, CTLA4, CTSB, CXCL10, CXCL11, CXCL9, DUSP4, EIF5A, ETV5, FOLR2, GAD1, GZMB, HAVCR2, HFE, HMOX1, HP, IDO1, IFNA2, IFNB1, IFNG, IGFBP3, IGLL5, IQGAP3, LAG3, MEST, MST1, MT2A, MTA2, PDCD1, PDCD1LG2, PLA2G4A, PLAU, RAC2, REG4, RNH1, SERPINE1, SRSF6, STRN3, TGFB1, TIGIT, TIMP1, TLR9, TNFRSF18, TNFRSF4, TNFSF18, TRIM7, USF1, and ZIC2;
 - the ANN comprises an input layer, a hidden layer, and an output layer; and
 - the presence of an angiogenic TME indicates that the subject can be effectively treated with an anti-angiogenic therapy.
2. The ANN of claim 1, wherein the input layer comprises one or more nodes (neurons) and wherein each node (neuron) in the input layer corresponds to a gene in the gene panel.
3. The ANN of claim 1 or 2, wherein the RNA expression levels are transcribed RNA expression levels determined using Next Generation Sequencing (NGS) selected from the group

consisting of RNA-Seq, EdgeSeq, Nanostring, WES, or combinations thereof; and wherein optionally the RNA expression levels are subject to quantile normalization comprising transforming the RNA expression levels to a normal output distribution function.

4. The ANN of any one of claims 1-3, wherein:
 - (i) the ANN is trained with a training set comprising RNA expression levels for each gene in the gene panel in a plurality of samples obtained from a plurality of subjects;
 - (ii) each sample is assigned a TME-class determined by a population-based classifier, wherein the population-based classifier comprises determining a Signature 1 Z-score and a Signature 2 Z-score by measuring the RNA expression levels for each gene in the gene panel in each sample in the training set; and
 - (iii) the gene panel used to calculate Signature 1 Z-score comprises one of more genes selected from the group consisting of ABCC9, AFAP1L2, BACE1, BGN, BMP5, CAVIN2, COL4A2, COL8A1, COL8A2, CPXM2, CXCL12, EBF1, ECM2, EDNRA, ELN, EPHA3, FBLN5, GNAS, GNB4, GUCY1A1, HEY2, HSPB2, IL1B, ITGA9, ITPR1, JAM2, JAM3, KCNJ8, LAMB2, LHFPL6, LTBP4, MEOX1, MGP, MMP12, MMP13, NAALAD2, NFATC1, NOV, OLFML2A, PCDH17, PDE5A, PDGFRB, PEG3, PLSCR2, PLXDC2, RGS4, RGS5, RNF144A, RRAS, RUNX1T1, SELP, SERPINE2, SGIP1, SMARCA1, SPON1, STAB2, STEAP4, TBX2, TEK, TGFB2, TMEM204, TTC28, and UTRN and the gene panel used to calculate Signature 2 Z-score comprises one of more genes selected from the group consisting of ADAMTS4, AGR2, C10orf54, C11orf9, CAPG, CCL2, CCL3, CCL4, CD19, CD274, CD3E, CD4, CD79A, CD8B, CTLA4, CTSB, CXCL10, CXCL11, CXCL9, DUSP4, EIF5A, ETV5, FOLR2, GAD1, GZMB, HAVCR2, HFE, HMOX1, HP, IDO1, IFNA2, IFNB1, IFNG, IGFBP3, IGLL5, IQGAP3, LAG3, MEST, MST1, MT2A, MTA2, PDCD1, PDCD1LG2, PLA2G4A, PLAU, RAC2, REG4, RNH1, SERPINE1, SRSF6, STRN3, TGFB1, TIGIT, TIMP1, TLR9, TNFRSF18, TNFRSF4, TNFSF18, TRIM7, USF1, and ZIC2.
5. The ANN of claim 4, wherein the TME-class assigned is
 - (i) immune active if the Signature 1 Z-score is negative and the Signature 2 Z-score is positive;

- (ii) immune suppressed if the Signature 1 Z-score is positive and the Signature 2 Z-score is positive;
 - (iii) immune desert if the Signature 1 Z-score is negative and the Signature 2 Z-score is negative; and,
 - (iv) angiogenic if the Signature 1 Z-score is positive and the Signature 2 Z-score is negative.
6. The ANN of claim 5, wherein the calculation of a Signature 1 score comprises:
- (i) measuring the expression level for one or more of ABCC9, AFAP1L2, BACE1, BGN, BMP5, CAVIN2, COL4A2, COL8A1, COL8A2, CPXM2, CXCL12, EBF1, ECM2, EDNRA, ELN, EPHA3, FBLN5, GNAS, GNB4, GUCY1A1, HEY2, HSPB2, IL1B, ITGA9, ITPR1, JAM2, JAM3, KCNJ8, LAMB2, LHFPL6, LTBP4, MEOX1, MGP, MMP12, MMP13, NAALAD2, NFATC1, NOV, OLFML2A, PCDH17, PDE5A, PDGFRB, PEG3, PLSCR2, PLXDC2, RGS4, RGS5, RNF144A, RRAS, RUNX1T1, SELP, SERPINE2, SGIP1, SMARCA1, SPON1, STAB2, STEAP4, TBX2, TEK, TGFB2, TMEM204, TTC28, and UTRN in a test sample from the subject;
 - (ii) for each gene, subtracting the mean expression value obtained from the expression levels of that gene in a reference sample from the expression level of step (i);
 - (iii) for each gene, dividing the value obtained in step (ii) by the standard deviation per gene obtained from the expression levels of the reference sample; and
 - (iv) adding all the values obtained in step (iii) and dividing the resulting number by the square root of the number of genes in the gene panel;
- wherein if the value obtained in (iv) is above zero, the signature score is a positive signature score, and wherein if the value obtained in (iv) is below zero, the signature score is a negative signature score.
7. The ANN of claim 5 or 6, wherein the calculation of a Signature 2 score comprises:
- (i) measuring the expression level for one or more of ADAMTS4, AGR2, C10orf54, C11orf9, CAPG, CCL2, CCL3, CCL4, CD19, CD274, CD3E, CD4, CD79A, CD8B, CTLA4, CTSB, CXCL10, CXCL11, CXCL9, DUSP4, EIF5A, ETV5, FOLR2, GAD1, GZMB, HAVCR2, HFE, HMOX1, HP, IDO1, IFNA2, IFNB1, IFNG, IGFBP3, IGLL5, IQGAP3,

LAG3, MEST, MST1, MT2A, MTA2, PDCD1, PDCD1LG2, PLA2G4A, PLAU, RAC2, REG4, RNH1, SERPINE1, SRSF6, STRN3, TGFB1, TIGIT, TIMP1, TLR9, TNFRSF18, TNFRSF4, TNFSF18, TRIM7, USF1, and ZIC2 in a test sample from the subject;

(ii) for each gene, subtracting the mean expression value obtained from the expression levels of that gene in a reference sample from the expression level of step (i);

(iii) for each gene, dividing the value obtained in step (ii) by the standard deviation per gene obtained from the expression levels of the reference sample; and

(iv) adding all the values obtained in step (iii) and dividing the resulting number by the square root of the number of genes in the gene panel;

wherein if the value obtained in (iv) is above zero, the signature score is a positive signature score, and wherein if the value obtained in (iv) is below zero, the signature score is a negative signature score.

8. The ANN of any one of claims 1-7, wherein the hidden layer comprises at least 2 nodes (neurons), and a hyperbolic tangent sigmoid activation function is applied to the hidden layer.
9. The ANN of any one of claims 1-8, wherein a logistic regression classifier comprising a Softmax function is applied to the output layer of the ANN, wherein the Softmax function is implemented through an additional neural network layer interposed between the hidden layer and the output layer, and wherein the Softmax function assigns a class probability for the angioneic TME.
10. The ANN of claim 9, wherein the class probability is overlaid on a latent space plot of the activation scores of the nodes of the ANN.
11. The ANN of claim 9, wherein the logistic regression classifier is trained on the latent space.
12. The ANN of claim 9, wherein the logistic regression classifier is optimized for BOR (Best Objective Response), ORR (Overall Response Rate), MSS/MSI-high (Microsatellite Stable/Microsatellite Instability-high) status, PD-1/PD-L1 status, PFS (Progression-Free

Survival), NLR (Neutrophil Leukocyte Ratio), Tumor Mutation Burden (TMB) or any combination thereof.

13. Use of an anti-angiogenic therapy in the manufacture of a medicament for treating a subject afflicted with a cancer, wherein the subject is identified as exhibiting an angiogenic TME as determined by applying an ANN classifier of any one of claims 1-12 to a plurality of RNA expression levels obtained from a gene panel from a tumor tissue sample obtained from the subject.
14. The use of claim 13, wherein the tumor is selected from the group consisting of tumors associated with gastric cancer, colorectal cancer, liver cancer (hepatocellular carcinoma, HCC), ovarian cancer, breast cancer, NSCLC, bladder cancer, lung cancer, pancreatic cancer, head and neck cancer, lymphoma, uterine cancer, renal or kidney cancer, biliary cancer, prostate cancer, testicular cancer, urethral cancer, penile cancer, thoracic cancer, rectal cancer, brain cancer (glioma and glioblastoma), cervicalparotid cancer, esophageal cancer, gastroesophageal cancer, larynx cancer, thyroid cancer, adenocarcinomas, neuroblastomas, melanoma, and Merkel Cell carcinoma; preferably, wherein the tumor is selected from the group consisting of tumors associated with ovarian cancer, peritoneal cancer, fallopian cancer, colorectal cancer, or gastroesophageal cancer
15. The use of claim 13 or 14, wherein the cancer is relapsed, metastatic, or refractory, preferably refractory following at least one prior therapy comprising administration of at least one anticancer agent.
16. The use of any one of claims 13-15, wherein the anti-angiogenic therapy comprises one of the following:
 - (i) an anti-VEGF antibody selected from the group consisting of varisacumab, bevacizumab, navicixizumab (anti-DLL4/anti-VEGF bispecific), and a combination thereof, preferably the anti-VEGF antibody is an anti-VEGF bispecific antibody;

- (ii) the antiangiogenic therapy comprises an anti-VEGFR antibody, preferably wherein the anti-VEGFR antibody is an anti-VEGFR2 antibody, more preferably the anti-VEGFR2 antibody comprises ramucirumab; and
 - (iii) navicixizumab, ABL101 (NOV1501), or ABT165.
- 17. The use of claim 16, wherein the anti-VEGF bispecific antibody is an anti-DLL4/anti-VEGF bispecific antibody.
- 18. The use of claim 17, wherein the anti-DLL4/anti-VEGF bispecific antibody comprises navicixizumab.
- 19. The use of any one of claims 13-15, wherein the anti-angiogenic therapy comprises (1) a VEGF-targeted therapy and (2) 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 an angiopoietin/TIE2-targeted therapy.
- 20. The use of claim 19, wherein one of the following conditions is fulfilled:
 - (i) the TKI inhibitor is selected from the group consisting of cabozantinib, vandetanib, tivozanib, axitinib, lenvatinib, sorafenib, regorafenib, sunitinib, fruquintinib, pazopanib, and any combination thereof, preferably the TKI inhibitor is fruquintinib;
 - (ii) the VEGF-targeted therapy comprises an anti-VEGF antibody or an antigen-binding portion thereof, preferably the VEGF-targeted therapy comprises an anti-VEGF antibody or an antigen-binding portion thereof, optionally wherein the anti-VEGF antibody comprises varisacumab, bevacizumab, or an antigen-binding portion thereof,

- or optionally wherein the anti-VEGF antibody cross-competes with varisacumab, or bevacizumab for binding to human VEGF A, or wherein the anti-VEGF antibody binds to the same epitope as varisacumab, or bevacizumab;
- (iii) the VEGF-targeted therapy comprises the administration of an anti-VEGFR antibody, preferably wherein the anti-VEGFR antibody is an anti-VEGFR2 antibody, more preferably wherein the anti-VEGFR2 antibody comprises ramucirumab or an antigen-binding portion thereof;
 - (iv) the angiopoietin/TIE2-targeted therapy comprises endoglin and/or angiopoietin; and
 - (v) the inhibitor of DLL4 or the anti-DLL4 antibody comprises navicixizumab, ABL101 (NOV1501), or ABT165.
21. A method of assigning an angiogenic TME class to a cancer in a subject in need thereof, the method comprising applying the ANN classifier of any one of claims 1-12 to a plurality of RNA expression levels obtained from a gene panel from a tumor tissue sample obtained from the subject, wherein the ANN classifier identifies the subject as exhibiting or not exhibiting an angiogenic TME.
22. A method for identifying a subject afflicted with a cancer as suitable for treatment with an anti-angiogenic therapy, the method comprising applying the ANN classifier of any one of claims 1-12 to a plurality of RNA expression levels obtained from a gene panel from a tumor tissue sample obtained from the subject, wherein the presence of an angiogenic TME-class indicates an anti-angiogenic therapy to be administered to treat the subject.